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Geriatric Oncology

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With 76 Figures and 143 Tables

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Foreword

The management of new information is a major challenge for the modern practitioner of oncology. The reports in authoritative medical journals are weeks or months old and may sound obsolete to the readers. Big pharma learned how to bypass the news embargoes of scientific organizations and floods the internet with preliminary information concerning their products.

National guidelines organizations, such as the National Cancer Center Network (NCCN) practice guidelines, so far have provided a realistic approach to the sorting of incoming data. Thanks to panels of national experts, these organizations are able to incorporate new information in their guidelines very timely. In such informational landscape, it is legitimate to ask whether there is still room for medical textbooks that may require years to complete.

The new textbook of *Geriatric Oncology* by Martine Extermann, M.D., Ph. D., and colleagues provides several affirmative answers to this question.

The easiest answer is that the book lends itself to rapid updates thanks to a digitalized format. Most medical textbooks nowadays offer a digitalized edition, so this approach is definitely important but certainly not new or novel.

A number of more substantial answers may be found in the content of the book. More than a new discipline or a new specialty, more than a task force aimed to collect data on the management of older patients with cancer, *Geriatric Oncology* is a new frame of mind. As such it needs to be properly articulated in the chapters of a book and cannot be collapsed in tweets or headlines. For the formation of practitioners of oncology and of geriatrics, a textbook of geriatric oncology may have the same weight as a textbook of human anatomy or human physiology for a first-year medical student.

The study of geriatric oncology includes the definition of age from a clinical and a biological standpoint, the interactions of age with cancer development, cancer growth and cancer treatment, the inclusion of social issues in medical decisions, and a decisional frame of reference aimed to provide personalized care based on individual life expectancy, tolerance of stress, and treatment goals. To further complicate the issue, aging itself is evolving. In his novel *La fin de la nuit* published in the early mid-1930s, François Mauriac describes the main character as “an older woman” at age 45! Today it is not unusual for a woman to carry on a pregnancy even at a later age. It is common to hear that

today's seventies are yesterday's fifties in terms of function and health. Parallel to the evolution of age are the advances in cancer understanding and treatment. We do need a construct of aging capable to accommodate these advances.

These different aspects of aging and cancer intersect each other as the threads of a carpet and generate what we call a complex situation. Complex from the Latin cum *plexere* means to "weave together." In a sentence, we could say that geriatric oncology involves the management of complexity.

Management of complexity is definitely a new direction in medicine. Evidence-based medicine has been fed by the results of clinical trials that by definition excluded complex patients. The design of traditional trials was focused on the disease and for these reasons the selection criteria included excellent performance status, absence of multimorbidity, and social independence. Though most trials have removed an upper age limit from the inclusion criteria, nonetheless the majority of older people have been "de facto" excluded. While the older population has increased dramatically during the last decades and individuals over 65 represent now more than 50% of cancer patients in the Western world, the participation of older individuals to clinical trials of cancer treatment has not augmented, until clinical trials have been designed specifically for older individuals. Despite their role in advancing the treatment of cancer, clinical trials may not prove the best instruments to study complexity.

Based on decades-long experience in treating and studying of older patients, Dr. Extermann and her associate editors, all from the most prestigious institutions in the USA and abroad, have provided in this book a most valuable blueprint to the management of complexity. For the practitioners of oncology (physicians, advance practice professionals, nurses, pharmacist, dietitians), this book illustrates the assessment of functional age along with the unexpected interactions of aging and cancer treatment and alerts the readers about some unexpected findings, such as the higher risk of cancer-related mortality with advancing age. On this core message the practitioner may add new information as they emerge.

For the practitioners of geriatrics, *Geriatric Oncology* provides important information about new forms of cancer treatment that can be adapted to individual situations. Such information is essential to advise the patient and to establish a meaningful cooperation with their oncological counterpart. Until very recently, the only treatment available for metastatic non-small cell lung cancer was cytotoxic chemotherapy, which was unsuitable for frail patients. Today targeted treatment as well as immune checkpoint inhibitors may prolong the life and the quality of life even of these patients. Likewise, the management of oligometastatic disease with loco-regional treatment may relieve the symptom and prolong the survival of patients affected by different forms of cancer without the toxicity of systemic treatment.

For clinical scientists this book is an invaluable resource. In addition to summarizing state-of-the-art research, it illustrates alternative approaches to the study of older cancer patients. These involve clinical trials for patients with

functional deficit and comorbidity, including previous malignancies, the exploration of biological markers of aging in cancer patients, and the institution of rapid access databases.

Finally, perhaps the most important message of the book is that a team approach is essential to unravel complexity. Only a team involving practitioners of both specialties may lead to the most effective medical decisions and the most promising study protocols.

Dr. Lodovico Balducci

Preface

As the world population is aging, other diseases are increasingly replaced by cancer as a cause of morbidity and death. Half of all cancers occur beyond the age of 70 in developed countries, and that proportion is steadily increasing. Developing countries are beginning to be confronted with the problem as well. In older patients the challenge of treating cancer is compounded by other factors such as comorbidities, high variability in interindividual functional status, social support, polymedication, and other geriatric issues. As the field has grown and knowledge of the interaction of aging and cancer has expanded, we felt the need of creating a common resource where a large amount of information could be found and tailored to a reader's individual needs. A decade or two ago, this would have meant a straightforward printed comprehensive textbook, such as the one published by Lodovico Balducci et al. (2004). In this digital age, we took the opportunity to use a combined format: an online format in the Springer reference collection which allows chapters to be published individually as soon as they are written or updated and a printed textbook for the reader who wants the convenience of browsing through the pages to get an overview of a topic or wants to cross-reference back and forth several chapters. The online chapters can also be downloaded individually by readers with a focused interest without needing to buy the whole book.

In building this reference book, we wanted it to be useful to the multidisciplinary community involved in geriatric oncology: both geriatric and oncology specialists, clinicians, and researchers. We therefore divided the book into eight parts. The first part, on epidemiology and public health, addresses the worldwide scope of the epidemics and how to address it. The second part, on the biology of cancer and aging, explores several aspects in which the biology of aging either favors or protects against cancer and how it impacts cancer biology and behavior. Researchers and translational clinicians interested in understanding the underpinnings of aging and cancer will find there a trove of information. The third part, on the pathophysiology of aging and cancer, gets closer to the clinic, as it explores several aspects of physiologic aging and disease that will interact with cancer development, outcomes, and treatment. Knowledge of these issues will be very helpful for the clinicians treating these patients. The fourth part addresses how geriatric assessment and management can help guide and improve the treatment of these patients. This is a field in rapid evolution as several randomized trials are in progress and one that will be well worth looking at periodically in the online chapter updates.

The fifth and the sixth parts, on hematologic malignancies and solid tumors, respectively, delve into individual cancers and will appeal to the oncology specialists treating these specific tumors with data specific to older patients as well as to clinicians seeking practical solutions. The seventh part is centered on patient care issues. Geriatric oncology is the ultimate personalized care, as personalization is not only to the cancer but also to the highly diverse patients that we become with aging. From symptom control to spiritual issues, this part explores many aspects that matter highly to our patients. The final part is aimed specifically at researchers in geriatric oncology. Our authors share their hard earned experience in research methods to advance the evidence on which we base the treatment of these patients. It is a well-known fact that older patients are underrepresented in cancer research. By sharing methodological insights, we hope to inspire researchers young and old to address the gap in knowledge for the good of older cancer patients worldwide.

We wish you an enjoyable and instructive reading and will welcome your feedback.

January 2020

Sincerely
Martine Extermann (Principal Editor)
Etienne Brain (Section Editor)
William Dale (Section Editor)
Tamas Fulop (Section Editor)
Heidi D. Klepin (Section Editor)
The Editors

Reference

Balducci L, Lyman GH, Ershler WB, Extermann M. Comprehensive geriatric oncology. 2nd ed., Taylor & Francis, Oxon, UK, 2004.

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The Editors

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About the Editor

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She is Past President of the International Society of Geriatric Oncology (SIOG), of which she is also a founding board member. She served or is serving on several ASCO committees and on the Editorial Board of the *Journal of Clinical Oncology*. Dr. Extermann was presented at ASCO 2009 with the B.J. Kennedy Award for Scientific Excellence in Geriatric Oncology. In October 2014, the International Society of Geriatric Oncology (SIOG) presented Dr. Extermann with the Paul Calabresi Award. On October 10, 2015, Dr. Extermann was presented with a Lifetime Achievement Award in Geriatric Oncology by the German Society of Geriatrics and German Society of Hematology/Oncology in Basel, Switzerland.

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Etienne Brain has been working since 1998 as a medical oncologist at Institut Curie (Paris and Saint-Cloud). He obtained his M.D. in Medical Oncology from Paris-Descartes University in 1995, as well as a Ph.D. in Pharmacology (2005) after initiating (pre)clinical works on alkylation in the USA (Dana-Farber Cancer Institute and Boston University 1995–1996). He got a diploma to supervise research (Versailles/Saint-Quentin University 2010) and in Management and Health Economics (Bocconi University, Milan, 2014–2015).

Dr. Brain is Chair of the EORTC Breast Cancer Group. He also chairs the French DIALOG Intergroup (GERICO/UCOG), dedicated to clinical trials in older cancer patients (geriatric oncology). He is Past President of the International Society of Geriatric Oncology (SIOG) and the co-organizer of the SIOG International Course in Geriatric Oncology (Treviso, Italy) with the Università Cattolica del Sacro Cuoro.

His work comprises clinical practice and research in oncology, mostly for breast tumors and sarcomas, striving constantly for the older populations.

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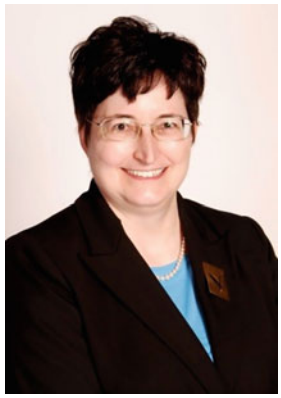
Dr. Dale completed his medical and graduate school training at the University of Chicago and did his residency in Internal Medicine and fellowship training in Geriatrics at the University of Pittsburgh. He is a board-certified geriatrician and palliative medicine physician with a doctorate in Health Policy.

Dr. Dale has devoted his career to the care of older adults with cancer. In 2006, he established the Specialized Oncology Care and Research in the Elderly (SOCARE) Clinic at the University of Chicago, which offers interdisciplinary, individualized, and integrated treatment to optimize quality of life for older cancer patients.

He has over 100 publications on medical decision making, behavioral economics, quality of life, and frailty evaluation in older adults, primarily those with cancer. He has been funded by the National Institute on Aging (NIA), National Cancer Institute (NCI), American Cancer Society, the John A. Hartford Foundation, and the Foundation of Informed Medical Decision Making, among others. He is a co-investigator for the National Social Life, Health, and Aging Project (NSHAP), a national survey and biomeasure collection on the health, well-being, and social life of over 3,000 older adults.



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He is Recipient of the Presidential Award of the International Association of Gerontology and Geriatrics (IAGG) and Fellow of the Gerontological Society of America since 2001 and member of the Canadian Academy of Health Sciences. He served on the executive committee of IAGG. He serves on the GSA Publications Committee and BS Leadership Committee. He is on the Editorial Boards of *Experimental Gerontology*, *Biogerontology*, *Gerontology*, *Immunology and Aging*, and *European Geriatric Medicine* and is Section Editor of the *BMC Geriatrics*. He is the Editor in Chief of the *Interdisciplinary Topics in Gerontology and Geriatrics* and *Advances in Geriatric Medicine and Research*.

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Heidi D. Klepin, M.D., M.S., is Professor in the Department of Internal Medicine, Section on Hematology and Oncology, at the Wake Forest School of Medicine. She is a dually trained geriatrician and oncologist with a clinical and research focus on geriatric oncology. She also earned a master's degree in Health Sciences Research from Wake Forest University. Her clinical work focuses on a Geriatric Oncology Clinic, providing cancer care to adults 75 years of age or older. Her scholarly work is dedicated to improving the lives of older adults with cancer. Her research investigates the following themes among older adults with cancer: (1) patient-level characteristics as predictors of treatment outcomes; (2) the impact of chemotherapy on physical, cognitive, and emotional health; and (3) interventions such as exercise to minimize treatment-associated disability and improve quality of life.

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Part I

Epidemiology and Public Health

Martine Extermann

Population Trends in Aging and Cancer

1

Lars Lund

Contents

Abstract

Several recent studies from Denmark have shown that age is the strongest risk factor for developing cancer. These reports gave an overview of the trends in cancer incidence, mortality, prevalence, and relative survival in Denmark from 1980 to 2012 focusing on age, comparing persons aged 70 years or more with those aged less than 70 years. Data was collected from the NORDCAN database with comparable data on cancer incidence, mortality, prevalence, and relative survival in the Nordic countries. The Danish data originate from the Danish Cancer Registry and the Danish Cause of Death Registry with follow-up for death or emigration until the end of 2013. The studies found a higher incidence and mortality rates of all sites, but in nonmelanoma skin cancer, the relative survival was lower among persons aged 70 years or more than those aged less than 70 years. The age distribution remained constant over time while the percentage of persons dying from cancer decreased with time up to the age of 79 years but increased for those aged 80 years or more, in whom about a third of all cancer deaths occurred in 2012. There was an increase in the number of prevalent cancer cases aged

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70 years or older. Politicians and healthcare providers have to make a strategy for treatment of elderly cancer patients due to expected increase in the elderly population.

Keywords
Aging · Cancer · Elderly · Survival · Mortality

Introduction

For the last decades, cancer has been recognized as the leading cause of death in the western world. This, combined with large birth cohorts after World War II, has led to a high proportion of elderly where age is the strongest risk factor for developing cancer (Ewertz et al. 2016). The number of incident cancers is expected to increase up to 30% in Denmark and 45% in the States especially among persons aged more than 65 years (Ewertz et al. 2016; Engholm et al. 2014; Smith et al. 2009).

It is important to prevent cancer by different efforts, e.g., stop smoking, which is the main cause of cancer-related deaths in Europe and the States with a quarter and one-third of all deaths. It is also possible to prevent or diminish cancer-related deaths. There are many other preventable risk factors such as overweight, lack of physical activity, unhealthy diet with high content of fat or sugar, excessive red meat, foods high in salt, lack of whole grain, excessive alcohol intake, and too much exposure to UV radiation (Independent UK Panel on Breast Cancer Screening 2012). Screening is another tool for preventing cancer or early detection, and thereby leads to higher chance of curative treatment, e.g., breast-, bowel-, and prostate cancers.

Recent research also provide insight in different tissue types which gives rise to human cancers millions of times more often than other tissue types (Tomasetti and Vogelstein 2015). The authors from Johns Hopkins University, USA, reported in *Science* that the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis. They concluded that the majority is due to "bad luck," i.e., random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes. Others claim that it is a too pessimistic view, and one of the recent studies concluded that stem cell divisions per se do not cause cancer (Rozhok et al. 2015). The correlation between stem cell divisions and cancer risk is a product of age(ing), and the lifetime number of stem cell divisions is an inappropriate product of division rate and standing number of stem cells to predict risk. The mutation rate per stem cell division could be higher in some tissues and at older ages, or immune surveillance might change in different tissues and compromised at older ages. Aging and cancer could have shared mechanisms. The authors concluded that in future etiologic studies, it is crucial to involve the age at which cancer occurs. Studies of changes that happen over age, such as reduced immune surveillance and stem cell aging, could yield interventions that help prevent cancer.

Bladder Cancer

Bladder cancer (BC) is a disease of the elderly that occurs most commonly beyond the age of 70 years and is the sixth most common cancer in the US (Jemal et al. 2010). BC is a highly deadly disease if untreated having a five-year mortality approaching 90% after diagnosis and an overall five-year survival around 50% (Clark 1978; Ferlay et al. 2007). In the coming years, the incidence of BC in the elderly will rise, and therefore, it will become increasingly important to understand whether the elderly with BC are either "fit or frail" with respect to undergoing radical cystectomy or bladder preservation therapy with chemoradiation. The recent study found an increase in average annual number of bladder cancers from 1478 to 1810 (22%) during 1980 to 2012, with close to 60% occurring in the elderly population (Jensen et al. 2016). The incidence rates were 7–10 times higher in persons aged 70 years or more compared with younger persons.

Mortality rates were decreasing with time in all age groups but 90+ year old men. The one- and five-year relative survival improved significantly with time for all age groups both in men and women. The prevalence increased two times among men and women. Incidence rates of cancer of the urinary bladder and urinary tract increased up to around 2005 and then decreased while mortality rates decreased slightly over the period resulting in an increasing survival and prevalence. Incidence and mortality rates were much higher and survival rate was lower in persons aged 70 years or more than in younger persons. The incidence of BC has increased over time across most age groups in Denmark. It is important to perform randomized clinical trials for determining the influence of age on the decisions of the surgical approach as well as chemo/radiotherapy for the elderly patients with urothelial cancer compared to younger patients.

Kidney Cancer

The incidence of kidney cancer increased dramatically during the past two decades in the western world (Engholm et al. 2010; Chow et al. 1999). This increase reflects mainly smaller tumors due to increased use of abdominal imaging, such as computed tomography (CT) and ultrasound (Janzen et al. 2003; Jemal et al. 2008). A number of risk factors have been identified for developing kidney cancer, such as cigarette smoking, obesity, hypertension, and antihypertensive medication, but the etiology remains unknown (Lipworth et al. 2009). Data from NORDCAN showed that the proportion of patients diagnosed with kidney cancer over the age of 70 years has decreased from 43% in 1980 to 32% in 2012 in men and remained almost constant in women, around 50%. Incidence rates were at least five times higher in men aged 70 years or more but there was no particular trend with time (Azawi et al. 2016). In men aged less than 70 years, the incidence rates started increasing around 2000. The incidence rates were lower in women but with a similar pattern as in men. Mortality rates remained stable over time in persons aged 70 years or more while they decreased with time in younger women. Both the one- and the five-year relative survival increased steadily over time for all age groups but the survival was lower for patients aged 70 years or more than for younger patients. The prevalence increased three times from 1559 patients being alive after kidney cancer in 1980 to 4713 in 2012. In the present study, the elderly over 70 years represented more than one-third of all kidney cancer patients. The surgeon facing the elderly patient has to get validated methods to assess the patient's functional and cognitive level, their nutritional status, comorbidities, and the impact of polypharmacy, all of which are common in the elderly. Patients with metastatic disease can now be treated with systemic medication such as targeted therapy with thyrosine kinase inhibitors (TKIs) and inhibitors of the mammalian target of rapamycin (mTORinhibitors). More patients with metastatic kidney cancer are now being offered systemic treatments with metastatic disease. A recommendation of dose modification for elderly patients with metastatic kidney cancer is needed (Azawi et al. 2016) and TKI or mTOR treatments should be offered to elderly patients on the same terms as younger patients. The study concludes that when managing kidney cancer in the elderly it is essential to establish interdisciplinary collaborations between different specialties, such as surgeons, clinical oncologists, and geriatricians, to be able to deliver the best possible care in the future.

Prostate Cancer

Prostate cancer has become the most common nonskin cancer diagnosed in the developed countries and the third leading cause of death among men (Jemal et al. 2011). In Europe, about 190,000 men are diagnosed annually with prostate cancer and around 80,000 men die annually of prostate cancer (Damber and Aus 2008) Prostate cancer is generally a disease of the elderly ($\geq$70 years) and few men are diagnosed before the age of 50 years (Heidenreich et al. 2014). A Danish epidemiological study examined the incidence, prevalence, and survival

rates of prostate cancer for men in Denmark during a 32-year period (Poulsen et al. 2016). The series demonstrated that the overall incidence and prevalence of prostate cancer have been increasing steadily. The average annual number of newly diagnosed prostate cancers rose from 1297 patients in 1980 to 4315 patients in 2012. The prevalence increased consistently in all age groups more than seven-fold in the period, from 3987 patients in 1980 to 28,951 patients in 2012. The cancer-specific mortality in Denmark has slightly increased over the observed period, in coherence with the growth of the population, resulting in unchanged mortality rates, with the exception of the patients above 80 years, where the mortality rates are increased. This observed difference may be due to a number of factors including diagnostic and treatment approaches in more frail or terminally ill men. The one- and five-year relative survival for prostate cancer improved significantly for all age groups over the time period from 1980 to 2012. However, as the authors note, the major difference in findings compared to other countries including those in the Nordic region is the relatively late introduction of treatment with curative intent in the Danish medical system.

Gynecologic Cancer

Gynecologic cancers comprise cancers of the cervix uteri, corpus uteri, ovaries, fallopian tubes, vulva, and vagina. They accounted for 19% of the 5.1 million estimated new cancer cases, 2.9 million cancer deaths, and 13 million five-year prevalent cancer cases among women in 2002 (Sankaranarayanan and Ferlay 2006). Cervical cancer accounted for 493,000 new cases and 273,000 deaths; uterine body cancer for 199,000 new cases and 50,000 deaths; ovarian cancer for 204,000 new cases and 125,000 deaths; cancers of the vagina, vulva, and choriocarcinoma together constituted 45,900 cases. More than 80% of the cervical cancer cases occurred in developing countries and two-thirds of corpus uteri cases occurred in the developed world.

Cervical cancer is a sexually transmitted disease caused by human papilloma virus (HPV) in almost all cases. The disease is more prevalent in lower socioeconomic groups and in women with multiple sexual partners. Smoking is an independent risk factor for squamous cell cervix uteri cancer (Idehen et al. 2017). Cervical cancer is the fourth most common cancer in women worldwide with an estimated 528,000 new cases in 2012 with approximately 85% occurring in low-resource countries. In 2012, there was an estimated 266,000 deaths due to cervical cancer with 87% occurring in low-resource countries. A recent study want to explore factors associated with immigrants' lower participation rates in cervical screening participation among women of Russian, Somali, and Kurdish origin in Finland (Alam et al. 2008). They found that women who refrain from using reproductive health services where those who are unemployed and less educated, as well as those with poor language proficiency, and they might need more information on the importance of screening participation.

In Denmark and other high-resource countries, cervical cancer is primarily diagnosed in women aged 25–70 years with a peak in the incidence at 30–40 years and a smaller peak at 75–80 years. The cause of cancers of the ovaries and fallopian tube cancer is multifactorial and until recently basically unknown. Use of hormonal contraceptives for at least 5 years, multiple deliveries, and, to a lesser extent, breast feeding decreases the risk, whereas the number of years with ovulation is positively associated with an increased risk. A recent, large meta-analysis (Collaborative Group on Epidemiological Studies on Ovarian Cancer 2015) ovarian and fallopian tube cancer is most common in high-resource countries and is worldwide the sixth most common cancer in women with approximately 238,000 new cases and approximately 152,000 deaths in 2012. Danish women have the second highest incidence of ovarian and fallopian tube cancer worldwide (Ewertz and Kjaer 1988). Worldwide, the incidence of corpus uteri cancer (endometrial cancer) almost displays the same geographical distribution as ovarian cancer and is most commonly diagnosed between the age of 40 and 75 years with a peak

incidence around 70 years in Denmark. A study from Denmark described the trends in incidence, mortality, prevalence, and survival in Danish women with gynecologic cancer from 1980 to 2012 comparing women aged 70 years or more with younger women (Ør Knudsen et al. 2016). The incidence for cervical cancer decreased among women aged less than 70 years and remained stable among the elderly. The mortality rate was 2–3 folds higher among 70+-year-olds than younger women. The mortality rates, however, decreased in all age groups from 1980 to 2012. For ovarian and fallopian tube cancers, the incidence was almost constant, whereas the average annual number of deaths decreased over time from 466 in 1980 to 396 in 2012. The mortality rate was 3–4 times higher among the elderly. The mortality rate decreased among women less than 70 years during the entire period. The average annual number of newly diagnosed corpus uteri cancer increased from 631 in 1980 to 773 in 2012. The mortality rate was higher among the 70+-year-olds as compared with younger women. Overall, the mortality rates decreased during 1980 to 2012. They concluded that mortality rates and survival are age-dependent with a significantly shorter survival in the group of elderly.

Breast Cancer

Breast cancer is the frequent cancer among women and the incidence has been increasing steadily in Denmark since the 1960s and the mortality has declined resulting in an improvement in survival. The improved prognosis is assumed to be the result of earlier diagnosis and better treatment. Gender is the strongest risk factor for developing breast cancer with a male:female ratio of approximately 1:100 (Mouridsen et al. 2008). Age has a risk of developing breast cancer both in men and in women with increasing incidence rates with increasing age. The menopause has a protective effect in women in contrast to men with an age-specific incidence curve as a straight line of a constant increase with age (Clemmesen 1948).

The BRCA1 and BRCA2 genes increase the risk for developing breast cancer (Brinton et al. 2014). A recent study found that the proportion of patients diagnosed with breast cancer over the age of 70 years increased with time to 29% of women and 44% of men in 2012 (Jensen et al. 2016). Incidence rates increased with time and peaked around 2010 in all age groups except for those aged 90 years or more. Mortality rates were clearly separated by age with increasing mortality rates by increasing age group for both women and men. Patients aged more than 70 years had a poorer relative survival than those aged less than 70 years. There is a substantial variation in breast cancer treatment by age, probably because of the lack of knowledge about treatment effects in the elderly. Data collected from elderly women not treated in clinical trials show that clinician preferences influence the choice of adjuvant chemotherapy for elder patients. They concluded that poorer survival of Danish breast cancer patients over the age of 70 years is likely to be due to inferior treatment and nonadherence to treatment guidelines. There is a need for clinical trials focusing on patients over the age of 70 years.

Hematological Cancer

The etiology of hematological malignancies remains largely unknown but radiation and previous chemotherapy predispose individuals to acute myeloid leukemia (AML) while immunosuppression has been linked to the development of lymphoma. The incidence of the majority of hematological malignancies increases with age, the only exceptions being acute lymphoblastic leukemia and Hodgkin's lymphoma (Smith et al. 2011). Half of the patients with hematological cancer are older than 70 years at diagnosis (Smith et al. 2011) with comorbidity as well as a higher risk of toxicity and mortality from treatment complications (Norgaard et al. 2006). Westin found a lower improvement in patients over the age of 55 compared with the younger population (Westin 2004). A recent study of 180,000 European patients with hematological lymphoid neoplasms demonstrated that the oldest age groups receive a suboptimal diagnostic workup and therefore treatment (Marcos-Gragera

et al. 2011). A nationwide Danish study investigated the incidences and mortality rates among patients with AML, multiple myeloma (MM), non-Hodgkin lymphomas (NHL), and chronic lymphocytic leukemia (CLL) focusing on the elderly and oldest-old population (Ocias et al. 2016). They found that the incidence rates of AML, MM, NHL, and AML were 10–50 times higher among the population aged 70 years or more than among the younger population. An increasing incidence with stable or decreased mortality rates was seen mainly among elderly patients with NHL during the last few decades, leading to increased survival and a greater prevalence of patients with NHL. There was an increased relative survival and prevalence in the elderly patients with MM and CLL, while the trends of the incidence rates were inconclusive for these diseases. Survival among patients with AML improved most notably in those aged below 70 years leading to an increased prevalence of AML patients predominantly in this age group. They concluded that the improvements in diagnostics and treatment had led to an increased survival and therefore prevalence of elderly patients with AML, MM, NHL, and AML during the last 30 years.

Upper Gastrointestinal Cancer

Malignancies in the upper G-I tract includes esophagus, stomach, and small intestine with a very poor prognosis. Gastroesophageal cancer is the second most frequent malignancy worldwide and the second most common cause of cancer-related death. Together, they account for nearly 1.4 million new cases and 1.1 million deaths every year (Jemal et al. 2011; Parkin et al. 2005). Knowledge about efficacy and toxicity to chemotherapy, radiation, and targeted therapy is primarily derived from clinical trials including highly preselected and fit patients. However, in several trials of patients with cancer, e.g., stomach cancer, older patients were often excluded leading to a median age of 60 years for patients included in clinical trials (Shitara et al. 2012). A recent study described incidence, mortality, and survival in patients diagnosed with esophageal, stomach, and small intestine cancer according to differences in age and time periods (Schønnemann et al. 2016). They found that the proportion of male patients over the age of 70 years diagnosed with esophageal cancer was constant over time but increased in females in 2012. Incidence rates increased with time and continued to rise in all ages. Mortality rates were clearly separated by age groups with increasing mortality rates by increasing age group for both sexes. Relative survival increased slowly over time in all age groups. The proportion of older male and female patients with stomach cancer increased to 50% and 54%. Mortality rates decreased and have been constant during the last decade for both women and men. Relative survival increased modest over time in both genders and all age groups. They conclude the need for clinical trials focusing on patients over the age of 70 years with coexisting comorbidity.

Colorectal Cancer

Colorectal cancer (CRC) constitutes nearly 13% of all malignancies in both males and females and with 447,000 new cases in Europe; CRC is the second most frequent (Ferlay et al. 2013) and is a disease of the old age. The development is multifactorial with genetic susceptibility, environmental, and dietary factors. Increased BMI, red meat intake, cigarette smoking, low physical activity, low vegetable consumption, and low fruit consumption are all associated with increased risk of CRC (Johnson et al. 2013). Over the past two decades, the survival of patients with CRC has increased constantly. The median overall survival for fit patients with metastatic CRC included in clinical trials has increased from 6 months to more than 24 months (Kopetz et al. 2009). An epidemiological study evaluates CRC in Denmark up to 2012 focusing on trends in incidence, mortality, and prevalence among older patients (Brændegaard Winther et al. 2016). They found that the incidence of CRC has increased over the past three decades. Incidence rate has increased in patients with colon cancer, but showed a

decreasing trend in the oldest patients with rectal and anal cancers. Mortality has diminished in younger patients with colon cancer, but increased with increasing age. In rectal and anal cancers, mortality has decreased, except in the elderly. This correlates to a decreasing incidence rate. Prevalence is widely increasing mainly because of increased incidence and longer survival, which is reflected in the increasing one- and five-year age-specific relative survival after a diagnosis of colon, rectal, and anal cancers. They concluded that there is limited knowledge on how to optimize treatment in older CRC patients and future focus must be on how to select and plan the treatment for especially elderly CRC patients.

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Integrating Geriatric Oncology in Public Health Planning

2

Jeanne-Marie Bréchot, Philippe-Jean Bousquet, Claudia Ferrari, Jérôme Viguier, and Norbert Ifrah

Contents

Abstract

If more than 30% of cancers occur at present in France among elderly people, it is estimated that this proportion will reach 50–60% within the next two or three decades. To deal with and anticipate this challenge, successive national Cancer Control Plans have included specific actions on the organization of the treatment of elderly cancer patients. The organizational framework is based on an oncologist-geriatrician partnership at the head of oncogeriatrics coordination units. After a pilot phase conducted in 15 health-care institutions, it has been deployed in 22 regions of mainland France and in one overseas territory. These units are mainly intended to ensure that patients receive cancer treatment suitable for their overall health and age. This organization evolves with both the

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evolution of the health landscape (in accordance with the modernization law of the health system of 26 January 2016) and the territorial reform that identifies 13 regions in mainland France and five regions in overseas. It also has to take into account not only the therapeutic initial decision but also the patients pathway and their quality of life during and after the cancer treatment. The ability to adapt is essential to fully optimize the treatment of these elderly people suffering from cancer who will shortly represent the vast majority of people with cancer.

Keywords
Geriatric oncology · Elderly · Cancer · Models of care

Introduction

Cancer is a common disease for elderly (≥ 75 years old) people. Various models of care are evaluated around the world to improve their care and are constantly evolving. In France, the successive Cancer Control Plans helped to structure the geriatric oncology into an organization which, though very hospital-centered during its pilot phase, expanded into regional frameworks to ensure fairness of treatment with a patient-centered system. The following chapter describes the work achieved during the first two Cancer Control Plans and, by analyzing the strengths and weaknesses of this organization, presents the development prospects of the treatment of elderly person suffering with cancer.

Epidemiology in France

Advanced age is the most important risk factor for cancer. The median age at cancer diagnosis is 68 years in men and 67 years in women in France.

Cancers occurring at a median age > 70 years are three among males: colorectal cancer (71 years), gastric cancer (72 years), and bladder cancer (74 years); and seven among females: kidney cancer (70 years), esophageal cancer (73 years), liver cancer (74 years), colorectal cancer (75 years), gastric cancer (77 years), and bladder cancer (79 years) (Les Cancers en France 2015).

The latest 2015 data estimated 63,551 (30.1%) new cancer cases among men and 58,385 (33.6%) among women aged 75 and over (Leone et al. 2015). After the age of 85, respectively 18,177 and 23,770 cancers were diagnosed. Three cancers represent half of the cancer in elderlies. In men, prostate, lung and colorectal cancers remain the most common cancer. In women, breast, colorectal, and lung cancer are the most common.

Around half of the deaths caused by cancer occur within the elderly, with 39,600 deaths out of 84,000 in men (i.e., 47.1%) and 36,840 out of 65,400 in women (i.e., 56.3%). For both sex, three cancers represent nearly half of the cancer death. However, in men, lung cancer is the first cause of death by cancer, followed by prostate cancer and colorectal cancer. In women, breast cancer remains the first cause of death by cancer, followed by colorectal cancer.

Prevalence of people with a cancer in France in 2008 is estimated at around 3 million people (Colonna et al. 2014). In elderlies, there are respectively 682,699 (43.5%) men and 466,769 (33.1%) women with a history of cancer during their life. Prostate cancer and breast cancer are the most common cancers.

These few data underline the imperative to cope with cancer in elderly patients, which will represent the vast majority of cancer patients within one or two decades.

Public Health Planning and Health-Care Policy in Geriatric Oncology in France

The French National Cancer Institute (INCa)

It was created by a public health law on 9 August 2004. It is a government health and science agency in oncology, whose mandate is to integrate cancer control and research in France and to implement the cancer control plan 2014–2019.

2003–2007 Cancer Control Plan

This first plan aimed at coordinating public health providers involved in cancer in the areas of

prevention, screening, health care, research, patient, and close relatives support.

One task of this plan was dedicated to oncogeriatrics, for the promotion and coordination in epidemiology, prevention, treatment strategies, and clinical trials for elderly persons with cancer (Measure 38). Major advances in healthcare organization for cancer patients occurred during this plan, as the mandatory multidisciplinary tumor board, the implementation of quality measures (announcement procedure, the delivery of a personal care plan, the access to supportive care, the fixation of activity threshold for authorizations to treat cancer patients, and the participation of the general practitioner (GP) in cancer care networks. These actions contributed to enhance cancer care, including for the elderly.

2009–2013 Cancer Control Plan

This second plan was built around three cross-cutting themes: to take more effectively into account health inequalities, individual and environmental factors, and to strengthen the role of the referring practitioner (GP).

This plan focused on the care management for elderly cancer patients. Setting up nationwide oncogeriatrics coordination units (UCOGs), expanding the use of a geriatric assessment tool, and developing recommendations for treatment strategies tailored to the elderly for cancers with the highest incidence were scheduled (Action 23.4). The target of 5% of elderly (> 75 years old) patients in clinical cancer trials was suggested (Action 4.2).

2014–2019 Cancer Control Plan

The management of this plan is provided by a committee co-chaired by the Ministers for Health and for Research. The French National Cancer Institute coordinates the monitoring of this plan.

One of the key objectives is "To cure and prevent cancers: giving every person everywhere in France equal opportunities." Objective 2 of this ongoing plan is to ensure quality and security of cancer care. Two actions are dedicated to elderly people, in order to address their specific needs: Action 2.16 evaluates and adapts the specific organization for elderly people with cancer, in order to improve clinical practices, and structures clinical research, as an integral part of this specific organization, while Action 2.17 targets mandatory university education in geriatrics for all oncologists and cancer specialists.

Current Assessment

Health-Care Modalities

INCa analyses and publishes every year data collected in the national hospital discharge data base in order to describe the hospitalizations related to cancer care.

A total of 6.64 million hospitalizations related to cancer care were identified in 2014, among them 1.6 (≈24%) concerning the elderly (≥ 75 years old) cancer patients (Cancers in France 2014). More than 370,000 patients were concerned, among them one third of them being ≥85 year old.

These hospitalizations were linked to chemotherapy (33%), radiotherapy (23%), surgery (10%), palliative care (4%), and to other care (30%) including transfusions, endoscopic examinations, and hemodialysis for cancer patients.

Hospital activity was mostly distributed in local hospitals (36%), clinics (23%), academic hospitals (21%), and cancer centers (12%). This distribution underlines the importance of a geriatric oncology organization at a local level.

Oncogeriatrics Coordination Units (UCOGs)

A call for projects was launched by INCA and the Ministry of Health at the beginning of 2011, with the aim of creating one UCOG in each of the 22 regions and the five overseas departments (Fig. 1 – Map of UCOGs in France).

These UCOGs do not represent a new additional structure. They are based on a formalized collaboration between an oncologist and a geriatrician. Most of these partners are MD-PhD in university hospitals authorized to treat patients with cancer and have received five missions:

- To adjust cancer treatments for the elderly

  There are two major and opposite challenges to face for elderly patients: firstly to prevent undertreatment only based on age, and, in the other side, to avoid an overtreatment

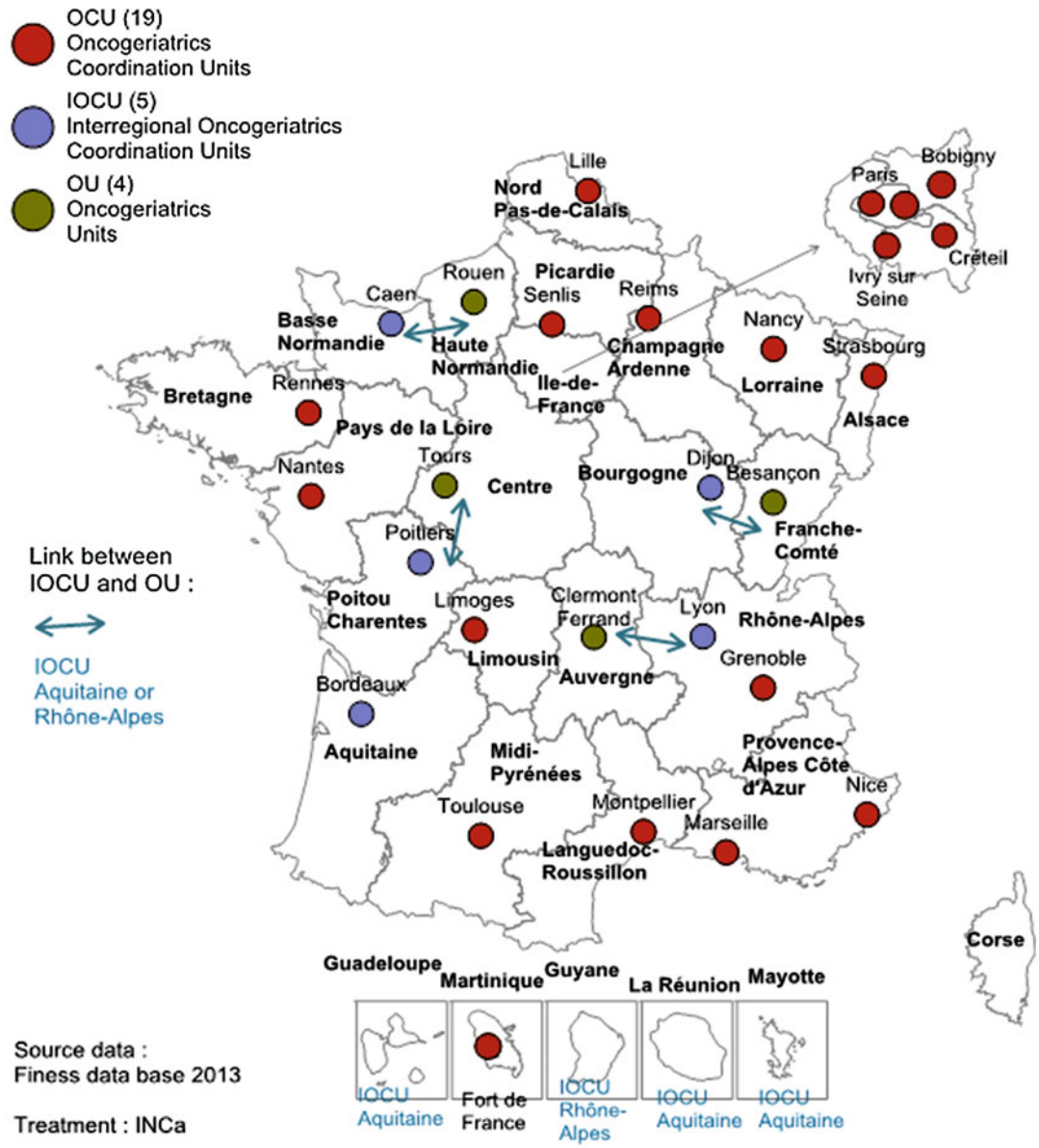

Fig. 1 Oncogeriatrics coordination units (Source: Monitoring of the scheme for care and clinical research in oncogeriatrics - January 2015, Support for the decision; INCA, March 2015; Date de publication: octobre 2015; ISBN: 978-2-37219-140-1; ISBN net: 978-2-37219-141-8; http://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Monitoring-of-the-scheme-for-care-and-clinical-research-in-oncogeriatrics-January-2015. Last access date: 25 Nov 2016)

that had not considered or weighted the frailty or vulnerability, comorbidities, and polymedication of the patient. The Comprehensive Geriatric Assessment (CGA), acknowledged as the gold standard, is time-consuming (Extermann and Hurria 2007). Therefore, the first identified step to an oncogeriatric approach is to obtain that cancer patients $\geq$75 years old have systematically a geriatric prescreening test, in order to detect those

patients who should benefit from specific supportive care or CGA assessment before the treatment decision (Soubeyran et al. 2014). The next step is to have the result of this prescreening test on time for the patient's file multidisciplinary team discussion (MTD) in order to define the most appropriate cancer treatment and the optimal appropriate geriatric support; a geriatrician should integrate the multidisciplinary team if necessary. In a survey conducted in five EU countries, multidisciplinary discussions about treatment patterns for elderly cancer patients were not part of standard procedure anywhere (Anhoury et al. 2009).

- To allow that each elderly cancer patient benefits from this oncogeriatric approach

  Organizing an oncogeriatric approach for all elderly cancer patients induces the involvement of two additional partners at a regional level: the Regional Health Authority and the cancer coordination network.

  Indeed, the French health-care system governance includes 17 Regional Health Authorities (covering mainland France and overseas departments) in charge of coordinating regional health projects at the interface with healthcare practitioners and users. Inclusion of geriatric oncology development in regional projects is major to promote close collaboration between the various stakeholders involved.

  Cancer coordination networks were set up during the first Cancer Control Plan as coordination structures at a regional level between health facilities and healthcare practitioners. In order to favor active collaboration between oncologists and geriatricians, a vast majority of these networks have already established a webpage dedicated to geriatric oncology, including the list of regional healthcare institutions authorized to treat cancer patients, the full range of geriatric health-care services as well as the list of healthcare providers in the domain of geriatric oncology. Regional cancer coordination networks also participate to diffuse the information about (i) cancer treatment and the modalities of a prescreening geriatric test, (ii) the access to a comprehensive geriatric assessment (CGA) and/or a geriatrician consultation, and (iii) national guidelines dedicated to elderly patients with cancer when available.
- To stimulate specific research projects in oncogeriatrics

  The development of new treatment strategies, the risks and benefits ratio of using new drugs, but also pharmacokinetic and pharmacodynamics data of common drugs, post-marketing studies, and interventional trials are urgently needed in this population of patients.

  Nevertheless, enrollment of patients above 75 years old in cancer clinical trials remains low (Sher and Hurria 2012). In France, 4858 patients above 75 years old were included in a clinical trial in 2015 (Fig. 2 – Chart showing the trend in the number of patients aged $\geq$75 years enrolled in a clinical trial from 2007 to 2015, either academic or pharmaceutic trials); the vast majority of these trials were academic. So, only around 6.3% of elderly people with cancer benefit in 2015 from a clinical trial, offering them accessibility to an innovative medication or an innovative strategy.

  In order to boost clinical research in geriatric oncology in France, INCa supported a cooperative research group "DIALOG" in 2014, pooling UCOGs teams and "GERICO" research teams (launched in 2002 by the French National Federation of Cancer Centers).

  Since 2007, all clinical trials conducted in France in the domain of cancer are registered on the website of INCa: http://www.e-cancer.fr/Professionnels-de-la-recherche/Recherche-clinique/Le-registre-des-essais-cliniques (last access date: 11/25/16). Analysis of this data basis shows 1947 trials open for elderly (>65 years old) cancer patients in August 2016. A more precise analysis shows that 209 of these trials are phase II or phase III randomized open trials, concerning 42 (20%) hematologic malignancies, of which 15 lymphoma, 28 (13%) breast cancers, 18 colorectal (8.6%) cancers, 17 non–small cell lung cancers (8,1%), and 12 (5,7%) prostate cancer. Clearly, the distribution of cancers in clinical

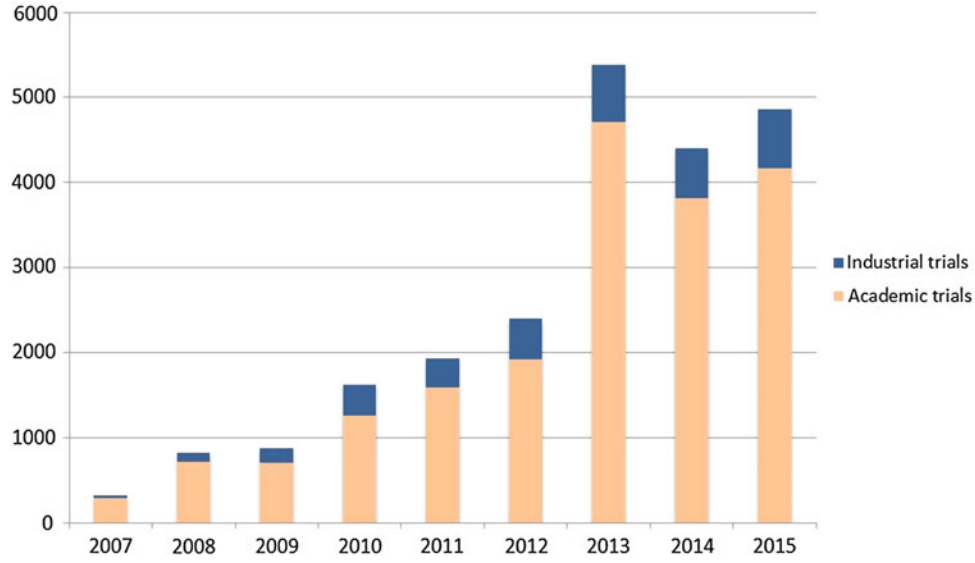

Fig. 2 Stimulate specific research projects in geriatric oncology (Source: ONCOG_EC | Traitement: INCa - lesdonnees.e-cancer.fr - 2016 (http://lesdonnees.e-cancer.fr/Themes/prise-en-charge/La-prise-en-charge-des-populations-specifiques/Oncogeriatrie#ind5807) (last access date 25 Nov 2016) and Monitoring of the scheme for care and clinical research in oncogeriatrics - January 2015, Support for the decision; INCA, March 2015; Date de publication: octobre 2015; ISBN: 978-2-37219-140-1; ISBN net: 978-2-37219-141-8)

research does not reflect the epidemiological data in the elderly. Among these trials, 41 are more specifically dedicated to senior cancer patients. However, there is a wide discrepancy in the design of these trials despite clear recommendation (Wildiers et al. 2013):

- 27 trials concern patients age range 18 to 70, 75, 80, or 85 years
- 1 trial concerns patients ≥50, 1 ≥ 60, ≥ 65, 4 ≥ 70 and 1 ≥ 80 years old
- 1 trial includes patients 60 to 75, two 65 to 85, and one 70 to 89 years old

A minimum geriatric data set is highly recommended in order to allow comparison of results in clinical trials and their adoption in general population (CGA remaining the gold standard). The classical exclusion criteria such as systemic hypertension or diabetes mellitus need to be revised, as well as biological parameters such as elevated serum creatinine or abnormal blood count. Wide inclusion criteria followed by subgroups analysis according to comorbidities should avoid selection bias in clinical trials in this specific population. Another possibility is to conduct a clinical trial for all adult people and analyze separately the elderly cohort (Huria et al. 2014).

Selection of endpoints in geriatric oncology research is being extensively discussed. Quantity of life gain (such as overall survival and/or progression-free survival) has to be balanced against "clinical benefit" and quality of life (such as preservation of functional capacity, ability to carry out daily tasks, and no rehospitalization).

Targeted therapy in older patients with solid tumors remains a largely unknown domain (Kelly et al. 2014). Under-representation of elderly patients in registration trials does not permit to predict potential adverse effects in these patients.

- To promote medical and paramedical training

  Academic medical training in oncogeriatry has been set up for more than 10 years, mostly organized by academic geriatricians. Around 800 health-care providers, half of them

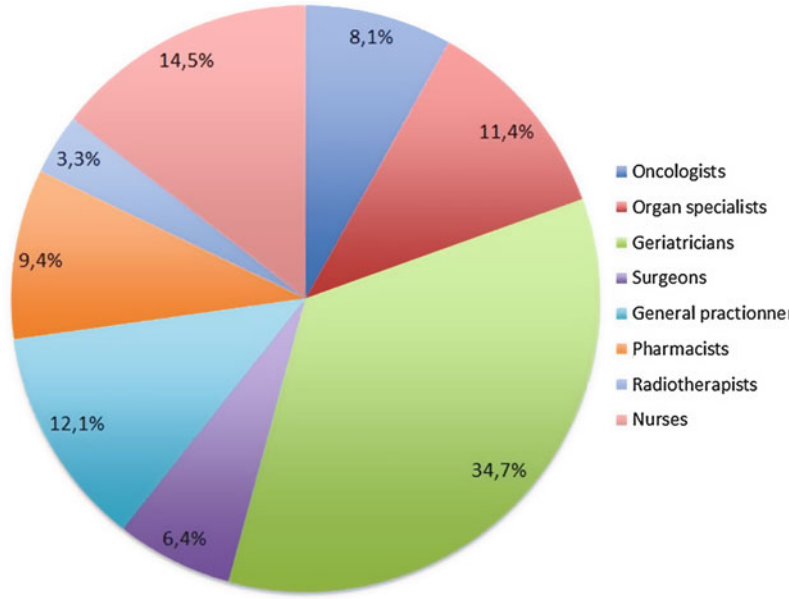

Fig. 3 Promote medical and paramedical training in geriatric oncology (Source: ONCOG_PRO_NAT | Traitement: INCa - lesdonnees.e-cancer.fr – 2016 (http://lesdonnees.e-cancer.fr/Themes/prise-en-charge/La-prise-en-charge-des-populations-specifiques/Oncogeriatrie#ind5805). Last access date: 25 Nov 2016)

geriatricians, follow this professional training each year (Fig. 3– Distribution of 841 health professionals with a university training in 2014, according to their category and specialty). Continuous training has also been organized for oncologists, geriatricians, as well as general practitioners (GPs), pharmacists, nurses, and mobile geriatric unit professionals.

However, in view of demographic trends, geriatric oncology should become a daily practice. In this context, it seems urgent to include theoretical and practical geriatrics training in the French university courses for oncologists, hematologists, but also surgeons, and other specialists. This action will be finalized in 2017.

– To promote information dedicated to patients, caregivers, and public

Communication should point out to the benefit of a personalized treatment adjusted to cancer (type, stage, etc.) and patient characteristics. The effectiveness of some of the innovative treatments such as targeted therapies should be described. The importance of participating in clinical trials should be explained to patients and their families. Communication should also target caregivers, particularly GP. There is an urgent need to improve the referral of elderly cancer patients by GP to cancer specialists, as well as to better integrate GP in the care pathway of this specific patient population (Kurtz et al. 2010; Chicoulaa et al. 2016).

– To implement databases enabling the prospective collection of data

Currently, there is no national data base allowing to improve the knowledge of this specific population and its medical care.

There are limited data. Thus, the French Society of Thoracic and Cardiovascular Surgery created in 2003 a national online database, Epithor®, inviting all the thoracic surgeons to register data concerning the types of thoracic surgical procedures, but also data concerning age, comorbidities, complications, and follow-up. More than 155,000 procedures from 102 institutions have been registered. Comparison of data on the surgical treatment of lung cancer between octogenarians and younger patients points out that surgical treatment should not be denied on the age criteria alone (Rivera et al. 2011).

At the present time, there are no available data concerning elderly patients with cancer treated at a community level and these data are urgently needed to optimize equity of care.

Funding

UCOGs benefit from a public annual funding of 5.2 M€. Most of this funding permits to recruit and pay health-care providers (geriatricians, oncologists, nurses, medical secretaries, and coordination actors).

UCOGs have to account for their activity in the form of online annual reports and a synthesis of their activities is published on the INCa website: http://lesdonnees.e-cancer.fr/Themes/prise-en-charge/La-prise-en-charge-des-populations-specifiques/Oncogeriatrie (last access date: 11/25/16).

Key Achievements and Strengths

Collaboration Between Oncologists and Geriatricians

The specific UCOGs organization aims to lead to a real bridge between these two specialties. Through the successive cancer control plans, this organization has been evolving from a pilot structure to a patient-centered organization, whatever the health-care setting.

Awareness of Clinical Research Importance in Geriatric Oncology

Eleven out of the 29 (38%) oncologists coordinating an UCOG published as first author or coauthor at least one article referenced in PubMed dedicated to geriatric oncology in 2015 or early in 2016 (Chicoulaa et al. 2016; Canouï-Poitrine et al. 2016; Corre et al. 2016; Farcet et al. 2016; Ferrat et al. 2015, 2016; Landre et al. 2015; Lange et al. 2016; Laurent et al. 2015; Oziel-Taieb et al. 2016; Pamoukdjian et al. 2015; Petit-Monéger et al. 2016; Rivoirard et al. 2016; Sabatier et al. 2015). These articles concern a wide variety of cancers: colorectal, breast, ovary, lung, pancreas, but also broader issues as geriatric assessment and chemotherapy toxicity. They include either prospective or retrospective cohort studies, randomized or not randomized clinical trials, systematic review with or without meta-analysis.

Weak Points

A Large Discrepancy of the Oncogeriatric Approach Between the Regions

Some of the UCOGs have been developing a close collaboration between oncologists and geriatricians at local level, with an effective coordination of the different health care practitioners through cancer regional network. Others have been favoring a more innovative model, developing virtual MTD meetings dedicated to elderly patients with cancer, or establishing an oncology unit dedicated to elderly patients care, or even a geriatric unit dedicated to cancer patients acute care. These models cannot be rolled out. The same applies to the organization of a systematic CGA assessment for each elderly cancer patient in a few UCOGs.

An Oncogeriatric Approach Limited to the Initiation of Cancer Treatment

The successive French Cancer Control Plans focused on a close collaboration between oncologists and geriatricians at the time of cancer diagnosis and of the first-line therapeutic proposals. However, elderly patients with cancer require a rigorous coordination of the health care practitioners during the whole care pathway. Indeed, cancer treatments may induce fast functional declines and/or severe adverse effects (Hoppe et al. 2013); cognitive impairment during or after chemotherapy may have a major impact in this vulnerable population (Mandelblatt et al. 2014). Improvement of survival even in this population entails optimizing life path by geriatric and oncologic interventions during the long-term survival (Mohile et al. 2016).

Performance Indicators Remain Hard to Determine

The evaluation of this model of care for elderly cancer patients is difficult (Magnuson et al. 2014). Indicators such as overall survival or disease-free survival are not available; so, improvement of outcome for patients who benefit from the

oncogeriatric approach cannot be demonstrated, compared to patients who did not. Improvement of cancer treatment decision-making was shown in limited groups of patients (Caillet et al. 2011; Chaïbi et al. 2011).

Future Prospects

From Oncogeriatrics to Geriatric Oncology

Oncogeriatrics is in our mind not a new medical specialty.

It is of extreme importance that all physicians involved in cancer treatment (oncologists, hematologists, radiation therapists, surgeons, etc.) grip with the geriatric oncology approach, and acquire a better knowledge of benefits and risks of the different cancer treatments in this specific population. The geriatric interventions proposed such as nutrition rehabilitation, social support, and management of cognitive problems have to be part of the supportive care and implemented right from the start of the treatment.

Strengthened Coordination Between the Different Health-Care Professionals

As previously underlined, a close cooperation between oncologists and geriatricians at a hospital level is the keystone to promote medical and paramedical training in geriatric oncology. But other health professionals play a key role during the care pathway of elderly cancer patients: general practitioners (GP), home nurses, and pharmacists. Assessment of daily medication leads to deprescribing, avoiding potentially inappropriate medication and/or polypharmacy, and lowering the risks of severe side effects (Nightingale et al. 2015; Scott et al. 2015). Deprescribing should be included in medical training in geriatric oncology.

Geriatric Oncology Across the Care Pathway

Cancer plans focused on the rolling-out of a screening tool and MDT discussion with geriatricians when needed at the first cancer treatment proposal. Good clinical practice recommendations have to be developed for frequent cancers in this population. A large availability of software tools such as the electronic medical records, cancer communication files, individualized care plans (PPS), and postcancer individualized care plan (PPAC) could facilitate information sharing and improve the coordination around the patient. Geriatric interventions have to be part of these healthcare plans, as well as supportive care interventions. Evaluation of the use of these tools in the elderly is easy and could be a good indicator of quality of care.

Better Access to Innovative Treatments

During the past decade, numerous recommendations and guidelines to develop clinical research and facilitate the access to innovative cancer treatments to elderly persons were published (Hurria et al. 2014; Wildiers et al. 2013). Trials to evaluate dosing scheme in accordance to frailty, to better predict toxicity/tolerability of chemotherapy, efficacy, and tolerance of targeted therapies, to better assess the impact of geriatric interventions are urgently needed. Since 2010, sixteen integrated centers specialized in early-phase clinical trials in cancer were granted designation by the INCa. The review of the first 3 years of designation shows that 27% of trials initiated in these centers are phase I trials. Availability of innovative treatments and development of phase I trials for elderly people with cancer have to be encouraged in these structures.

Evaluation of the Geriatric Oncology Approach

A few relevant indicators have to be defined in order to evaluate the benefit of such an approach during the care pathway, among them outcome and/or quality of life indicators.

Integrating e-Health Technology

The feasibility of computer-based self-administered cancer-specific geriatric assessment (CSGA) in older cancer patients has been demonstrated:

consent, touchscreen computer use, completion in a short time (20 min) with or without assistance (mostly due to lack of computer familiarity) (McCleary et al. 2013).

Mobile technology could be introduced in clinical practice, providing insights about patient experience and facilitate the detection and warning of potential adverse effects.

A web-based platform of symptom self-reporting could improve communication between elderly isolated patients and health-care providers.

New Forms of Financing

Discussion about a new allocation of funding is ongoing. Several factors need to be taken into account:

- The care of the elderly population in local health-care institutions authorized to treat cancer patients.

  The importance of an effective coordination, mainly provided by the cancer regional networks.
- Involvement of numerous health-care professionals during the whole care pathway.

Conclusion

The integration of the organization of geriatric oncology in French Cancer Control Plans allowed better adapting the therapeutic strategy for each patient and encouraging the implementation of clinical trials. The model based on the identification in each region of an oncologist–geriatrician partnership in charge of the coordination of the treatment is expected to evolve as the modernization act of the health system will impact the overall organizational framework in oncology. Several challenges have to be faced such as the implementation of a compulsory training program in geriatrics in the university oncology curriculum, or the coordination of health-care professionals all along the health-care pathway. The sharing of information through an oncology electronic medical record is critical.

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3 Healthcare Informatics and Technology in Managing the Older Cancer Patient

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Abstract

The population of older cancer patients continues to rise, and there is an increasing need for the continuing development of healthcare informatics and health technology. Rising healthcare costs among an aging population has shifted priorities toward cost-effective and value-based care. Inevitably, population health and predictive modeling becomes a greater focus in an attempt to better risk-stratify a physiologically and functionally diverse group of patients. Translational bioinformatics and precision medicine challenge the understanding of an individual environment and endeavors to enhance standard models of health and behavior on a more personalized level. Wearable sensors with an array of capabilities may represent an emerging tool for managing the older cancer patient. Though the use of modern technology has increased in older individuals over time, a broad implementation of health technology will require more senior adults to accept innovative approaches to healthcare. To bridge this digital divide, improvements must be made in terms of usability, data collection, privacy, speed, volume, and cost. With the aid of developing technologies, patient-reported outcomes may also become more easily collected and utilized in real-time patient care. The potential to utilize a smart and connected home that interfaces with patients and reports to providers is on the horizon.

Keywords

Healthcare informatics · Wearable technology · Sensors · Mobile health · Patient-reported outcomes

Introduction

The number of adults with cancer continues to increase and the general population has concurrently become older. Navigating a health system effectively for a growing group of older individuals requires both patients and providers to optimize the use of time- and cost-saving advances such as healthcare informatics and health technology. This chapter will explore the rising costs of healthcare and the need to prioritize value-based care, potentially with the use of population health management and predictive modeling. Novel health technologies are discussed in the context of their ongoing applications for the older cancer patient.

Rising Costs of Healthcare Among an Aging Population

Healthcare spending in the United States has grown markedly since the enactment of Medicare and Medicaid in the 1960s. Between 1970 and 1993, the increase in real national health expenditure (NHE) exceeded the growth of the gross domestic product (GDP) by 2.7% per capita annually (Blumenthal et al. 2013). The increase in healthcare spending has prompted multiple government efforts to implement change and to modify health policy and structure. In 2015, US healthcare spending reached nearly $10,000 per person and accounted for over 17% of the economy (National Health Expenditures 2015 Highlights n.d.). The largest components of this spending were inpatient hospital care, outpatient physician and clinical services, and prescription drugs. The United States consistently ranks highest in the world for healthcare spending by GDP (World Development Indicators).

As the population continues age, it is estimated that by the year 2030, over 20% of the US population will be over the age of 65 (Ortman et al. 2014). Older adults account for a greater percentage of healthcare spending due to having more comorbid medical conditions and requiring more acute and subacute care later in life. From the late

1980s to early 2000s, Medicare spending reflected a significant increase in chronic disease and outpatient management (Thorpe et al. 2010; Thorpe et al. 2004). Interestingly, raising the cost-sharing for ambulatory care among older adults was suggested to increase overall healthcare spending due to eventually relying more on inpatient services (Trivedi et al. 2010). As outpatient visits decreased, hospitalizations and days of inpatient care increased. Advances in medical innovation also account for a large portion of the increased healthcare costs (Blumenthal et al. 2013). These innovations consist of novel therapies including medications as well as medical devices that have been implemented for a spectrum of chronic diseases such as cancer and heart disease. Improvements in diagnosis have also been made with the increased use of advanced imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET).

Value-Based Healthcare

In an effort to make healthcare advances sustainable, it is imperative to factor in value to medical decisions. Inherent to this medical decision making (MDM) is the concept of physician stewardship (Reuben and Cassel 2011). Fundamentally, every clinical decision is a value judgment and risk-benefit analyses by the provider. These decisions may be influenced by public policy and payer regulations, but nonetheless, the actions taken remain in the hands of the immediate provider.

As an example, a frail 92-year-old patient with end-stage heart failure and oxygen-dependent emphysema, who is admitted after sustaining a hip fracture from a mechanical fall and is incidentally found on imaging to have a new lung mass, has many important decisions to be made. Discussions regarding the possibility of surgery for hip repair, consideration of a diagnostic work-up for the lung mass, and conversations surrounding the overall trajectory and goals of care are likely topics. Healthcare decisions involving value, especially among older adults with competing comorbidities and tenuous life expectancies, are understandably challenging.

Medical value can be defined as health outcome achieved per dollar spent (Porter 2010). However, outcome may have different meanings depending on perspective. Economic analyses of medical spending in the latter portion of the twentieth century revealed increasing cost per year of life gained as each decade passed (Cutler et al. 2006). Adults over the age of 65 had the largest cumulative change from 1960 to 2000 by average per capita spending. In order to be sustainable, healthcare spending must have limits. Increased cost affects both public and private payers. A common strategy in managing healthcare cost is to reduce payment, benefits, or eligibility. An alternative plan would be aimed at minimizing waste or low-value care (Berwick and Hackbarth 2012). Indeed, there have been increased efforts toward informed discussions and decisions about commonly used tests, treatments, or services. The Choosing Wisely campaign was a collaboration among several medical societies in an effort to reduce waste in the healthcare system (Cassel and Guest 2012; Morden et al. 2014).

One possibility for abstracting more healthcare value from the existing models of care is to better identify and understand each population of patients and then target interventions toward the specific individuals most likely to receive benefit. Such an approach may have the potential to lead to change in reimbursement and eventually policy reform.

Population Health

As the population of older individuals continues to rise, the prevalence of chronic medical conditions and functional impairments will also increase. Given the rise in the cost of healthcare, innovative approaches to combine technology with increased care coordination are going to be essential to improve outcomes and reduce cost. Population health management (PHM) represents the aggregation of patient data across multiple health information technology resources (e.g., primary care providers, other health professionals, caregivers, family members, home health, and patients) (Philips). This data can be analyzed and constructed into actionable patient records, which

healthcare providers can utilize to implement actions with the goal of improving health outcomes while decreasing cost. PHM is an important model in healthcare reform because it entails evaluating patients, determining and assigning risk, and applying interventions to manage individuals at highest risk.

Predictive Modeling

Predictive analytics uses data and statistical tools to forecast which patients are most likely to be at increased risk for health problems and cost more healthcare dollars (Berardo). Health care organizations are beginning to apply predictive analytics to large clinical data sets in an effort to identify higher-risk patient populations and intervene prior to serious illness. Translating predictive analytics into changes in patient care represents a significant culture change. It requires the collection of real-time, or near real-time, data and the timely processing of this information into reports that are easy to interpret and act upon. Inevitably, automated tools will need to be developed in order to apply these analytic and management strategies across populations of patients (Berardo 2017). This model also requires that novel health technologies enable users and providers to confidentially access and assess health risk data. When individual risk is identified and requires attention, personalized guidance can be provided to patient, caregiver, or provider (Berardo 2017). This model for population health management is invariably linked to precision medicine and thus a personalized approach to healthcare.

Precision Medicine

The core of precision medicine couples established clinical and pathologic indices with state-of-the-art patient profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each individual patient (Mirnezami et al. 2012). Implementing precision medicine requires integration of clinical data with genomics or other physiologic profiling to characterize an individual patient's disease process. For example, recent studies have examined the potential usefulness of precision medicine through pharmacogenomic testing to optimize drug regimens and manage polypharmacy in older adults (Finkelstein et al. 2016a, b). There are now also many examples of such targeted interventions in tumor molecular profiling and cancer genomics. Identifying gene mutations and molecular abnormalities is becoming a fundamental component of the diagnostic work-up of a malignancy. In fact, over the coming years, cancer treatment may shift away from traditional determination by cell type or tissue of origin to instead targeting identified molecular changes within the tumor itself (NCI). It is not surprising that oncology research receives a substantial portion of the NIH funding to advance precision medicine (NCI). Efforts to characterize individual physiology and health states will continue to emerge and become integrated into medical research (Li-Pook-Than and Snyder 2013). This integrated personal profiling is a key component to assessing individual risk and planning targeted interventions, the backbones for precision healthcare.

Translational Bioinformatics

Translational bioinformatics is the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical and genomic data into proactive, predictive, preventive, and participatory health (AMIA). Progress has been made toward utilizing genomic medicine at the point of care and seamlessly integrating into the electronic medical record (EMR) (Baselga 2013). However, the diversity of data has now extended beyond just genomics. An *individualome* is a data model that encapsulates elements of environmental, social, behavioral, biomedical, and clinical factors of an individual patient (Shameer et al. 2017). This data can be generated by wearable devices (e.g., distance or steps walked) or biosensors (e.g., continuous heart rate or blood glucose monitoring). Further investigation of this data

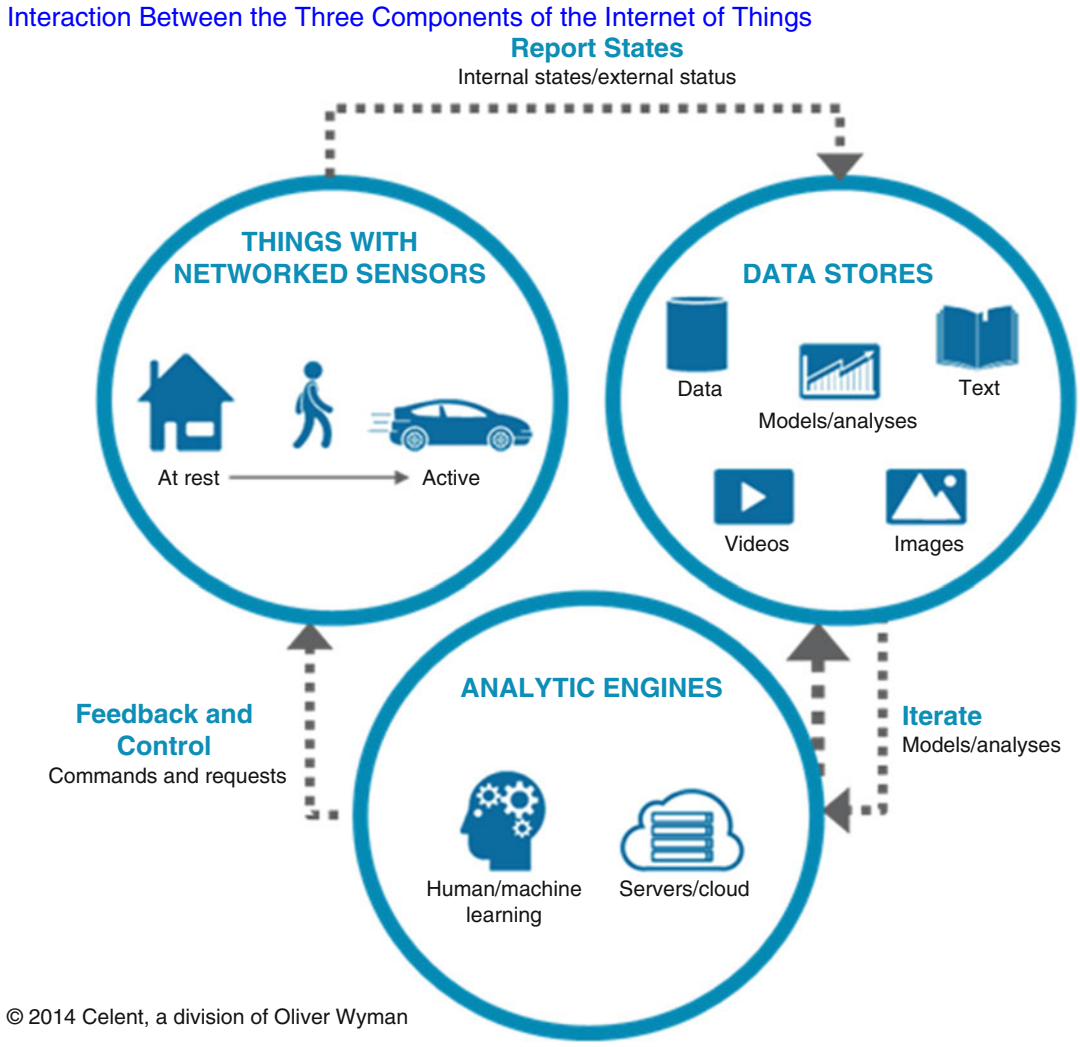

Fig. 1 Interaction between the three components of the internet of things (reprinted with permission from Celent)

incorporating individual socioeconomic information as well as local variations in environment may provide additional precision in developing predictive models capable of identifying and estimating causal or reactive roles that contribute to illness or wellness (Shameer et al. 2017).

Internet of Things

The Internet of Things (IoT) is the network of physical objects or "things" embedded within electronics, software, sensors, and network connectivity, which enables these objects to collect and exchange data (Fig. 1) (Mann 2015). The essence of IoT in healthcare resides in the source of the data, which are the sensors. Smart devices now have the capability to generate constant data on activities, events, and influencing factors that provide visibility into health and support the decision-making processes in medicine. There are also, however, several inherent challenges in leveraging data from IoT including volume, speed, computing ability, analytics, and security (Mann 2015). Remote data is collected in high volume and with rapid speed. With multiple data

streams generating information simultaneously, integrating all of it becomes even more data intensive. The computing ability of each individual device is likely insufficient to analyze all of the data, thus it must be transmitted to a central unit capable of both big data storage and high-performance analytics. Any large-scale data transmission inevitably extends the computing environment and the associated security risk.

The Smart Home

A smart home is one that includes internet connection with one or more devices that can be controlled through applications on a smart phone, smart watch, tablet, or smart television (Baik 2016). Connected homes are important as the vast majority of baby boomers desire to age within their own homes or communities (AARP 2014). Technology within smart and connected homes usually plays a role in home functionality, health monitoring, or lifestyle enhancement. The potential benefits for aging adults are overwhelming – light and temperature control, sensors that detect movement and environmental conditions, automated medication dispensers, and personal health monitors for blood pressure, heart rhythm, blood glucose, weight, physical activity, or falls (Baik 2016).

There are several inherent challenges to consider including signal clarity, bleed through, and user support (Better Connecting Seniors At Home 2016). Ensuring signal clarify is crucial as home environments can be expected to have multiple technologies that can increase the risk of interference or cross signals. Common household items such as microwaves are known to emit output that could be potentially disruptive (Better Connecting Seniors At Home 2016). Further, if an older individual were living in a dense community, technologies from neighboring environments may bleed over. It is also unrealistic to expect constant in-home user support to resolve technical issues, thus a remote support system must be developed and implemented to reach a wide population (Better Connecting Seniors At Home 2016).

The smart home represents a way for older adults to become more connected. Individuals in less populated areas can have access to a larger network of providers through the use of technology. This can also be helpful for seniors with disability or those who simply have transportation difficulties. Access to timely care is becoming an important metric for healthcare systems (Better Connecting Seniors At Home 2016). When applied across a population, the remote monitoring via a smart home system can help to risk-stratify patients and identify at-risk patients who require prompt medical attention. When used on an individual level, the system also has the potential to detect abrupt changes or deviations from one's norm to send immediate alerts or communication. In this manner, these smart systems extend an older individual's safety and social support (Better Connecting Seniors At Home 2016).

Evolving Technology and the Use of Health Technology

Over the course of the twentieth century, an abundance of new technologies and communication methods has evolved. Large, wired home telephone lines have steadily been replaced by smaller, wireless cellular phones. The emergences of lightweight, high-speed laptops and tablets have similarly substituted for the use of bulky desktop computers. Arguably, the transmission of data and sharing of information has undergone the most change. With an ever-increasing virtual and connected space, the sharing of files no longer requires a physical vehicle such as a floppy disk, compact disc (CD), or universal serial bus (USB) flash drive. Storage capacity and processing speed have also increased markedly.

With this growth in technology, comes the opportunity to utilize these tools to improve healthcare systems. Implementation may consist of patient reminders, education, counseling, screening, or intervention (Balas et al. 1997). Indeed, the primary goals of incorporating technology into healthcare are to improve communication and access to health resources while simultaneously managing cost (Dorsey and

Topol 2016). The true value of health technology stems from the dual ability to remotely monitor and remotely intervene. This has been increasingly studied in the fields of cardiology (Chaudhry et al. 2010; Inglis et al. 2015; Ong et al. 2016) and endocrinology (Lanzola et al. 2016), where remote monitoring has been used to collect diagnostic data, which can accelerate timely intervention. A critical limitation to these types of studies centers around compliance with health technology use. In fact, this is a component that large studies have been inconsistent about standardizing or ensuring.

Technology and Health Technology Use Among Older Adults

The use of technology by older adults has increased in the new millennium. In the year 2000, less than 10% of individuals over the age of 75 had internet access or went online. Recent studies have reported that 50% of individuals over the age of 75 have internet access and 60% of individuals over the age of 65 go online (Perrin and Duggan 2015). Challenges to internet access and use include the cost of an internet service plan, lack of training and support, physical disability or impairment, privacy concerns, and general skepticism. Among older adults with an annual household income of greater than $75,000, 90% go online (Older Adults and Technology Use 2014). For older adults who are connected to the internet, over 70% report being online daily and over 80% are online multiple times a week. Nearly half of online seniors are using social media and networking websites (Older Adults and Technology Use 2014). A 2016 survey of adults over the age of 60 demonstrated that over 65% had cellular phones and over 90% has cable or satellite television. This survey also showed that only 40% had a smart phone and only 25% had a fitness tracker (2016 Technology Survey Older Adults, Age 59–85+ 2016).

As older adults increase their use of general technology, the growing application of health technology becomes a logical integration of this behavior. A systematic review specifically on sensor monitoring to measure and support daily functioning in older people showed a scarcity of studies (Pol et al. 2013). Another systematic review explored the priorities for technology acceptance among elders and identified cost, privacy, safety, and utility as key components (Peek et al. 2014). Health information technology was suggested to be more accepted by community-dwelling elders if it contributed to aging in place (Fischer et al. 2014). A survey of over 200 adults over the age of 60 found that in-home monitoring of activities by ambient sensors was valued for the purposes of living at home longer, more safely, and independently and for timely detection of emergencies as well as gradual health problems (Claes et al. 2015). Visualizing activity data was also of importance. Interviews with a group of older adults showed sensor monitoring was valued as a strategy for independent living and encouraged the participants to remain more active (Pol et al. 2016). Additional features that improved older adults' perceptions of health technology was whether they were simple, reliable, effective, and tailored to individual need (Hawley-Hague et al. 2014).

Patient-Reported Outcomes and Technology

Health outcomes can be reported by various domains: provider account (e.g., global impression, physical exam findings), physiologic results (e.g., vital signs, lab or imaging tests), or patient-reported (e.g., symptom control, function, overall quality of life). Physiologic results tend to be the most objective measure of outcomes; however, patient-reported outcomes (PROs) for older adults may be more insightful of the patient perspective (Testa and Simonson 1996; Schwartz and Sprangers 2002). A patient-reported outcome is the measurement of any aspect of a patient's health status that comes directly from the individual, without modification or interpretation by another observer. PROs can be collected in many formats including paper forms, online surveys, or in-person response. Questionnaires may be generic instruments to evaluate broad symptoms

and quality of life metrics or they could be targeted instruments examining specific symptoms of interest. PROs can be used to evaluate symptoms, adherence, health status, or care satisfaction. PROs are also being explored as a quality measure in cancer care (Stover and Basch 2016). When used longitudinally, PROs offer insight into variation in symptoms or function. PROs may also allow the opportunity to monitor for disease progression. Integrating PROs into treatment assessments has been increasingly common and continues to expand rapidly (Testa and Simonson 1996; Basch et al. 2016a).

However, it is well known that PROs are inadequately reported in clinical trials, which limits the value of partial assessments (Calvert et al. 2013). Efforts to improve upon PRO measurements in terms of reliability, validity, sensitivity, and specificity will be important in ongoing research as technology becomes adapted into healthcare. With advances in technology, survey methods have improved and the ability to collect PROs via the internet or on a smart device now exist (Basch 2017). In fact, the speed of technology now offers the ability for providers to receive timely alerts or notifications when worrisome symptoms or a decline in function is noted (Basch 2017).

Patient-reported outcomes for cancer symptoms, treatment-related symptoms, and quality of life can significantly influence physician decision-making and cancer care (Lipscomb et al. 2007; Clauser et al. 2007). Commonly followed symptoms in cancer patients include pain, nausea, and fatigue (Di Maio et al. 2016). The National Cancer Institute has developed a patient-reported outcome version of the common terminology criteria for adverse events (PRO-CTCAE) to improve the extent to which these measures can be captured in cancer clinical research (Basch et al. 2014). The PRO-CTCAE was subsequently validated in a large outpatient study of nearly 1000 adults undergoing cancer treatment (Dueck et al. 2015). More recently, a randomized controlled trial of over 700 cancer patients showed that symptom monitoring with patient-reported outcomes accompanied by appropriate interventions had the potential to decrease emergency room visits and improve survival (Basch et al. 2016b).

Assessing Cancer and Aging

Cancer incidence increases with age and the number of older individuals with cancer will increase dramatically over the coming decades. It is estimated that by 2030, 70% of cancer diagnoses will be made in persons age 65 or older (Smith et al. 2009). There is tremendous heterogeneity within the geriatric population, encompassing a wide range of performance status and functional capability. Given this variability, older cancer patients are at increased risk of both undertreatment and overtreatment, which can affect toxicity and survival (Wildiers et al. 2014). Several treatment guidelines have recommended utilizing geriatric assessment for older cancer patients; however, this is no consensus on the best instrument to use (Extermann et al. 2005; Decoster et al. 2015; NCCN 2016). Completing a comprehensive geriatric assessment (CGA) can be time-intensive in a busy oncology practice and abbreviated screening tools remain poorly sensitive (Hamaker et al. 2012; Augschoell et al. 2014). Prior studies have shown that collecting simple measures of functional status activities of daily living (ADLs) and instrumental activities of daily living (IADLs) have prognostic value in elderly cancer patients (Maione et al. 2005). Gait speed and Timed Up and Go (TUG) have also been shown to be strong predictors of mortality, functional decline, and complications (Soubeyran et al. 2012; Hoppe et al. 2013; Ferrat et al. 2015; Pamoukdjian et al. 2015). Multiple tools and scales have been developed and validated for predicting cancer treatment-related toxicity (Hurria et al. 2011; Extermann et al. 2012; Hurria et al. 2016). For example, Hurria et al. combined objective parameters of baseline diagnostic data, such as hemoglobin and creatinine clearance, with baseline functional assessments, such as hearing, gait, and falls to generate a risk score that prognosticates one's chances of experiencing chemotherapy toxicity. These assessment tools may in certain cases be superior at risk stratifying older cancer patients compared to more subjective physician assessments such as the Karnofsky Performance Status (KPS). As health technology expands in use, it is anticipated that functional

assessments can be done more consistently and objectively. Prospective, randomized studies are currently underway to further explore the use of health technologies in older adults with cancer (Meguerditchian et al. 2016; Paul et al. 2016).

Wearable Sensors and Geriatric Assessment

The use of sensors in healthcare has been increasing over the past several decades. Inertial sensors have been used to record mobility assessments such as the Timed Up and Go (TUG) and to stratify older patients by sensor-identified frailty (Greene et al. 2014; Toosizadeh et al. 2015). Wearable sensors have also allowed for the objective and discriminative assessment of older adults' physical function during activities such as gait and position change (Grimm and Bolink 2016). Sensor-based assessments of sit-to-stand performance have been shown to reflect objective and self-reported aspects of functional status in the elderly (Regterschot et al. 2015). Data from wearable sensors can be incorporated into machine learning models to distinguish extremity use from ambient movement, which provides a critical level of distinction (McLeod et al. 2016).

The prominence of falls in the geriatric population makes this an important parameter to monitor for and potentially predict. There have been numerous studies utilizing wearable sensors to quantify limb movement and gait and to compare these metrics with fall outcomes (Marschollek et al. 2011). A few studies have suggested the superiority of sensor-based classification compared to other standard measures such as the TUG test or the Berg balance score (Greene et al. 2012). In a population of dementia patients, sensor-derived physical activity data was found to be independently predictive of fall risk and may have had higher diagnostic accuracy compared to conventional fall risk measures (Schwenk et al. 2014). The next important step will be to utilize sensor-based data to formulate protocols for intervention in high-risk patient populations (Danielsen et al. 2016).

Wearable sensors have developed the ability to capture subtle physiologic changes in posture, movement, localization, vital signs, and sleep patterns. Having an extensive volume of information for an individual allows for unique baselines to be established. Sensors can then detect personal differences in physiologic parameters that may be suggestive of early disease (Li et al. 2017). Smartwatches have also incorporated sensing technology into their applications and studies to validate these interfaces have been performed with prospective comparisons ongoing (Mortazavi et al. 2015). A feasibility study of a small sample of older adults was followed longitudinally using sensor technology applications to monitor mobility and daily activities (Chung et al. 2016). Wirelessly collected sensor data can be used to generate objective ADL assessments (Zhang et al. 2014).

New technologies are potentially advantageous over traditional geriatric oncology assessments due to increased objectivity when compared to performance scales such as Karnofsky (KPS) or Eastern Cooperative Oncology Group (ECOG), which may be subject to provider bias and variability (Kelly and Shahrokni 2016a). This is a topic of growing research interest as commercially available wearable devices have become readily available and accessible to patients and providers (Kelly and Shahrokni 2016b). Simple pedometry and PROs were assessed on a hematopoietic stem cell transplant unit and regression models showed correlation of activity data to patient-reported symptoms such as pain, fatigue, nausea, and shortness of breath (Bennett et al. 2016). The symptom severity and decline in physical health were reflected by decrements in the objectively captured performance of daily activities. A recent systematic review exploring the relationship of functional performance status with PROs showed that these domains captured some consistency in the patient experience but also varied and provided unique information (Atkinson et al. 2015). A system that can dually capture both functional assessment and patient-reported outcomes would be a tremendous tool for geriatric oncologists.

As wearable sensors continue to improve in sensitivity and capability, the opportunity to utilize these electronic devices for assessing older adults with cancer becomes a promising prospect. In the future, as more predictive metrics become developed through the use of modern technology such as wearable sensors within a smart and connected home, it will be important to compare this information to traditional assessments. In order to successfully integrate growing, innovative technologies into the healthcare system, their value must be proven on both a cost and utility level. With the growing population of older adults with cancer, this would be a prime population to further clinical trials that examine the potential for population health management through risk stratification and targeted intervention, to improve care and quality on both an individual and population level.

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Part II

Biology of Aging and Cancer

Tamas Fulop

Role of Cell Cycle Control, Checkpoints, and DNA Repair Mechanisms in Stem Cells and Changes with Aging and Cancerogenesis

4

Andreas Brown and Hartmut Geiger

Contents

Abstract

The regulation of cell cycle progression, checkpoint activation, and DNA repair in stem cells is distinct from the regulation in progenitors and differentiated cells. For a broad range of types of stem cells, such as embryonic, muscle, and hematopoietic stem cells, these mechanisms have already been described. Either a complete absence or corrupted activity of checkpoints such as the G1/S damage response and the decatenation checkpoint was found or strong alterations in DNA repair mechanisms could be identified. Moreover, stem cells also activate their own distinct checkpoints, such as the novel differentiation checkpoint. It is currently not completely understood why stem cells maintain these distinct regulatory checkpoints and how they contribute to tissue homeostasis, stem cell function, and genome integrity. Furthermore, it is unclear how these mechanisms change upon aging and whether alterations in them significantly contribute to the

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transformation process and the development of diseases, such as MDS and leukemia. The following chapter will provide a general overview of cell cycle control, checkpoint activity, and DNA repair mechanisms in hematopoietic and other adult stem cells as well as progenitor cells and their relevance for genome integrity, homeostasis, aging, and disease. We will further highlight checkpoint proteins as potential pharmaceutical targets to treat age-related diseases.

Keywords
Cell cycle · Hematopoietic stem cell · Checkpoints · Leukemia

Introduction

Proper cell cycle progression and the associated control mechanisms ensure high fidelity of cell division, maintenance of genome integrity, and tissue homeostasis. Every round of cell division though might result in threats to the cell and the genome, such as stalled replication forks, entangled chromosomes, improper mitotic spindle formation or the generation of reactive oxygen species (ROS), and DNA intercalators (Lopes et al. 2001). For instance, more than 100,000 DNA lesions are generated each day in every cell (Jackson and Bartek 2009). Many of these incidents have the potential to induce DNA or chromosomal damages which, if unrepaired, will eventually result in mutations or aneuploidies (Pellman 2007). To ensure proper repair of DNA damage and resolution of chromosomal abnormalities, the cell possesses a comprehensive portfolio of cell cycle–checkpoint mechanisms. These signaling cascades play a role primarily during cycle transitions, such as the G1/S, the G2/M, or the mitotic (M) checkpoints, but are also active during the progression through replication, such as the intra-S-phase checkpoint. A growing body of evidence suggests that these checkpoints are essential for ensuring the low rates of mutations and high functionality even after several rounds of cell duplication. Especially long-lived adult stem cells depend on the reliable function of these mechanisms as they need to self-renew and thus generate perfect copies of themselves to ensure the lifelong availability of a functional stem cell pool. In addition, they do also need to give rise to differentiated cells and generate tissue, and therefore, for example, DNA mutations will eventually affect all offspring and thus a large number of cells in a tissue. It is speculated that upon aging and cancerogenesis checkpoint and DNA repair mechanisms become compromised leading to the inability to correctly arrest at cell cycle boundaries to properly repair DNA damages, or, if required, to induce senescence and apoptosis (Sperka et al. 2012). Abrogation of checkpoint control might also contribute to both the deregulation of the self-renewal ability and loss of differentiation. Indeed, an increasing amount of evidence suggests that many of these mechanisms are deregulated in hematopoietic stem and progenitor cells (HSPC)–derived malignancies, such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

This chapter focuses on the current knowledge of cell cycle regulation, checkpoints, mechanisms of genome maintenance, and DNA repair in HSPCs as well as in other adult stem cells and how these mechanisms can change and become disrupted upon aging and contribute to malignant transformation. We will also discuss current efforts using inhibitors targeted against important regulators of these checkpoints to treat diseases like leukemia.

Regulation of the Cell Division Cycle, Genome Maintenance, and Checkpoint Activity in Stem and Progenitor Cells

General Overview

Hematopoietic as well as other stem cells mostly reside in a quiescent state in which most cellular activities including metabolism are held to a minimum level (Cheung and Rando 2013). So, why is cell cycle control so important to them? The majority of blood cells is short-lived and needs to be replaced on a daily basis. These mature cells

ultimately originate from stem cells. So while they cycle infrequently, stem cells need to undergo cell division cycles, in which they need to balance self-renewal and differentiation, while maintaining DNA and structural integrity.

A eukaryotic cell cycle is divided into several phases: G1, S, G2, and M phase. The entry and progression through these phases are essentially controlled by cyclin-dependent kinases (CDKs) together with their binding partners and regulators termed cyclins (Sánchez and Dynlacht 2005). The transitions between cell cycle phases are tightly controlled, and upon these transitions, the activation of the corresponding checkpoints prevents the entry into the consecutive phases. Before the cell enters S phase, potential existing DNA damage, such as pyrimidine dimers and single and DNA double-strand breaks (DSBs), needs to be efficiently recognized and eliminated by repair systems to ensure proper DNA replication. To do this, cells might not enter S phase but stay arrested at the G1 boundary. This is especially important as DNA damage that occurred during G1 phase, if neglected, would most likely result in mutations and be distributed to sister chromatids during S phase. Similarly, unrepaired DNA damage which occurred during the G2 phase of the cell division cycle would be even more severe given that the resulting mutations would be delivered to daughter cells, as mitotic cells do not really initiate DNA repair processes due to impeded accessibility of DNA upon condensation (Orthwein et al. 2014). DNA damage pathways are active also during S phase: Here, the cell can initiate mechanisms that will result in a temporal halt of replication.

A special cell cycle phase is G0 phase, as it does not occur in highly proliferative cells (like in cell culture). Especially HSCs and many types of progenitor cells (MPPs) primarily reside in this phase which, in contrast to senescence, is not a permanent cell cycle arrest. Up to 90% of adult HSCs reside in this G0 phase during which transcription, translation, and metabolism are held at a minimum level. Some HSCs thus only divide a few times during the lifetime of the organism. In contrast, during early fetal development, most HSCs are actively cycling with a doubling rate of roughly 14 h with no or few cells resting in G0 (Catlin et al. 2011). The percentage of quiescent HSCs increases further with aging and ultimately reaches levels above 95% in HSCs (Bowie et al. 2006; Ema and Nakauchi 2000). It is speculated that this maintenance of quiescence protects HSCs from the accumulation of mutations (Weiss and Ito 2015), as proliferation goes along with cellular stress, such as the generation of ROS and other DNA-intercalating agents, although this dogma has been recently critically discussed (Beerman et al. 2014; Mohrin et al. 2010). An overview of checkpoint control mechanisms in HSCs is shown in Fig. 1.

Role of CDKs, Cyclins, and CKIs in HSPCs

CDKs (cyclin-dependent kinases) are enzymes that drive progression depending on the current position within the cell division cycle. Together with cell-cycle specific expression of their activators (cyclins), they are the key regulators of the cell cycle. Most of the cell cycle defects found in tumors, such as unregulated proliferation, chromosomal, and genomic instability, are directly or indirectly mediated by the deregulation of CDKs (Malumbres and Barbacid 2005). What is the function of the various CDKs? Whereas CDK2 is required to drive G1/S transition and S phase progression together with Cyclin A or E, respectively, CDK1 is essential for transition through G2 and M. Besides these kinases, also CDK4 and CDK6 play important roles in cell cycle progression: CDK4 operates during the G1-S transition phase where it is mostly bound to cyclin E and regulates the activity of retinoblastoma (pRb), an important player of the DNA damage response (DDR). A similar role is performed by CDK6. Recently, interesting findings have been published illustrating the role of CDK4 and CDK6 in adult stem and progenitor cells: Whereas CDK4 seems to have a role in ensuring proper G1-S transition in neuronal stem cells and prevents their premature differentiation (Lange et al. 2009; Lim and Kaldis 2012), CDK6 has been claimed to be a novel negative regulator of HSC maintenance and quiescence: It was shown that expression and activity of this kinase is essential

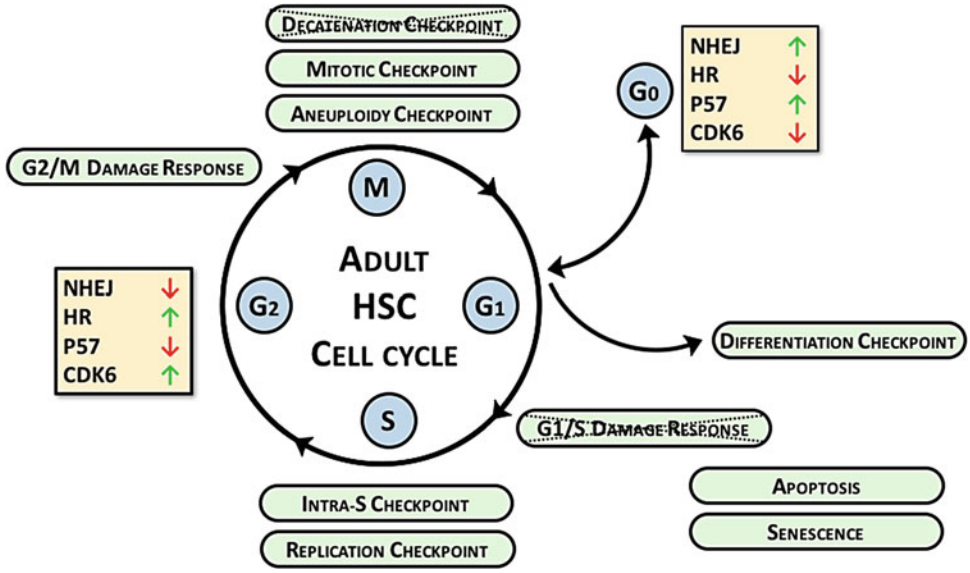

Fig. 1 Mechanisms of genome integrity in adult HSCs. A broad range of evidence suggests that cell cycle control, checkpoints, DNA repair pathways, and other mechanisms to ensure genome and functional integrity greatly differ compared to the corresponding mechanisms in mature tissue. Whereas HSCs lack proper G1/S and decatenation checkpoints, they activate the so-called differentiation checkpoint upon DNA which is not present in somatic cells. Depending on the cell cycle phase, HSCs activate different mechanisms to repair DSBs and different cell cycle regulators

for enabling the entry of HSCs into the active cell cycle. Consistent with this, ST-HSCs already show high expression of CDK6 (Laurenti et al. 2015; Scheicher et al. 2015). Interestingly, more and more data point into the direction that CDK2, CDK4, and CDK6 seem to be rather dispensable for somatic tissue and only crucial for HSPCs and other highly specialized (stem) cell types. For instance, CDK2 has been reported to be dispensable for normal somatic tissue development but pivotal in certain types of cancer stem cells (Berthet et al. 2003; Ortega et al. 2003).

For most of the known cyclins important roles in HSPC regulation have been demonstrated: Whereas cyclin A has been shown to be required for proliferation of HSCs and ES cells, it seems to be dispensable in differentiated tissue, such as fibroblasts (Kalaszczynska et al. 2009). Cyclin C has been suggested to be involved in the transition from quiescence to active proliferation, as deletion of the gene results in an increase of the quiescent HSC fraction and engraftment benefits upon transplantation (Miyata et al. 2010). Also critical for proper stem cell function is cyclin D: Loss of cyclin D (gene deletion) reduces the duration of the HSC cell cycle leading to functional defects (Choi et al. 2014). Finally, especially under stress conditions, such as 5-FU treatment, cyclin E is required for proper cell cycle entry and colony forming ability of HSPCs (Campaner et al. 2013).

Over the last decade, a growing body of evidence revealed that CDK inhibitors (CKIs) are also important mediators of stem cell function. CKIs form two families, the INK4 family and the Cip/Kip family with their major members p21(Clip1), p27(Kip1), and p57(Kip2). P57 plays a crucial role in maintaining HSC and neuronal stem cell quiescence, and it is rapidly downregulated upon differentiation into less primitive progenitors (Furutachi et al. 2013; Matsumoto et al. 2011). In a similar fashion, p27 together with p57 regulates the size of the HSC pool (Zou et al. 2011). As defects within the HSC pool and hematopoiesis mainly occur in p57 knockout mice and not in p27 or p21 knockout strains, it is tempting to speculate that it is the most critical CKI of the Cip/Kip family for HSC maintenance

and functionality (Matsumoto et al. 2011). P21 is one of the most important targets of p53 within the G1/S damage response pathway. Whereas some researchers claim an important role of p21, especially in the DDR of HSCs (Insinga et al. 2013), other publications support a minor role of the protein in ES cells as well as HSCs (van Os et al. 2007; Zhang et al. 2013). Expression of the INK4 family member p16 has been shown to be high in human HSCs while its expression decreases upon differentiation into progenitors, indicating that p16 might play a role in maintaining HSC dormancy (Furukawa et al. 2000). However, the deletion of p16 in mice does not affect hematopoiesis indicating that p16 might act in HSCs species specific (Serrano et al. 1996). P15 is not expressed in murine HSCs and similar to p16, upon genetic deletion the hematopoietic compartment is not altered. P18, on the other hand, shows high expression in quiescent HSCs and HSCs devoid of p18 harbor severely compromised cell cycle progression and overall engraftment (Yu et al. 2006). P21 and p27 are also involved in the regulation of self-renewal of other types of adult stem cells, like neural and intestinal stem cells (Fasano et al. 2007; Kippin et al. 2005), while the members of the INK4 family, p15, p16, and p18 contribute to the regulation of the self-renewal of brain, lung, and pancreatic stem cells (Janzen et al. 2006; Pei et al. 2007).

Together, these findings demonstrate that a large number of CKIs have a pivotal role in regulating self-renewal and cell cycle progression in HSCs and other types of stem cells, whereas some CKIs, however, seem to be dispensable.

DNA Repair and Cell Cycle Arrest Pathways in HSPCs

Cells encounter up to 10 DSBs per day. Although the number is likely to be lower in quiescent HSCs due to their hypoxic nature and low metabolic activity, it is clear that HSCs need an efficient strategy to repair DSBs and other types of DNA damage. ES cells and adult stem cells are very unique in terms of cell cycle regulation, DNA repair, and checkpoint activity. The resilience of HSCs toward DNA damage though remains controversially discussed. While the laboratory of Emmanuelle Passagué and others claim that HSCs are more resistant toward DNA damage than progenitors (Insinga et al. 2013; Mohrin et al. 2010; Pietras et al. 2014), other data support that HSCs do not accumulate a lot of DNA mutations and rather induce apoptosis or senescence upon DNA damage (Milyavsky et al. 2010; Moehrle et al. 2015; Shao et al. 2014). In general though, the common denominator seems to be that HSCs do not easily accumulate DNA mutations.

In order to ensure this genomic integrity, cells harbor distinct sets of pathways which are activated upon various types of DNA damage. The most important of this pathway is the DNA damage response (DDR) pathway, which is usually activated by DSBs. The key sensor of damage in this pathway is the MRN complex which consists of the three proteins Mre11, Rad50, and Nbs1. Upon a DSB event, this complex is rapidly assembled at the site of damage, ensuring the spatial proximity of matching DSBs and the activation of mediators, such as ATM. The presence in for example embryonic and adult stem cells of this basic but very critical DNA damage response pathway has been confirmed by multiple groups. However, although the activation of this pathway in HSPCs does not differ from the one found in fibroblasts, the effectors are distinct and the outcome depends also on the kind of stem cell. For example, it has been suggested that in HSCs, when situated in G0/G1 phase of the cell cycle, the predominant pathway in repairing DSBs is most likely the error-prone nonhomologs end-joining pathway (NHEJ) (Mohrin et al. 2010; Shao et al. 2012). Upon activation or differentiation of HSCs, however, the cell switches to the homologs repair (HR) pathway which has got a higher fidelity rate as it can rely on sister chromatids as source templates for DNA repair. Interestingly, different types of adult stem cells use mechanisms to repair DSBs distinctly: LGR5+ intestinal stem cells, for instance, mostly use the HR pathway in contrast to HSCs (Hua et al. 2012), whereas hair follicle bulge stem cells also preferentially use the NHEJ pathway (Sotiropoulou et al. 2010). Other DNA repair mechanisms, such as nucleotide excision

Table 1 Role of checkpoints, cell cycle regulators, and DSB repair pathways in HSCs and upon leukemogenesis in AML

Checkpoint/DNA repair pathway/ Cell cycle regulator	Situation in (quiescent) HSCs	Situation in AML
DNA damage response (DDR)	Active (Milyavsky et al. 2010)	Upregulated (Malumbres and Barbacid 2009)
G1/S damage checkpoint	Downregulated/absent (Moehrle et al. 2015)	Active/inactive (Malumbres and Barbacid 2009)
G2/M damage checkpoint	Unknown, probably active (Brooks et al. 2014; Moehrle et al. 2015)	Active (Didier et al. 2008)
S-phase checkpoint	Unknown	Inactive (Seedhouse et al. 2009)
Mitotic checkpoint	Unknown, probably active (Rohrabaugh et al. 2008)	Inactive (Boyapati et al. 2007; Schnerch et al. 2013)
Decatenation checkpoint	Inactive (Damelin et al. 2005)	Active/inactive (Brooks et al. 2014; Wray et al. 2009)
CDK6	Not expressed (Laurenti et al. 2015; Scheicher et al. 2015)	Overexpressed (Placke et al. 2014)
P57	Upregulated (Matsumoto et al. 2011)	Downregulated (Chim et al. 2005)
Nonhomologues end-joining pathway (NHEJ)	Upregulated (Mohrin et al. 2010)	Upregulated (Brady et al. 2003)
Homologues recombination repair pathway (HR)	Downregualted (Mohrin et al. 2010)	Abrogated/downregulated (Jacoby et al. 2014)

repair (NER), base excision repair (BER), and mismatch repair (MMR), have also been shown to be active and pivotal in HSCs (Beerman et al. 2014; Desai and Gerson 2014; Li et al. 2012). Thus, various DNA repair pathways in HSCs are necessary to maintain cell function (Table 1).

The G1/S and G2/M damage checkpoints initiated by the DDR pathway are important mechanisms that arrest cells at the corresponding transitions to enable DNA repair, differentiation, apoptosis, or senescence. Whereas the G1/S checkpoint plays an important role in differentiated cells, its role in stem cells remains still unclear as we and others demonstrated that this checkpoint might be impaired in stem cells: Embryonic stem (ES) cells, HSCs and less primitive progenitor cells do not arrest at the G1/S boundary in response to DNA damage induced by gamma irradiation, but enter the active cell cycle via S phase following the induction of massive amounts of apoptosis (Aladjem et al. 1998; Malashicheva et al. 2000; Moehrle et al. 2015). We also demonstrated by in vivo analyses that the lack of the retinoblastoma protein in HSPCs, usually critical for activation of the G1/S checkpoint (Weinberg 1995), did not alter the G1/S checkpoint response, further supporting that the G1/S response is impaired in HSCs (Moehrle et al. 2015). Similarly, other groups reported that DNA damage in conjunction with p21 activity induces HSC activation, cell cycle entry, and several rounds of cell duplication and thus not a G1/S arrest (Insinga et al. 2013). Considering an impaired G1/S checkpoint of HSPCs in vivo, it is tempting to speculate that HSCs are not really resilient toward DNA damage but employ a different strategy to resolve the issues: It could be more beneficial to remove damaged cells from the stem cell pool instead of trying to repair damage, even if this damage is less severe. Considering that HSCs have to preserve lifelong genome stability, this strategy could be advantageous. The absence of a strong G1/S activation in HSPCs is though still controversially discussed. The Passegué group presented data on purified HSPCs which were treated with cytokines to allow proliferation before irradiating them. These HSPCs stop proliferating upon DNA damage. The HSPCs then also, under these conditions, try to repair DNA damage instead, displaying a general low level of apoptosis after irradiation. In this experimental set-up, HSCs devoid of P53 continue to proliferate and do not induce an arrest upon irradiation. While most laboratories rely on

AnnexinV as a marker for early and global apoptosis, the Passegué group assessed the cleavage of Caspase 3 as an apoptosis marker. However, as HSCs are very different in terms of cell cycle control and checkpoint activation, it cannot be ruled out that HSCs might also activate distinct, p53 and Caspase 3 independent apoptotic pathways. Surprisingly, in contrast to murine ES cells, it has been reported that human ES cells indeed activate a G1/S response, suggesting that the activation of cell cycle checkpoints might be species-dependent (Bárta et al. 2010).

In contrast to the G1/S checkpoint, the Geiger group hypothesizes that HSCs arrest at the G2/M boundary upon DNA damage, although this mechanism has not really been studied yet in HSPCs. Maybe a proper G2/M damage response, which is induced upon DNA damage in HSCs, in combination with the ability to induce apoptosis would actually be beneficial for HSCs, as it were fatal to let DNA-damaged cells entering M phase, during which DNA repair processes are downregulated.

Besides boundaries at the end of the G1 and G2 phases of the cell division cycle, cells also apply checkpoints to limit the likelihood of mutations during DNA replication. Not only DNA damage but also basic mechanical and supply problems, such as stalled replication forks, nucleotide deficits in addition to DNA lesions can lead to a halt of the replication process. Whereas the replication checkpoint is only activated as a response to the aforementioned replication problems, the intra-S-checkpoint is activated by DSBs. Similar to the activation of the G1/S damage checkpoint also sensor/transducer proteins like ATM/ATR, Chk1/2, and p53 are required for this process. However, there are also other sensors involved, such as Rad3 and Mec1 (Labib and De Piccoli 2011). In general, it is believed that these S-phase checkpoints play a minor role in (embryonic) stem cells and are not fully developed (Hyka-Nouspikel et al. 2012), but up to now there are no clear data about the existence of these checkpoints in stem cells. ES cells, when treated with replication inhibitors, rather initiate S phase than activating replication specific checkpoints (Desmarais et al. 2012; Desmarais et al. 2016). Novel data from our laboratory also suggest the absence of this checkpoint in HSCs, at least in response to irradiation: HSCs display relatively high S and G2/M phase contents 16 h after irradiation in conjunction with high levels of apoptosis and no block in S-phase, further indicating that S phase-specific checkpoints might be absent in HSCs (Moehrle et al. 2015).

Mitotic, Decatenation, Differentiation, and Other Checkpoints

The mitotic or spindle assembly checkpoint (SAC) is an essential safety mechanism that generates a "wait anaphase" signal during mitosis. This signal remains active until the spindle apparatus is established at all chromosomes. Subsequently, the cohesion rings which entangle the sister chromatids will be dismantled, initiating anaphase. Strikingly, one single unattached kinetochore is sufficient to rapidly activate the checkpoint and to halt sister-chromatid segregation. This essential checkpoint has been extensively studied in eukaryotic cell lines. Key players of the checkpoint are the Aurora kinases which phosphorylate components of the kinetochore. These are the phosphorylation sites to which Mad2, Bub1, and Bub3 will bind leading to the stable formation of the mitotic checkpoint complex (MCC), followed by binding of Cdc20. In this situation, Cdc20 is unable to operate as the main coactivator of the anaphase-promoting complex (APC/C), the most important upstream trigger of sister chromatid segregation. Consequently, mitosis is temporarily halted (Musacchio and Salmon 2007).

Surprisingly, this checkpoint has so far not been studied in detail in embryonic or adult stem cells. One recent publication, however, demonstrates its requirement for muscle stem cell differentiation (Kollu et al. 2015). Furthermore, a study made in *Drosophila* embryos strongly suggests a role of this checkpoint in neuronal stem cells: Loss of the SAC leads to brain damage, reduction of the progenitor cell pool, and increased apoptosis (Poulton et al. 2017). Rohrabaugh and colleagues suggested already in 2008 that

undifferentiated hematopoietic cells arrest in mitosis as a response to spindle drug treatment and interpreted this arrest due to mitotic checkpoint activity. They further found out that prolonged treatment of these cells with spindle drugs induces apoptosis (Rohrabaugh et al. 2008). Furthermore, the laboratory of Sean Morrison provided evidence that an intact spindle apparatus in HSCs is crucial for preventing aneuploidy, making a proper mitotic checkpoint in HSCs likely (Gan et al. 2010). In accordance, aneuploidy also leads to microcephaly in neuronal stem cells (Marthiens et al. 2013). Using trisomic HSCs in a competitive transplantation experiment, decreased engraftment was observed, suggesting that a compromised mitotic checkpoint (an underlying problem in trisomies) indeed impairs HSPC function (Pfau et al. 2016). Furthermore, when the authors used bone marrow cells isolated from mice hypomorphic for the essential checkpoint component BubR1, engraftment defects were observed in a serial transplantation approach starting from the 2nd transplantation round. In the 3rd round, these deficient HSPCs did not engraft at all. In total, the authors speculate that HSPCs harbor a special mechanism that selects against aneuploidy. However, it cannot be ruled out that this mechanism may represent a unique pathway, which acts independently from the SAC. In summary, although there is only limited knowledge on the mechanisms of the SAC in adult stem cells, its deregulation, and likely subsequent events like aneuploidy seem to critically impair stem cell function.

Another important instrument ensuring genome integrity and preventing aneuploidy in somatic tissue is the so-called decatenation checkpoint. This mechanism involves the activity of topoisomerase II and is triggered during mitosis as a response to chromosome entanglement (Luo et al. 2009). This checkpoint has been demonstrated to be active primarily in cancer cells (Wray et al. 2009). The activity of the checkpoint can be tested by applying the topoisomerase inhibitor ICRF-193 (Downes et al. 1994). Using this approach, it could be shown that the decatenation checkpoint is impaired or absent in mouse ES and human HSPCs (Damelin et al. 2005). Interestingly, when ES cells are undergoing differentiation in response to all-trans-retinoic acid, a reduction of aberrant chromosome segregation can be observed indicating that upon differentiation the checkpoint regains activity (Damelin et al. 2005). Whether this checkpoint is also inactive in murine HSPCs and other adult stem cells has not been determined yet.

A stem cell-specific mechanism to DNA damage is the differentiation checkpoint. One of the key characteristics of HSCs aging is the preference toward myeloid differentiation (Rossi et al. 2005). The team of Lenhard Rudolph illustrated that HSCs activate a specific checkpoint upon severe DNA damage, namely the differentiation checkpoint. This checkpoint which is initiated very early after irradiation enables lymphoid differentiation of HSCs and thus their removal from the stem cell pool (J. Wang et al. 2012). Consistently, this checkpoint was also observed in melanocyte stem cells (Inomata et al. 2009). As it is also induced by G-CSF treatment, the checkpoint might also play a role in rapidly regenerating lymphoid cells after injury.

Besides the aforementioned checkpoints, HSCs also activate other distinct mechanisms to prevent DNA damage to occur. First of all, HSCs are mostly quiescent, have very low metabolic levels, and reside in a hypoxic niche. All these factors contribute to low levels of ROS, one of the main causes of DNA damage in HSCs. They also have to ability get rid of intracellular ROS via high expression of connexion-43 gap junctions (Taniguchi Ishikawa et al. 2012). Yamazaki et al. suggested in 2007 that quiescent HSCs also lack lipid raft clustering by simultaneously high P57 (Kip2) expression enabling low mutation rates (Yamazaki et al. 2006). In addition, for the efflux of other various potential DNA-damaging agents, HCSs express high levels of certain ABC transporters (Zhou et al. 2001). Strikingly, the maintenance of HSC quiescence remains the most important mechanism of HSCs to ensure life-long functionality and low rates of mutations. Consequently, serial rounds of transplantation lead to complete HSC exhaustion (Yahata et al. 2011).

Apoptosis and Senescence

Apoptosis and senescence are central for ensuring the functional and genomic integrity of somatic and stem cells. As mentioned before, HSCs induce massive apoptosis in response to DNA damage (Moehrle et al. 2015). Similarly, HSCs can also undergo senescence upon irradiation (Shao et al. 2014). Both of these pathways are highly active also due to the high abundance of the p53 protein in HSCs, and its activity is crucial for inducing cell death in these cells. Together with its regulators PUMA and ASPP1, p53 induces apoptosis in these cells (Shao et al. 2010; Yamashita et al. 2015). Although some data argue that HSCs are rather resistant to irradiation and DNA damage unlike progenitors or differentiated cells (Mohrin et al. 2010), others clearly see a dramatic increase in apoptosis as judged by AnnexinV staining and loss of HSCs in bone marrow after irradiation (Moehrle et al. 2015). The differences described in the literature might be explained by the use of distinct markers for apoptosis assessed in such experiments. Similarly, high levels of apoptosis were observed in human HSCs isolated from cord blood indicating that murine and human activate similar mechanisms upon irradiation (Milyavsky et al. 2010). It is not clear yet which apoptotic pathways are the dominant ones in HSCs. It is possible that HSCs activate both p53-dependent and independent pathways.

Alterations upon Aging and Malignant Transformation

In human and mice, the bone marrow of aged individuals consists of up to 10 times more HSCs compared to young entities (Morrison et al. 1996). Most of these aged HSCs are myeloid biased and may be derived from only a few clones, a process known as clonal expansion, which is a major hallmark of stem cell aging (McKerrell and Vassiliou 2015). It is currently unclear how the mechanisms discussed in this chapter change during aging and whether these changes are engaged in the decline of functionality of HSCs and the increase in the incidence of leukemia and other diseases. Interesting findings indicate that the number of mutations found in AML patients only increases moderately with age whereas the number of leukemia cases is known to increase exponentially (Rozhok et al. 2014). This finding contradicts a dogma in which malignant transformation is mainly driven by the accumulation of DNA mutations.

Changes of Cell Cycle and Checkpoint Control upon Aging

Most researchers agree that one aspect of HSC aging is clonal expansion that goes along with an overall decline in reconstitution ability and a bias toward myeloid differentiation. It has been shown that aged HSCs are more quiescent than young HSCs and, as a response to genotoxic stress, they initiate less cell cycle entry and proliferation (Moehrle et al. 2015; Pietras et al. 2011). Studies from our laboratory indicate that HSCs from irradiated old mice are still not able to activate a functional G1/S arrest. Similarly, a relative increase in the G2/M population in these cells can be observed indicating that also aged HSCs activate a G2/M damage response. However, the same study points in the direction that the relative number of old G0/G1 HSCs is not reduced as dramatically upon DNA damage compared to young HSCs, suggesting that more old than young HSCs remain transiently in a G0/G1 status and do not enter the active cell cycle (Moehrle et al. 2015). One possible explanation for this observation may be increased senescence in these cells. Regarding functional aspects of DDR mechanisms, changes upon aging have been described as well: The deficiency of the DDR components ATM and ATR leads to exhaustion and induces a premature aging phenotype (Maryanovich et al. 2012; Ruzankina et al. 2007). Furthermore, aged HSCs which were irradiated with low doses show reduced self-renewal capacity. Other checkpoints also seem to be altered in aged stem cells: BubR1 has been identified as one candidate gene which influences the aging process. BubR1 heterozygous or

hypomorphic mice display many aging aspects also in the stem cell department indicating that reduced mitotic checkpoint activity may be involved the aging process (Baker et al. 2004). As mentioned before, the myeloid-biased shift in HSCs is very likely linked to their clonal expansion. However, it is not clear why there is a preference for myeloid biased and not lymphoid biased HSCs upon aging. One possible explanation might be proliferation advantages of these HSCs or due to alterations in cell cycle control mechanisms (Cho et al. 2008; Dykstra et al. 2011). Not only HSCs are affected by clonal drifts: This phenomenon also occurs in other stem cells, such as muscle and neuronal stem cells (Collins et al. 2007). Interestingly, in other stem cell departments, such as intestinal stem cells the clonal drift seems to be neutral and nonbiased (Lopez-Garcia et al. 2010; Snippert et al. 2010). Another aspect of stem cell aging is the apolar nature and a preference for symmetric cell division indicating that aged HSCs activate altered cell cycle control mechanisms (Florian et al. 2012). Strikingly, in the past several years, successful efforts have been presented in terms of stem cell rejuvenation (Florian et al. 2012; Loffredo et al. 2013). It still has to be assessed, however, whether also youthful checkpoint activities and cell cycle regulation are restored upon rejuvenation.

Role of Checkpoint and DDR Deregulation in Leukemogenesis

Many types of leukemia are thought to be driven by cancer stem cells. A broad range of evidence suggests that AML, CML, and other types of leukemia, as well as hematopoietic malignancies such as MDS, are derived from HSPCs in a process called leukemogenesis (Eriksson et al. 2015).

A massive amount of evidence suggests the deregulation of important key players of cell cycle and checkpoint control mechanisms in leukemia. Although there are no clear data yet about the activity of the SAC checkpoint in HSPCs, there have been several publications suggesting the deregulation of the SAC in leukemia, especially in AML: The important regulator of the SAC, BubR1, is very often deregulated in AML and other types of leukemia. Appropriate activity of BubR1 has been demonstrated to be crucial for proper function of megakaryocytes, a cell type which essentially relies on sustained checkpoint activity due to its polyploid nature (Wang et al. 2004). Schnerch and colleagues reported that in most AML patients a downregulation of the corresponding protein is common. This goes along with high activity of the APC/C and premature degradation of the anaphase inhibitors cyclin B1 and securin. Importantly, by stabilizing cyclin B1 or by overexpressing BubR1 in AML cell lines, the sensitivity of these cells to spindle drug treatment and appropriate mitotic checkpoint activity can be regained (Schnerch et al. 2013).

Furthermore, other reports indicate that patients with t(8;21) AML also harbor an abrogated SAC. This form of leukemia is characterized by the appearance of the fusion protein AML-ETO (Yuan et al. 2001). Researchers have shown that securin and cyclin B1 are downregulated in the presence of AML-ETO (Boyapati et al. 2007). Upon overexpressing of a truncated variant, AML1-ETO exon 9a, which is present in patients as well, cell lines fail to appropriately arrest upon spindle drug treatment and show several indications of failed mitotic checkpoint activity, such as premature degradation of securin, chromosome bridges, micronuclei, and aneuploidy. This aspect can be explained by downregulation of BubR1 upon overexpression of the fusion protein (Boyapati et al. 2007). Similarly, the expression of other components of the mitotic checkpoint, such as Mad2 and Bub1, also have been shown to be deregulated upon leukemogenesis (Ru et al. 2002). In some leukemia, a deregulation of the SAC has been found that involves Blinkin, a mitotic regulator, which is frequently found as an MLL-fusion partner in AML. As Blinkin is required for the recruitment of MCC components, its MLL-fusion form it can no longer regulate the SAC, leading to genetic instability (Kiyomitsu et al. 2007). Moreover, Mad2, another MCC component, is downregulated in ALL

(Krapf et al. 2010). In addition, also Aurora kinases are frequently mutated or overexpressed in AML. Consequently, they have been suggested to be promising targets for pharmaceutical treatments (Ye et al. 2009). Specifically, Aurora B is very often overexpressed in AML. Using an inhibitor against Aurora B together with other anticancer drugs, cell cycle arrest and apoptosis could be induced (Oke et al. 2009). Furthermore, a growing body of evidence suggests the essential contribution of the abrogated functionality of cohesins in leukemogenesis. These genes are important regulators of genome stability and their presence prevents premature sister chromatid segregation during mitosis. Consequently, cohesin genes, such as *STAG2*, are very frequently found to be mutated in AML and MDS (Wong et al. 2015).

Whereas CDK6 is not expressed in quiescent HSCs but required for ST-HSCs, it is overexpressed in leukemia (Laurenti et al. 2015; Placke et al. 2014; Scheicher et al. 2015). Another component of the DDR, pRb often presents with downregulated expression in leukemia (Paggi et al. 1995). Furthermore, the expression of BRCA1 and BRCA2, two DDR genes, are also often downregulated in AML, leading to decreased cell cycle arrest ability and low DNA repair fidelity (Yoshida and Miki 2004). Importantly, mutations in these genes are very frequently found in therapy-induced AML (t-AML) patients (Cole and Strair 2010). This can mostly be explained by hypermethylation of the corresponding promoter regions caused by loss of proper DMT3A function, one of the most frequently mutated genes in AML (Cole and Strair 2010). Interestingly, it has been shown that many mutations associated with leukemia, such as concerning p53 among others, already exist/are found before the pathogenic rise of leukemia (Wong et al. 2015).

There is a broad range of evidence for impaired DDR and DNA damage repair mechanisms in leukemia-derived cells. It is suggested that leukemic cells harbor intact DNA damage repair mechanisms but these are uncoupled from DDR pathways and other checkpoints (Boehrer et al. 2009). Cancer stem cells like glioma stem cells present with an enhanced cell cycle checkpoint response as well as DNA repair activity (Bao et al. 2006). In lung cancer stem cells, an enhanced repair of DSBs and a lack of S-phase checkpoint activity were found (Desai et al. 2014). It may not be surprising that many cancers including leukemia often show the (re)activation of DDR mechanisms indicated by high ATM, Chk1, and Chk2 expression. As the G1/S checkpoint is downregulated in ES and some adult stem cells including HSPCs, it is tempting to speculate that one consequence of leukemogenesis might be the reactivation of the G1/S damage response, at least in some types of leukemia. Consequently, proteins involved in DDR are promising targets for anticancer therapy. Very important contributors of leukemogenesis are also histone and epigenetic modulators. Five of the ten most mutated genes in AML and MDS encode for histone-modifying enzymes and DNA methyltransferases. This often directly affects the gene expression of cell cycle regulators. Very well documented, for instance, is the downregulation of CKIs in leukemia, such as p14, p15, and p16, due to aberrant promoter methylation (Melki et al. 1999). In conclusion, the deregulation of checkpoints and the DDR is frequently observed in leukemia. This indicates that changes in these mechanisms might critically contribute to leukemogenesis.

Treatment of Malignancies by Intervention of Checkpoint/Cell Cycle Control

As discussed in this chapter, deregulation of checkpoint and cell cycle control may play an important role in aging and aging-associated diseases such as leukemia. Consequently, checkpoint components could be novel promising targets for pharmacological treatment. As p53 is very frequently mutated in AML and MDS (Christiansen et al. 2001; Ok et al. 2015), DNA damage checkpoint responses cannot act appropriately and very often apoptosis cannot be initiated as a response to severe DNA damage (Li et al. 2016). The

overwhelming evidence of deregulated p53 activity in cancer makes it a promising target for anticancer therapy. Indeed, there are several studies suggesting the reactivation of a mutated and dysfunctional P53 protein by small chemical compounds, for instance by Apr-246. This molecule aims to help mutated and truncated P53 to its native folding thus restoring its function as a transcriptional activator (Bykov et al. 2002; Saha et al. 2013). Other strategies involve affecting downstream- or upstream targets of p53 or direct binding partners to restore the ability of cells to induce apoptosis (Andreeff et al. 2016; Stivala et al. 2012). A supporting approach during leukemia treatment could involve maintaining quiescence in HSCs: By inhibiting CDK4/CDK6 in these cells upon simultaneous chemotherapy, cell cycle entry and HSC exhaustion can be prevented (He et al. 2017).

Especially components of the DDR, such as ATM, ATR, and Chk2, are commonly mutated and deregulated in leukemia cells (Guarini et al. 2012; Morgado-Palacin et al. 2016; Takai et al. 2002). Often unfavorable mutations in these genes lead to the inability to appropriately react to DSBs mostly due to upregulation or gain of function. Consequently, some of the corresponding proteins have also been suggested to be suitable targets for inhibitors. Indeed, inhibitors against ATM (KU-59403) (Batey et al. 2013), ATR (AZD6738) (Kwok et al. 2016), Chk1/Chk2 (UCN-01) (Gojo et al. 2013) are currently under development or in various clinical phases. All these inhibitors are suggested to treat leukemia, in part by inducting checkpoint override or restoring apoptotic pathways. In addition, it has been shown that in AML cells by stabilizing p53 and p21 to induce a G1 arrest, apoptosis can be reinitiated (Kojima et al. 2008). Moreover, the inhibition of Chk1 in conjunction with genotoxic therapeutics to induce DNA damage also seems to be a promising approach (Didier et al. 2008). Finally, targeting Plk1 has been suggested for the treatment of hematopoietic malignancies as well, as it is often overexpressed in these cells: Indeed, inhibition of Plk1 by small chemical molecules leads to cell cycle arrest and apoptosis (Brandwein 2015).

Conclusions/Directions

Adult stem cells are of pivotal importance for the whole organism: They are responsible for the renewal of most somatic tissue at every step of life and therefore fundamental for tissue homeostasis. One hallmark of aging is the functional decline of stem cells leading to increased exhaustion, clonality, biased differentiation, and higher susceptibility for malignant transformation. However, it is yet unclear how stem cells age and which mechanisms support this process. In this chapter, we discussed how primarily HSCs regulate cell cycle progression and DNA repair and how changes in these processes contribute to the functional decline of stem cells. The probability of developing leukemia is dramatically increased upon aging, and this phenomenon cannot exclusively be explained as a consequence of the accumulation of DNA mutations. HSPCs seem to rather "deregulate" mechanisms upon aging like checkpoints that are critical for preventing leukemic transformation. However, more research will be necessary to better understand these mechanisms in stem cells and how they contribute to aging and disease.

Cross-References

- ▶ Acute Myeloid Leukemia in Older Adults
- ▶ Aging and Cancer Biology
- ▶ Hematopoietic Stem Cell Aging and Malignant Hemopathies
- ▶ Normal and Abnormal Aging (General Perspective for the Oncologist)

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Cellular Senescence and Tumor Promotion

5

Marco Demaria

Contents

Abstract

Cellular senescence is a state of irreversible growth arrest activated by a complex response to stress signals that lead to DNA or mitochondrial damages. Thus, cellular senescence derives from stress-activated programs, as opposed to other cellular states of irreversible growth arrest, such as post-mitosis and terminal differentiation, which are a consequence of developmental-activated programs. Senescent cells are characterized by the expression of different nonexclusive markers with various functions, and most senescent cells secrete a suite of cytokines, growth factors, and proteases, known as the senescence-associated secretory phenotype (SASP). The senescence growth arrest represents a potent barrier to prevent the propagation of damaged cells and to maintain tissue homeostasis. Moreover, the senescence program is a well-established

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tumor suppressive mechanism, and different anticancer therapeutic strategies are aimed to induce cancer cells to senesce. However, an excessive accumulation of senescent cells and their secretory phenotype can drive different pathologies associated with age, including cancer. Thus, cellular senescence can begin as a potent tumor suppressive mechanism and end with a tumor-promoting passing through positive modulation of tissue repair. For this reason, interventions aimed at interfering with the deleterious functions of senescent cells are under development.

Keywords
Cellular senescence · SASP · Irreversible growth arrest · Tumor suppression and promotion · Aging

Introduction

Cancer is the second most common cause of mortality worldwide. Nonetheless, cancer death rates have declined by more than 1% per year in men and women over the past 10 years, most likely due to advances in biomedical research; still, 15 million new cancer cases and more than 8 million deaths from cancer occurred worldwide in 2013 only. It is notable that the yearly decline in the cancer death rate is most prominent in younger, compared to older (>45 years of age), individuals. Age is the single most significant risk factor for developing cancer, and the vast majority of malignant tumors that are treated in clinics today occur in older patients (Extermann 2010).

In general terms, aging represents the slow and progressive deterioration of key biological functions, resulting in the accumulation of multiple pathologies and ultimately leading to organismal death (Kirkwood 2005). Aging is a well conserved phenomenon, and similar age-associated marks can be observed in a variety of different species going from yeasts to humans. However, the aging process is highly variable and intrinsically complex, due to its establishment and development from intricate interactions between genetic, environmental, and stochastic factors (Montesanto et al. 2012). Several fundamental mechanisms that drive the age-related deterioration of cellular and organismal functions have been described, but a uniform theory on how these processes arise, interact, and exert their roles is lacking.

A key discovery for the understanding of the aging process emerged more than 50 years ago when Hayflick and Moorhead found that human diploid cell strains undergo irreversible growth arrest after extensive serial passages in culture, a phenomenon described as "cellular senescence" (Hayflick and Moorhead 1961). This intrinsic clock that limits the life-span of human cells might potentially explain the restricted capacity of the human body to regenerate tissues in the long-term. Thus, aging could be explained by the "wear and tear" theory, first introduced by Dr August Weismann in 1882: body parts eventually wear out due to accumulation of senescent cells that are not able to proliferate and regenerate damaged tissues. Moreover, additional paracrine functions of senescent cells, such as the senescence-associated secretory phenotype (SASP) – a complex secretory program which includes several proinflammatory and pro-growth factors – can contribute to degenerate tissues (Loaiza and Demaria 2016).

However, the deleterious role of age-associated senescent cells for tissue homeostasis is contrasted by beneficial functions during development and in young age. The senescence growth arrest serves as an alternative to apoptosis during embryogenesis, where senescent cells appear to play an essential role in optimizing the development of certain embryonic structures (Munoz-Espin et al. 2013; Storer et al. 2013). Likewise, the non-cell-autonomous SASP can be beneficial by promoting wound healing and regeneneration and by limiting excessive fibrosis (Demaria et al. 2014; Jun and Lau 2010). Thus, based on experimental evidences, the senescence program can be seen as an example of "antagonistic pleiotropy," a theory introduced by Dr George Williams in 1952: An evolutionary selected mechanism which has beneficial effects during youth but has deleterious side effects at older ages.

The antagonistic pleiotropy of senescent cells can also be seen in the context of tumorigenesis. The activation of the senescence program restrains the onset and accumulation of damaged, and potentially oncogenic, cells early in life (Campisi 2001). Moreover, the SASP reinforces the tumor immunosurveillance, further limiting the spread of cancer cells throughout local and distal tissues. Tumors are often characterized by loss-of-function mutations of essential senescence players, such as p53 or p16, and mice that can bypass senescence develop tumors early in life (Campisi 2001). Many standard anticancer therapies, such as radiation or chemotherapy, induce senescence and exploit its tumor suppressive functions. However, cells harboring mutations in key genes for the induction and establishment of the senescence program are often able to develop resistance to such therapies. Moreover, these treatments hit noncancer cells and induce senescence in normal cells, with accumulation of nonproliferating cells in tissues and development of low levels of chronic inflammation, a situation that resembles an aged environment. These therapy-induced senescent cells might be responsible for a number of adverse reactions to cancer interventions (Demaria et al. 2017). To overcome the late deleterious effects of cellular senescence, an increasing interest is raising towards interfering with harmful aspects of the senescence program (Soto-Gamez and Demaria 2017). This approach is being developed around two different strategies: (1) elimination of senescent cells to reduce the SASP and to create space for the spread of healthy and undamaged cells; (2) inhibition of specific SASP factors to reduce chronic levels of harmful inflammatory and growth factors. However, these strategies come with new costs for the homeostasis of the organism.

This chapter offers a summary of the complexity of senescence phenotype, and an overview of the steps that lead a potent tumor suppressive mechanism to become pro-tumorigenic. Moreover, it discusses how senescent cells can be pharmacologically targeted in view of new anticancer therapeutic strategies.

Cellular Senescence

Induction of Cellular Senescence

The first example of cellular senescence was shown by the limited replicative potential of human cells, initially described by Hayflick and colleagues (Hayflick and Moorhead 1961). This so-called replicative senescence (RS) derives from a DNA damage response (DDR) signaling which is activated as a consequence of critically short telomeres. Telomeres shorten during each mitotic cell division and quickly become critically short and dysfunctional (Shay and Wright 2005). However, telomere length does not reflect organismal life-span, as mice carry telomeres 5–10-times longer than in humans but have a life-span 30-times shorter.

Telomere attrition activates a DNA damage response without effective repair, leading to activation of p53 (Herbig et al. 2004). p21 and p16 are the two main tumor suppressor pathways responsible for the replicative arrest of senescent cells. p21 binds and inhibits CDK1, CDK2, and CDK4/6 complexes and is tightly controlled by the activity of p53 in response to DNA damage (He et al. 2005). p16 is a CDK4/6 complexes inhibitor, and its expression is controlled by either epigenetic and transcriptional changes (Rayess et al. 2012). During replicative senescence, P53-mediated p21 accumulation acts as an early event in inhibiting cellular proliferation, while p16 levels reach maximum level at a later stage and are possibly independent from telomere shortening (Stein et al. 1999).

Conditions of persistent activation of the DDR without repair are caused by strong genotoxic stress such as ionizing radiation and chemical agents. These stresses can cause DNA double-strand breaks (DSB) across the genome and consequent induction of DDR signaling and p53 activation. After X-rays, a large fraction of exogenously induced persistent DDR markers is associated with telomeric DNA in a telomere length-independent fashion (Fumagalli et al. 2012). The accumulation of persistent damage at telomeres might be due to the irreparability of telomeric tracts, which is a consequence of their functions

in preventing chromosomal fusions. In contrast, heavy ions promotes a different type of DNA damage – two or more individual lesions within one or two helical turns of the DNA molecule – which is in some instances irreparable (Zhang et al. 2016).

Different types of chemicals used in cancer therapy are based on inducing mutations in target cells. Topoisomerase poisons, such as etoposide and doxorubicin, interfere with the activity of the topoisomerase enzymes, mostly leading to single- and double-strand breaks. Alkylating agents and platinum compounds cause generation of monofunctional DNA adducts and arrest of replication, leading to the formation of random-strand breaks. The senescence program that is activated upon genotoxic stress is commonly defined as "therapy-induced senescence" (TIS).

Consistent with its role as a tumor suppressor mechanism, senescence is also induced upon strong mitogenic signals. Expression of oncogenic *Ras* in primary human and rodent cells results in a permanent G1 arrest, mediated by p53 and p16, and in the induction of a phenotype indistinguishable from replicative senescence (Serrano et al. 1997). The cell-cycle arrest through DDR signaling is triggered by the production of reactive oxygen species (ROS) and aberrant DNA replication, which lead to persistent DSB (Lagouge et al. 2006). The aberrant expression of oncogenes is not the only mitogenic signal that can induce senescence. Indeed, prolonged exposure to interferon-β triggers a senescence program that involves p53 activation and DNA damage signaling, which is activated by the accumulation of ROS (Moiseeva et al. 2006).

Primary ROS, such as hydrogen peroxide and superoxide anion radical, are released from the reduction of oxygen during ATP synthesis from the mitochondria and can further react with metal ions or other reactive oxygen species and form secondary ROS, such as hydroxyl radical. These secondary ROS are highly unstable and can react with all kinds of macromolecules causing cellular damage (Correia-Melo and Passos 2015). Indeed, oxidative stress can induce telomere damage and activate DDR, which leads to senescence. Furthermore, it has been shown that telomeric DNA is more sensitive to oxidative stress, since guanine rich regions are more susceptible to oxidative modifications. The role of ROS in telomere damage and senescence has been confirmed by the increased life-span in cell cultures when ROS have been decreased by the addition of antioxidants, reactive oxygen scavengers, and low ambient oxygen concentration (Correia-Melo and Passos 2015).

ROS levels increase in senescent cells as a result of signaling through p21-MAPK14 and TGFβ pathway, which causes further DNA damage induction and DDR, creating a persistent feedback loop (Passos et al. 2010). High oxygen concentrations promote accumulation of p21 but not of p16, possibly in a Reactive Oxygen Species (ROS)-dependent manner (Passos et al. 2010). In contrast, conditions of hypoxia seem to favor the induction of p16 (Zygmunt et al. 2002). Additionally, recent reports indicate that mitochondrial perturbations can induce senescence beyond production of free radicals. For example, inhibition of the ETC complexes I, II, or III by rotenone, 2-thenoyltrifluoroacetone, or antimycin A, respectively, activates senescence (Wiley et al. 2016).

A less-explored inducer of cellular senescence is represented by epigenetics perturbations. Indeed, changes in chromatin organization can trigger the senescence response, although the mechanisms are not well understood. A potential explanation relies on a p16-dependent and p53- and telomere-independent activation of a senescent state in response to disruption of heterochromatin by chromatin relaxation mechanisms, partly mediated by histone deacetylase agents (Munro et al. 2004). An alternative explanation relies on the indirect activation of DDR signaling: Deacetylase inhibitors, which induce senescence, can activate ATM and promote DDR signaling in the absence of actual DNA damage (Pazolli et al. 2012).

Phenotype of Senescent Cells

In addition to growth arrest, senescent cells exhibit a number of additional features. However,

none of these features is unique for the senescent phenotype, making the identification of senescent cells a challenging task, particularly in vivo (Hernandez-Segura et al. 2017). Senescent cells are metabolically active and characterized by accumulation of stress granules response, including lysosomes. Increased lysosomal content is associated to the activation of acidic β-galactosidase, a common marker to detect senescent cells in culture and in tissues which is not necessary to induce senescence (Dimri et al. 1995).

Senescent cells exhibit enlarged cellular size, flattening, larger nuclei, irregular nuclear envelope, and changes in the composition of the nuclear lamina and in chromosome condensation. At dysfunctional telomeres and at nontelomeric sites, senescent cells present DNA damage foci, such as γH2AX or 53BP1, which activate the (ATM)–p53–p21 signaling required for growth arrest (Nakamura et al. 2008). However, these foci do not constitute a specific marker because most cells can repair the DNA damage without undergoing senescence, and because the DDR signaling can be activated without actual DNA damage, as it occurs upon treatment with histone deacetylase inhibitors. Chromatin domains stained densely by DAPI and rich in H3K9me3 and HP1, possibly at silenced pro-proliferative genes, are also visible in senescent cells (Narita et al. 2003). However, SAHF are detected only in human cell culture and they have not been observed in tissues positive for p16 expression and possessing other features of cellular senescence (Kosar et al. 2011). The loss of lamin B1 is also observed in senescent cells, which has been found to be a key factor in chromatin reorganization during senescence, including dramatic changes in the distribution of trimethylation on histone H3 (Shah et al. 2013).

Gene expression profile during senescence is profoundly affected (Hernandez-Segura et al. 2017). For example, increased expression of p16 is a common marker to identify senescent cells in vivo and in vitro. This protein is generally absent in healthy young cells, but it becomes progressively upregulated with aging (Baker et al. 2016). Other important changes in gene expression, already mentioned before, correspond to the loss of lamin B1 and the activation of the p53 pathway (Serrano et al. 1997). Most senescent cells upregulate the transcription of a number of genes encoding for secreted proteins, known as senescence-associated secretory phenotype or SASP (Coppe et al. 2008). This secretory phenotype is transcriptionally activated by the DDR (Rodier et al. 2009), and cells that undergo senescence due to ectopic overexpression of p21 or p16, but without activation of DDR, do not develop a SASP (Coppe et al. 2011). The SASP is positively regulated by several proteins acting upstream in the DDR cascade such as ATM, NBS1, and CHK2 (Rodier et al. 2009). However, a main regulator of DDR, p53, has an inhibitory effect, and its inactivation in senescent cells causes hyperexpression of SASP (Coppe et al. 2008). The SASP is also regulated by NF-kB and C/EBP-β, which are transcription factors that modulate immune and inflammatory responses (Loaiza and Demaria 2016). Another transcription factor, GATA4, is stabilized to activate the transcription factor NF-κB, which initiates the SASP and facilitates progression to senescence (Kang et al. 2015). The SASP is composed of pro-inflammatory cytokines (e.g., IL-1α, IL-1β, IL-6, and IL-8), growth factors (e.g., HGF, TGFβ, and GM-CSF), chemokines (e.g., CXCL-1, -3, and -10), and matrix remodeling enzymes (e.g., MMPs). The diverse biochemical activities induced by the components of the SASP suggest that it constitutes a mechanism to communicate with other cells and to modulate the local microenvironment.

From Tumor Suppression to Tumor Promotion

Tumor Suppression

Cellular senescence is caused by several pro-tumorigenic stimuli, including proto-oncogenes, growth factors, and metabolic stress. A common feature of senescent cells induced by different stimuli is the activation of pathways which inhibit the cell cycle. Thus, cellular senescence acts as a potent tumor suppressive

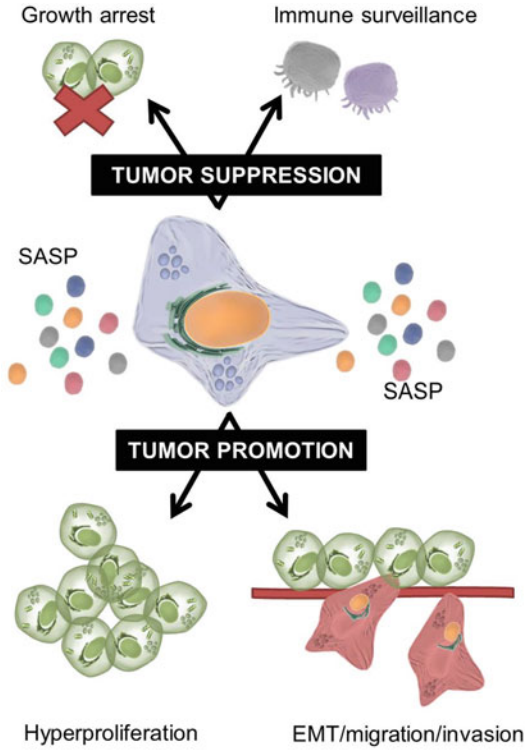

Fig. 1 Senescent cells (middle panel) can exert opposite functions during tumorigenesis. As tumor suppressors, they can inhibit growth and promote immune surveillance (top panel); as tumor promoters, they can enhance proliferation of surrounding cells and activate epithelial-to-mesenchymal transitions (EMT), favoring migration and invasion of cancer cells (bottom panel)

mechanism to prevent excessive and uncontrolled proliferation (Fig. 1). As described above, this oncosuppressive role is mainly dependent on two pathways: the p53 and the pRB/p16 pathways (Loaiza and Demaria 2016).

p53 activation is essential for the establishment of senescence. p53 is mainly induced in response to DNA damage by the kinases ATM and ATR, which are able to suppress the levels of the p53 inhibitors MDM2 and MDM4 (Stommel and Wahl 2004). Several genes are transcriptionally regulated by p53 and have been linked to the induction of senescence (Yasaei et al. 2013). However, one of the most established p53-target genes is p21, an inhibitor of the activity of cyclin-CDK2, CDK1, and CDK4/6 complexes.

p16 covers important roles for both initiation and maintenance of senescence. p16 binds to CDK4/6 and prevents its interaction with cyclin D (Serrano et al. 1993). This binding inhibits the phosphorylation of pRB and the nuclear localization of E2F (Stevaux and Dyson 2002), thus arresting the cell at the G1/S checkpoint of the cell cycle. p16 expression is repressed by the PRC complex and by specific epigenetic marks (Witcher and Emerson 2009), and induced by transcription factors, including PPAR-γ and ETS1 and ETS2 (Gan et al. 2008; Ohtani et al. 2001).

In support of the potent oncosuppressive role of cellular senescence, defects in either the p53 or p16 pathway greatly increase organismal susceptibility to cancer. Indeed, the majority of the human cancers harbor mutations of p53 and/or p16, while KO mice for either of the proteins develop cancer at a very early stage (Donehower et al. 1992; Sharpless et al. 2001).

In both human and mice, cells that express senescence markers are abundant in premalignant lesions but scarce in the cancers that eventually developed, including SA-βgal and DDR signaling (Collado et al. 2005).

Thus, cellular senescence restrains cancer by imposing a cell-autonomous block to the proliferation of oncogenically damaged/stressed cells (Loaiza and Demaria 2016).

In some tissues, reactivation of p53 induces senescence and tumor regression (Ventura et al. 2007; Xue et al. 2007), and a large number of small molecules to reestablish normal p53 functions has been developed for cancer treatment (Khoo et al. 2014).

The tumor regression observed after the reactivation of p53 is partially due to the inflammatory response induced by the secretory phenotype of senescent cells. SASP components elicit the recruitment and activation of immune cells, particularly NK and T cells, which can remove senescent, damaged, and/or potentially tumorigenic cells (Soto-Gamez and Demaria 2017). The SASP-mediated activation of the immune system might be an important player in premalignant lesions. Indeed, the secretion of chemokines and cytokines by senescent hepatocytes control

the premalignant niche through a $CD4^+$ T cell-mediated adaptive immune response that is defined as "senescence surveillance" (Kang et al. 2011).

Some of the SASP factors are also essential to maintain the senescence state and to propagate the senescence state to the surrounding cells.

During oncogene-induced senescence, the inflammatory signaling initiated by the cytokines IL-6 and IL-8 cover an essential role to maintain the growth arrest and the secretory phenotype (Kuilman et al. 2008). In addition to the autocrine mechanism, the SASP can transmit senescence to healthy cells. The insulin-like growth factor binding protein-7 (IGFBP-7) promotes both apoptosis and senescence in cells expressing the BRAF oncogene (BRAFV600E), via either autocrine or paracrine mechanisms (Wajapeyee et al. 2008). Moreover, the propagation of senescence can also be modulated by TGF-B family ligands and IL-1 signaling. Interestingly, this "secondary" senescence cannot further induce senescence via paracrine action, arguing in favor of a self-limiting process of senescent cells and the SASP (Acosta et al. 2013).

From Wound Healing to Tumor Promotion

Hyperproliferation is a well-defined feature of cancer cells, but it also covers an essential role for generating new tissue after damage. A well-defined tissue repair mechanism has been demonstrated in the skin. Skin wound healing is divided in four different phases: (1) hemostasis, responsible for blood clotting; (2) inflammation, which is responsible to clear out the tissue from damaged cells and pathogens, (3) proliferation, whose role is to synthesize new tissue, and (4) remodeling, when the tissue acquire its original functionality and composition. The proliferative phase begins with the formation of granulation tissue and new blood vessels, followed by re-epithelialization and wound contraction. It is not surprising that cellular senescence intervenes to limit the proliferation of the healing tissue in order to maintain homeostasis and prevent aberrant growth. Cellular senescence is activated during tissue repair by the induction of p16 and p53, similarly to the mechanisms that define tumor suppression (Demaria et al. 2014; Jun and Lau 2010; Krizhanovsky et al. 2008). Still little is known about how these pathways are engaged, but it has been suggested that the matricellular protein CCN1, which is rich in the damaged tissue environment, might promote senescence in a ROS-dependent fashion (Jun and Lau 2010). Tissue repair-induced senescent (TRIS) cells develop a secretory phenotype which is in part overlapping with the SASP associated with irradiated or oncogene-induced senescent (OIS) cells (Coppe et al. 2008; Demaria et al. 2014; Jun and Lau 2010; Krizhanovsky et al. 2008; Kuilman et al. 2008).

It is interesting to observe that these TRIS-associated factors can potentially promote cancer progression through non-cell autonomous mechanisms. PDGF-AA is a potent mitogenic factor for both normal and cancer cells and promotes angiogenesis stimulation of non-small cell lung carcinomas (Shikada et al. 2005), while different MMPs associated with TRIS cells can promote the progression of cancers of different origins (Egeblad and Werb 2002).

The apparent opposite role of the SASP in promoting both tissue repair and cancer progression is in accordance with observations that cellular behavior, signaling molecules, and gene expression are similarly regulated during wound healing and carcinogenesis. These similarities led Harold Dvorak in 1986 to define cancers as "wounds that do not heal." Since then, different studies addressed this definition, showing how qualitative differences in gene expression and divergence in the quantitative and temporal induction of secreted factors play a major role in defining repair and cancer.

One fascinating hypothesis is that the time of persistence of senescent cells in organs can partly contribute to tissue homeostasis through regulation of secreted factors. Indeed, TRIS cells appear to have a very fast kinetic of induction and clearance, at least in the skin (Demaria et al. 2014; Jun and Lau 2010), while senescent cells associated with aging and age-related pathologies have been

considered as chronically present (Loaiza and Demaria 2016).

Lack of in-depth information on the stresses and mechanisms driving senescence of both normal and cancerous cells at the organismal level constitutes a formidable barrier to advancing our insights into the relationship between cellular senescence and cancer through modeling in the mouse. Nevertheless, early animal studies have documented proof-of-principle for the idea that senescent cells have pro-tumorigenic properties (Fig. 1) (Krtolica et al. 2011). In these studies, co-transplantation of human epithelial cancer cell lines with senescent human fibroblasts was shown to accelerate tumor development in immune-compromised mice. Senescent cells demonstrated this tumor-promoting effect irrespective of whether the senescence-inducing DNA damage response originated from shortened telomeres, oxidative damage, or oncogenic Ras. It should be noted, however, that in these experiments, senescent cells and cancer cells were co-transplanted in a ratio of one to one, a ratio that is unlikely obtained in tumor microenvironments under physiological conditions. Thus, it will be interesting to explore the tumor-promoting properties of senescent cells at lower densities. Lui and Hornsby conducted similar co-transplantation experiments and found that the presence of a small molecule MMP inhibitor partially neutralizes the tumor-promoting effects of senescent cells (Liu and Hornsby 2007). The most straightforward interpretation is that MMPs secreted by senescent cells constitute a prominent tumor-promoting component of the SASP. This view is further supported by the identification of several additional pro-tumorigenic factors in the SASP, including VEGF, GRO-1, and factors that promote epithelial-to-mesenchymal transition such as IL-6 and IL-8 (Loaiza and Demaria 2016). The senescent secretome has been shown to play an important role in promoting liver and colorectal cancers (Pribluda et al. 2013; Yoshimoto et al. 2013).

The accumulation of senescent cells with age could potentially serve as a significant source of sustaining growth factors for tumor cells. Hence, the increased risk of incurring cancer with age could in part be a consequence of the increased number of SASP-expressing senescent cells during aging. However, despite increasing circumstantial and supporting evidence, the impact of senescent cells that accumulate naturally during aging has not yet been rigorously shown to promote late-life cancer progression in vivo.

Accumulation of Senescent Cells

Aging

As discussed in the previous section, the senescence program can contribute to either tumor suppression or tumor promotion. Since the most important single risk for tumorigenesis is age, a possible explanation is that the phenotype of senescent cells is determined by organismal aging. On one side, gene expression and epigenetic alterations that accompany aging can alter the normal senescence response, thus interfering with its anti-tumorigenic activity and increasing the risk of cancer. Thus, age-related deterioration of biological functions might lead to cellular and organismal changes that shift the senescence response from a tumor-suppressive to a tumor-promoting mechanism. For example, mutant H-Ras activation in mouse epidermis induced a differential outcome determined by age (Golomb et al. 2015): while the young skin responded with hyperplasia, the old skin developed dysplasia and gradual progression towards carcinoma. Importantly, old mice were characterized by exacerbated inflammation and excessive cellular senescence. The inflammatory response showed age-dependent increase of proinflammatory cytokines, but also activation of a strong anti-inflammatory Th2 response. Moreover, the expression of Pdl1, a ligand that promotes cancer immune evasion, was upregulated in the aged mice.

On the other side, senescent cells accumulate and persist in older organisms, and they seem to be detrimental for mammals, since they mediate aging features (Baker et al. 2011, 2016). The cause of their accumulation is not completely understood but might be due to the deterioration

of the immune system and/or to impaired DNA repair activity.

Tumor suppression by the senescent response involves cooperative interactions with the immune system, which is often responsible for the effective clearance of senescent cells. The importance of the cooperation between senescent cells and the immune system has also been shown in a liver fibrosis murine model, where natural killer cells preferentially kill senescent stellate cells in vitro and in vivo, thereby facilitating the resolution of fibrosis after acute tissue damage (Krizhanovsky et al. 2008). The progressive decline in tissue regenerative capacities during aging has been attributed mainly to degenerative changes in tissue-specific stem cells as well as in their niches and the systemic signals that regulate stem cell activity (Jones et al. 2014). However, ineffective immune clearance of senescent cells can partly explain the compromised capacity for tissue repair observed during aging. Another important observation for the role of the immune system for senescent cells clearance is evident in humans: immunocompromised patients, under immunosuppressive therapy or with an HIV infection, presented accumulation of senescent cells in the liver (Kang et al. 2011). A major problem with the generalization of the importance of immune-mediated clearance of senescent cells is that most studies focus specifically on the liver. Indeed, melanocytic nevi, clonal, and benign tumors of cutaneous melanocytes exhibit accumulation of senescent cells without immune response (Hoenicke and Zender 2012), suggesting that immune clearance of senescent cells is regulated in complex ways and might be more efficient in certain tissues than others, possibly due to differential expression of SASP components in specific cells. However, nevi typically remain in a growth-arrested state for decades and only rarely progress into malignancy, indicating that the immune system might not always be necessary to prevent cancer.

Age-related decline in cellular capacity to repair the DNA has been extensively studied in vivo and in vitro. Old cells express lower levels of DNA repair proteins and show lower efficiency and higher rate of errors (Gorbunova et al. 2007). Homologous recombination (HR), a highly accurate mechanism for DSB repair dependent on cell cycle, declines sharply with increasing replicative age in normal human fibroblast, showing up to 38-fold decrease in HR efficiency when comparing pre-senescent and young cells (Mao et al. 2012). HR is a repair mechanism dependent on cell cycle; therefore, senescent cells have an intrinsic limited DNA repair capacity as their cell-cycle arrest prevents DSB repair through HR, allowing repair only through nonhomologous end joining (NHEJ) pathway, which is a DSB repair mechanism more prone to error than HR, but independent of cell cycle. Remarkably, NHEJ pathway seems to be also altered during senescence. A study in senescent normal human fibroblasts showed a 4.5-fold decrease in NHEJ efficiency in pre-senescent and senescent cells compared with young cells, and the frequency of precise ligation was higher in young cells, whereas in old cells extended deletions were more frequently observed (Seluanov et al. 2004).

Upregulation of SIRT6 can contribute to improve the age-related decline in DNA repair mechanisms. SIRT6 has been found to be able to rescue the age-related decline in base excision repair. Specifically, SIRT6 reverted the decline of homologous recombination repair during replicative senescence (Mao et al. 2012). Therefore, pharmacological targeting of SIRT6 and other proteins may be an interesting approach to prevent the decline in genome maintenance and, consequently, reducing the amount of DNA damage and senescence that accumulate with age.

Cancer Treatments

Therapies for patients with advanced cancer generally include surgical tumor resection, intensive multimodal chemotherapy, radiation therapy, or a combination of these regimens. Because the tumor suppressive senescence growth arrest is so potent and essentially irreversible, regimens that induce tumor cells to senesce have been proposed as potential anticancer therapies (Nardella et al. 2011). This pro-senescence therapy approach has been developed and refined over the past few

years, and currently a number of compounds with senescence-inducing activities are in clinical trials. However, the induction of cellular senescence as an anticancer therapy strategy is complicated by the potential pro-tumorigenic properties of senescent cells and the SASP. Thus, the ability to harness the antitumor activity of the senescence growth arrest must be balanced against the tumor-promoting potential of the SASP.

Genotoxic and cytotoxic drugs act by non-specifically targeting proliferative cells through different mechanisms. The nonspecificity of these chemotherapies often leads to acute toxicities, which include immunosuppression, pain, fatigue, anemia, nausea, gastrointestinal distress, and hair loss. Moreover, clinical studies of cancer survivors treated during childhood suggest that chemotherapy causes a broad range of long-term side effects, similar to diseases associated with aging, including organ dysfunction, cognitive impairment, and secondary neoplasms (Hudson et al. 2013).

Many chemotherapeutic drugs induce diverse cellular states, including senescence, in the tumor microenvironment. Therapy-induced senescence (TIS) can stimulate immunosurveillance to eliminate tumor cells but can also be a source of chronic inflammation and drug resistance (Ewald et al. 2010). Indeed, a recent study showed that anthracycline treatment of breast cancer patients induces cellular senescence and a SASP in a p16-dependent and telomere-independent fashion (Sanoff et al. 2014). The SASP can potentially explain a number of adverse reactions to chemotherapy (Demaria et al. 2017).

PTEN, a key mediator of the AKT/PKB pathway, is one of the most commonly lost tumor suppressor genes in human tumors, particularly in prostate cancer. Loss of one copy of the PTEN gene strongly predisposes to cancer development (Di Cristofano et al. 1998), while complete PTEN loss can lead to a p53-dependent cellular senescence response (Chen et al. 2005). Therapeutic interventions that severely compromise PTEN activity or the AKT/PKB pathway can be an effective strategy to induce senescence in vivo. Importantly, PTEN-induced cellular senescence does not trigger a DNA damage response or hyperproliferative stage (Alimonti et al. 2010), which is typically induced by the activation of many oncogenes, and thus avoids induction of the SASP that can favor cancer progression.

Preclinical trials of pharmacological agents that activate the senescence-inducing p53/p21 pathway in cancer cells have been initiated. LY83583 (6-anilino-5,8-quinolinequinone), a pharmacological inducer of p21, can promote cellular senescence and inhibit tumor cell proliferation in cultured colorectal cancer cells (Lodygin et al. 2002). Small molecules, such as PRIMA-1 and MIRA-1, which can restore the function of mutated p53, can also promote tumor regression (Wiman 2010). Enhancing stability and/or activity of wildtype p53 by disrupting p53/Mdm2 (Hdm2) interaction has also been developed as a promising anticancer therapy (Nardella et al. 2011).

Tumor cells are thought to be dependent on one or more specific oncogene in order to maintain their malignant phenotypes. The inactivation of a single oncoprotein (e.g., Myc) in experimental mouse tumors can induce tumor-cell senescence and eventual regression of the tumors (Wu et al. 2007). Small molecules that downregulate Myc expression or target interactions between Myc and its obligatory partners (e.g., Max) are being developed as anticancer therapies.

Interfering with Senescent Cells

Senescent cells accumulate late in life, at sites of age-related pathologies or upon excessive genotoxic stress, and genetic interventions enabling the effective clearance of senescent cells in genetically engineered animal models is sufficient to delay a number of age-related phenotypes (Childs et al. 2017). Interfering with senescent cells may be beneficial for the overall health of the animal, and the development of specific interventions that target senescent cells may serve as a therapy to delay age-related tumorigenesis. This strategy can be achieved using three different approaches, but it is important to note that current drugs would not allow for long-term treatments due to intrinsic toxicities.

Selective Induction of Cell Death

"Senolytics" interventions (i.e., drugs that eliminate senescent cells) not only demonstrated the feasibility of extending healthspan, but also evidenced the alleviation of a wide range of preexistent age-related symptoms, including: improved cardiovascular function, reduced osteoporosis and frailty, enhanced adipogenesis, reduced lipotoxicity, increased insulin sensitivity, improved established vascular phenotypes associated with aging, and chronic hypercholesterolemia as well as radioprotection and rejuvenation of aged-tissue stem cells (Childs et al. 2017; Soto-Gamez and Demaria 2017).

Currently, a limited number of senolytic agents have been identified. 2-DG, a false substrate for the glycolytic metabolism, or bafilomycin A1, a specific inhibitor of the lysosomal V-ATPases, were sufficient to reduce the survival of chemotherapy-induced senescent cells and to improve survival of chemotherapy-treated mice bearing lymphomas (Dorr et al. 2013). However, this strategy has not been replicated in other systems or conditions.

Combination of dasatinib and quercetin-reduced senescent cells in fat and liver tissues of old mice, as well as in muscle and fat tissues of irradiated mice. Moreover, this combined treatment alleviated several age-related pathologies, such as impaired cardiovascular function and extended healthspan of the *Ercc1*$^{-/\Delta}$ progeroid mouse model, supporting the therapeutic potential of eliminating senescent cells at old age (Zhu et al. 2015). However, these findings have not been replicated by other laboratories.

The most promising senolytic agent is possibly ABT263, which targets both the antiapoptotic proteins BCL-xL and BCL-2, which has been shown to specifically induce senescent cells to apoptosis (Chang et al. 2016). The anti-senescence properties of ABT263 have been replicated in different other systems and by different laboratories. However, severe side effects associated to long-term treatments with ABT263 make the use of this compound into humans a challenge.

More recently, a peptide interfering with the interaction between p53 and Foxo4 has been shown able to kill senescent cells and improve a number of age-related diseases (Baar et al. 2017). Potential limitations for long-term treatments reside in the poor biodistribution of the peptides and the high risk of immune reactions.

Improvement of the Immune System

Another possible way of eliminating senescent cells is to increase the number and/or activity of immune cells that can selectively recognize and remove senescent cells. Indeed, natural killer (NK) cells and T cells trigger cytolytic responses on senescent cells (Krizhanovsky et al. 2008). Moreover, $CD4^+$ T cell-mediated adaptive immune response initiates an immune-dependent clearance of senescent cells termed senescence surveillance (Kang et al. 2011). The decline in immune function with age is consistent with the high number of senescent cells at old age (Loaiza and Demaria 2016), further supporting the idea that the immune system may limit the number of senescent cells through clearance of these cells. Hence, it may be worth developing a strategy that boosts the immune cells capable of specifically eliminating senescent cells.

Inhibition of the SASP

Decreasing the effect of the SASP may potentially be an alternative strategy to dampen the negative effects of long-lived senescent cells, particularly the pro-tumorigenic functions. NF-κB re-enforces the SASP response (Acosta et al. 2008), and interfering with NF-κB activity and/or targets can be an effective strategy to lower the SASP. An important activator of NF-κB and the SASP is interleukin 1 alpha (IL1A or IL-1α). Increased expression of plasma membrane-bound IL1A in senescent cells activates the plasma membrane bound IL-1 receptor in juxtacrine cells, resulting in upregulation of several transcripts associated with inflammation (Orjalo et al. 2009). IL1A blocking antibody or knockdown of IL1A by RNA interference diminished SASP expression in senescent cells (Orjalo et al. 2009). Compounds

that disrupt IL1A receptor signaling may serve as a strategy to dampen the SASP. Indeed, the glucocorticoids cortisol and corticosterone suppress IL1A signaling in senescent cells and decrease expression of the SASP components, but co-treatment with recombinant IL1A reestablishes the SASP (Laberge et al. 2012). Overexpressing the microRNA miR-146a/b, which knocks down the levels of the IL1A downstream target IRAK1 (also an upstream regulator of NFκB), resulted in decreased SASP expression (Bhaumik et al. 2009). Treatment with the mTOR inhibitor rapamycin also caused downregulation of IL6 and other SASP factors, partly due to suppressing translation of the membrane-bound IL1A (Laberge et al. 2015). Chronic resveratrol treatment also dampens the SASP (Pitozzi et al. 2013), likely through its ability to decrease IκB kinase activity, which leads to decreased IκBα phosphorylation and subsequent NF-κB activation. Other natural compounds, such as apigenin, wogonin, and kaempferol inhibit the SASP by blocking IκBζ expression and reducing NF-κB activity (Lim et al. 2015). Moreover, an increase in NF-κB transcriptional activity is sufficient to activate p38MAPK (Freund et al. 2011), and treatment with p38MAPK inhibitors dampens the SASP (Alimbetov et al. 2015). Other regulators of the SASP include p53, C/EBPβ, Sirt1, and NAD+/NADH redox balance. Functional loss of p53 protein exacerbates the SASP (Coppe et al. 2008). C/EBPβ is implicated in upregulating the SASP and may cooperate with IL-6 to amplify the SASP (Acosta et al. 2008; Kuilman et al. 2008). Sirt1 suppresses SASP expression through histone deacetylation at the promoter regions of SASP factors (Hayakawa et al. 2015), and resveratrol, a compound that activate Sirt1 (Howitz et al. 2003), is capable of dampening the SASP (Pitozzi et al. 2013).

Conclusion

Cellular senescence covers a fundamental tumor suppressive role and prevents the onset of cancer at earlier ages. Moreover, senescent cells are important for proper wound healing and promote tissue regeneration upon injury. However, age-related accumulation of senescent cells with the concomitant development of aberrant secretory phenotypes might promote tumorigenesis at different levels (Fig. 1). Thus, removal of senescent cells and reducing the SASP are being considered potential therapeutic strategies to delay the onset or reduce aggressiveness of tumors. Several drugs have already been identified that selectively target senescent cells but an important aspect remains to fully evaluate the potential toxic effects of such interventions. Proper testing of dosage and timing must be investigated to determine if these drugs would be an intriguing improvement of standard anticancer treatments.

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Immunosenescence and Cancer Immunotherapy at Old Age: Basics

6

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Abstract

Age is the single most important risk factor for cancer development. Of the many age-associated changes paralleling increased cancer incidence, those of the immune system may play a major role in waning defense against tumorigenesis. Thus, immunosenescence may contribute to the higher rate of occurrence of tumors in the elderly. However, exactly how these age-related changes in immunity translate to cancer development is not well defined and understood. With the dramatic recent successes of immunotherapy in some patients for some tumors, there is an increasing concern that immunosenescence may temper responses in older patients. Nonetheless, existing anecdotal data suggest that success rates and side effects of first-generation checkpoint blockade immunotherapy in elderly patients are similar to those in younger subjects. However, success rates are still low, with only a fraction of patients obtaining clinical benefit in most trials, and it cannot yet be excluded that age may play a role in the failure of some therapies in some patients. Thus, although there are no reasons to refuse the elderly these treatments, appropriate clinical trials and not just anecdotal evidence are required to explore this issue further.

Keywords

Immunosenescence · Cancer · Aging · Inflamm-aging · Immunotherapy · Immune checkpoint inhibitors · Adaptive immunity · Innate immunity

Introduction

The immune system evolved to resist many challenges to organismal integrity over the life-span. Eradicating pathogens without doing harm to the host is the most desirable outcome for the organism, but collateral damage and immune pathology may be severe not only in acute infections but also in persistent infections or other sources of chronic antigenic stimulation. Although controversial for many years, it is now incontrovertible that cancers fall into the latter category (Duan and Thomas 2016; Pawelec 2017). Cancer cells probably arise quite commonly over the entire lifetime (Anisimov 2009; Zhang et al. 2017), and the organism must therefore defend itself against these internal challenges. The most efficient protective mechanism is the apoptotic process following a program initiated by DNA damage and mutation responsible for carcinogenesis (Fumagalli et al. 2012). Failing this, cancer cells may be recognized by immune cells which target

them by cytolytic mechanisms such as perforin and granzyme B (Kim and Cantor 2014; Martínez-Lostao et al. 2015). However, there is currently a consensus that, as in defense against microorganisms, the immune system can have opposing roles in cancer and that immunopathology in this instance may manifest as tumor-promoting effects as well as antitumor responses. This depends partly on when the cancer arises and which dynamic relations exist between the immune response and the cancer. For example, as with chemotherapy, immune selection can result in the emergence of non-susceptible variants ("immunoediting") and may explain some of the balance between the cancer and the immune system (Dunn et al. 2004; Vesely et al. 2011; Jacqueline et al. 2016). This concept proposes that initially there is a successful immune-mediated elimination of cancer cells. If some cancer cells would be able to escape from this immune surveillance, there would arise an equilibrium between the cancer and the immune system, which will ultimately favor the selection of cancer cells which will be able to escape elimination. This step may last for decades. Finally, the tumor will physically escape the immune surveillance and manifest itself clinically with even a perversion of the immune system helping tumor growth (Vesely et al. 2011).

This scheme implies that at least initially, the cancer has a certain immunogenicity which permits the immune system to exert its full activity (Imai et al. 2000; Pardoll 2003). This suggests that immune cells, mainly T cells, may sense the new antigens, even if they are weak, released from the tumor cells after the death of some of them due to chaotic growth and vascularization, or innate immune cell-mediated lysis, and presented by dendritic cells (DCs) (Chen and Mellman 2013). The tumor cells are fundamentally self-cells of the organism transformed as a result of genetic mutations. However, most mutations fail to give rise to peptides recognized by the immune system, and those that can be recognized may be tolerogenic depending on the circumstances of their presentation. These antigens thus behave as very weak stimuli, and the organism is not always able to eradicate the cancer cells carrying them, or the immune system is not able to detect them or react to them (Pardoll 2003; Pawelec 2017).

Nonetheless, it is likely that the major antitumor protective mechanisms that the immune system uses to eradicate cancerous cells are the T lymphocytes (Vesely et al. 2011; Martínez-Lostao et al. 2015). These cells are specialized to be able to respond to many specific antigens potentially including those presented by cancer cells. T cells are subdivided into two basic subsets expressing $CD4^+$ or $CD8^+$ coreceptors. The $CD4^+$ T cells are predominantly known as "helper T cells" interacting with other immune cells including B cells, macrophages, and $CD8^+$ T cells to facilitate their differentiation into antibody-producing cells or cytotoxic cells (Chaplin 2010). $CD4^+$ T cells recognize antigens presented by antigen-presenting cells such as DCs in the context of self-MHC II class molecules to initiate $CD4^+$ T-cell activation (Petrova et al. 2012). They are also further specialized into functional subtypes such Th1 (which primarily secrete pro-inflammatory cytokines), Th2 (for anti-inflammatory cytokine production and promotion of antibody production by B cells), and Th17 (pro-inflammatory and autoimmunity supporting) as well as several others (Chaplin 2010; Zhu et al. 2010). Th1 cells, characterized by their expression of the transcription factor Tbet, exert anticancer effects by inhibiting angiogenesis and recruiting actively cytotoxic $CD8^+$ T cells and natural killer (NK) cells (Haabeth et al. 2011; Kouidhi et al. 2017). The Th2 cells are thought to contribute much less to anticancer immunity. Th17 on the other hand may also actively contribute to tumor immunity by the secretion of cytokines Th17 and IL-21 as well as by activating effector $CD8^+$ T cells (Shapiro et al. 2016). The transcription factor RORγt has been identified as the master regulator of polarization of helper T cells toward the Th17 pathway (Ivanov et al. 2006; Guéry and Hugues 2015). Tregs are immune regulatory $CD4^+$T cells which suppress specific immune reactions, such as autoimmune processes, and thus favor cancer escape (Adeegbe and Nishikawa 2013). $CD8^+$ T cells are effector cytotoxic T cells able to kill cancer cells; they are commonly found infiltrating tumors

(tumor-infiltrating T cells or TILs) (Frey 2017; Barnes and Amir 2017). Natural killer cells are also able to destroy cancer cells mainly if they have escaped $CD8^+$ T-cell recognition by down-regulating HLA class I at their surface (Vacca et al. 2016). There are also some occasions when the production of antibodies is required for anticancer immunity involving B cells.

Therefore, the organism needs a functional immune system to resist and control cancer. Boosting immunity therapeutically by immune modulatory treatments (a form of immunotherapy) has recently resulted in a groundbreaking change in the way oncologists approach cancer therapy. Enormous strides in the development of immunotherapy over the last 10 years have not only revolutionized cancer treatment but also led to a better understanding of cancer/immune response interactions (Moynihan and Irvine 2017; Lowry and Zehring 2017; Galati and Zanotta 2017; Melssen and Slingluff Jr. 2017).

However, although clinical trials of immunotherapies may include patients of advanced age, the specific question of whether elderly people behave in the same manner as younger patients has not been put to the test in purposeful clinical trials (Johnson et al. 2017; Elias et al. 2017; Daste et al. 2017). Immunotherapy is of particular interest for the elderly because most clinically meaningful solid cancers arise in older people (Yang et al. 2012; Forman et al. 2013). It is commonly assumed that immune changes with age favor the development of cancers, but data supporting this contention are sparse (Fulop et al. 2013a; Turner and Brum 2017). Indeed, whether immunosenescence may play a role in the emergence of cancer with age is now a crucial question in the light of the marked success of immunomodulatory therapies mostly recorded in younger patients.

Cancer and Aging

Age is considered the single most significant risk factor for many chronic conditions including the majority of common malignancies (Anisimov 2009). Cancer incidence and prevalence increase with advancing age (Saavedra et al. 2017), and around 50% of all cancers are diagnosed in patients over 65 years old (Zhang et al. 2017). Several factors influence this increase, related both to the entire organism and the particular cancer. During aging, there is an increase in oxidative stress, implying that free radical production is increasing and antioxidative defenses are decreasing (Vina et al. 2013; Bauer and de La Fuente 2016). Among other changes, this is a consequence of mitochondrial dysfunctionality (Ristow and Schmeisser 2014; Gonzalez-Freire et al. 2015). With aging, there is a decrease in mitophagy, resulting in failure to eliminate defective mitochondria and more uncontrolled free radical production, leading to mutations and genomic instability (Park and Larsson 2011). This directly favors the emergence of a neoplastic cell.

It has been proposed that a mechanism for avoiding the emergence of malignancy is the phenomenon of replicative cell senescence, as first described by Hayflick (Hayflick and Moorhead 1961). However, senescent cells are metabolically active, presenting a different pattern of cytokine and chemokine secretion known as the "senescence-associated secretory phenotype" (SASP) (Coppé et al. 2008; Rao and Jackson 2016). They produce many pro-inflammatory factors which can favor the occurrence of chronic inflammation preparing a favorable soil for tumorigenesis (Coppé et al. 2008; Childs et al. 2015). Thus, like immunity, cell senescence as a defense mechanism against cancer is a two-edged sword; both mechanisms converge on the question of inflammation (Capece et al. 2017).

Older people tend to manifest a slightly higher basal level of pro-inflammatory serum factors, such as IL 6, thought to contribute to tissue damage and possibly to promote cancer (Minciullo et al. 2016; Setrerrahmane and Xu 2017). There are several pathways contributing to this low-grade inflammation in an aging organism, which can also contribute via several pathways to cancer development. This low-grade inflammation is maintained at least partially by an imbalance between the innate and the adaptive immune system, with the innate arm being overactive (Franceschi et al. 2000, 2007). Chronic antigenic stress from persistent infections, but also from cancer itself, also contributes to this state

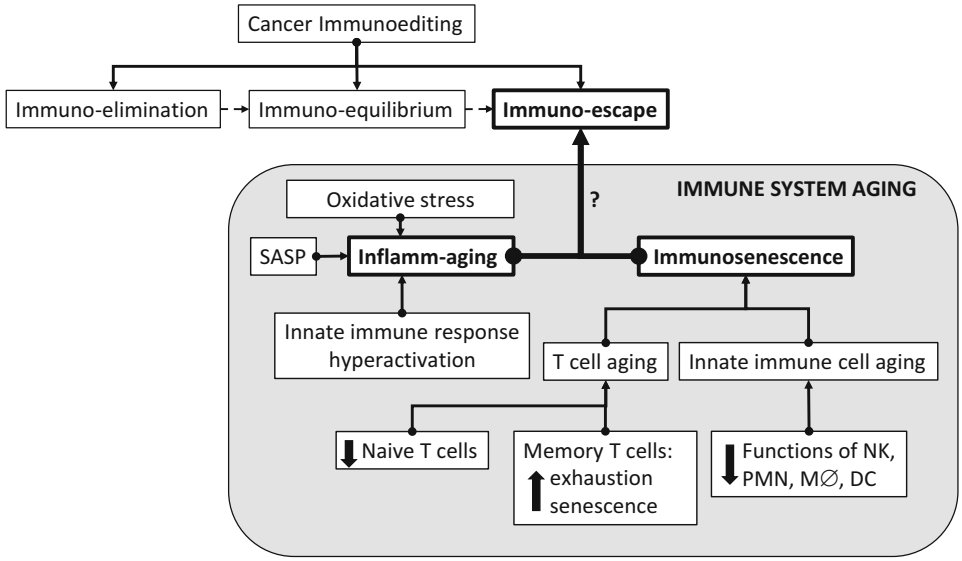

Fig. 1 Concept of the cancer immunosurveillance concept and the putative role of immunosenescence in the increase of tumorigenesis with aging. Initially, the immune system controls tumorigenesis. Cancer-immune system interactions may maintain an equilibrium over decades. Finally, the tumor may become clinically manifest because of immune escape. Immunosenescence and inflamm-aging may contribute to immune escape. *SASP* senescence-associated secretory phenotype

dubbed "inflamm-aging" (Chidrawar et al. 2009; Pawelec 2012; Fougère et al. 2017). It is not known with certitude what is the exact contribution of low-grade inflammation to cancer development with age, but certainly it may contribute by the SASP, the free radical productions, and the shift in immunometabolism (Turner and Brum 2017) (Fig. 1).

It may be the case that chronic infections, particularly by viruses, also contribute to the occurrence of certain cancers, indirectly via the SASP or more directly. Thus, with aging the occurrence of chronic persistent viral infections is increasing and probably either by the induction of chronic inflammation such as in the case of cytomegalovirus (CMV) or by themselves may contribute through oncogenic transformation such as in glioblastoma (Ferguson et al. 2016). Lifelong environmental challenges, such as UV exposure, air pollution, etc., may also be contributing factors. Although it is well established that the incidence of cancer increases with age, coinciding with a decline in immune competence, many other factors, including physical activity level, body composition, and diet, which also change with aging, likely interact (Anisimov 2009).

Finally, one can assume that as mentioned earlier, if the immune response plays a role in cancer immune surveillance, any immune changes occurring with aging (immunosenescence) may to some extent contribute to the increased cancer emergence with aging (Fig. 1). But is there really any evidence for this hypothesis, often assumed to be true in the literature but commonly unsupported by any data?

Immunosenescence and Aging: Does Immunosenescence Matter for Tumorigenesis?

As outlined above, immunity most likely plays a major role in controlling cancer. We also note that many processes contribute to the development of cancer over the life-span. So, what could be the contribution of immunosenescence if any to cancer development?

With aging, many changes have been reported, especially in the adaptive immune system (although these are mostly differences between younger and older individuals, because cross-sectional studies cannot reveal actual changes).

In particular, and reproducibly found in essentially every published study, there is a decrease in the number of naïve $CD8^+$ T cells ($CD45RA^+$, $CD27^+$, $CD28^+$, $CCR7^+$) in the peripheral blood because they have responded to cognate antigen at some point in the individual's life and have differentiated to memory cells (Fulop et al. 2013b; Goronzy et al. 2015; Yanes et al. 2017; Pawelec 2012). Moreover, because of thymic involution at puberty and acute and chronic antigenic stress over the lifetime, as well as age-associated hematopoietic stem cell insufficiency (Denkinger et al. 2015), recent thymic emigrants of new naïve cells are vanishingly rare in the elderly. Hematopoietic stem cells produce less lymphocytes because of the alterations induced by free radicals in their DNA and the decreased production of IL-7 (Hirokawa and Utsuyama 1989; Gruver et al. 2007) shifting the balance toward myelopoiesis. However, there is still a debate on whether the remaining naïve T cells arising either from the thymus or by homeostatic proliferation possess enough TCR repertoire diversity to be able to confront new and emerging antigens, such as new pathogens but also neoantigens from cancers (Appay and Sauce 2014; Goronzy et al. 2015; Pawelec 2017). Recent data suggest a shrunken but not absent TCR repertoire, so it may not be stochastic as to whether a patient can by chance respond to their tumor neoantigens and be protected (Nguyen et al. 2018). Furthermore, it is worth noting that the general decrease of thymic output may be a normal part of the immune adaptation/remodeling during aging, reducing the energy needed to maintain such a system and reducing the errors that might contribute to autoimmune diseases which also increase in the elderly.

Commonly, but not always, parallel to the decreased number of naïve CD8+ T cells, the number of late- and terminally differentiated memory T cells in the effector memory (EM) and TEMRA compartments increases with age (Larbi and Fulop 2014). This is mostly the consequence of chronic immune stimulation either through intrinsic or extrinsic antigens. The most important of these is the cytomegalovirus (Pawelec 2014). These late-stage memory cells are still functional, and some at least may share properties reminiscent of replicatively senescent cells (Effros 2003; Xu and Larbi 2017). These cells should be distinguished from the exhausted T cells arising also from continuous stimulation but not being terminally differentiated and bearing different surface markers (Wherry and Ahmed 2004; Wherry and Kurachi 2015). There is still debate in the aging field as whether all cells in memory compartments are fixed as "senescent" or "exhausted" or whether there is some plasticity in the system (Akbar and Henson 2011; Henson et al. 2015). Whatever the case, the proportions of these cells are increasing significantly with aging (Fulop et al. 2013b).

T-cell exhaustion defines a state of T-cell dysfunction emerging during many chronic infections and cancer (Wherry and Kurachi 2015). It is indicated by poor effector function, sustained expression of inhibitory receptors, and a transcriptional state different from that of functional effector or memory T cells. Chronic exposure to cognate antigen can upregulate PD-1 expression, and PD-1 can, by interacting with its ligand PD-L1, lead to the development of an exhausted T-cell phenotype, characterized by a hierarchical loss of proliferation and cytolytic activity, followed by defects in cytokine production, and eventually deletion (Zarour 2016; Catakovic et al. 2017). As noted above, the boundary between advanced differentiation states and senescence is unclear and its importance therefore hard to determine. CD8+ T cells that may most resemble replicative senescence are characterized by the phenotype $CD28^-$, $CD57^+$, Kand $LRG\text{-}1^+$, have shortened telomeres and increased p38 expression, may be nondividing or require certain special conditions for triggering cell division, and are able to secrete pro-inflammatory cytokines; many also retain significant cytotoxicity toward, e.g., CMV (Larbi and Fulop 2014; Henson et al. 2015; Xu and Larbi 2017). These are late-stage differentiated memory CD8+ T cells; some of which may indeed be senescent, but many of which are possibly retained in a non-proliferative state to preserve their effector function, which is necessary to protect the organism. A minority of these may be actively pathological in that they contain granzymes but not perforin and may

cause granzymopathy and inflammation when the release of the enzyme is triggered (McElhaney et al. 2012).

The other main T-cell subset, the $CD4^+$ T cells, is also essential for optimal antitumor immunity, as mentioned above. With aging the main change is the higher expression of the negative costimulatory receptor CTLA-4 and the concomitant decrease of CD28 expression. Together these changes lead to the decrease of their clonal expansion and function via changes in immunometabolism and signaling pathways. CD40 expression is also decreased. All these changes ultimately lead to their decreased ability to further the activation of $CD8^+$ T cells, instrumental for anticancer immunity.

In this context, it is of note that cancer cells may present two types of antigens to T cells. One type that has attracted a great deal of attention recently is a new antigen arising from mutations, at least some of which may be drivers of oncogenesis and necessary for continued carcinogenesis (Chen and Mellman 2013). These are individual tumor- and patient-specific. Additionally, cancer cells progressively accumulate multiple genetic and epigenetic alterations leading to the expression of numerous such neoantigens (Arlen 2017). The other main category of tumor antigens is shared between cancers of the same type as a result of tissue dedifferentiation or is lineage-specific (Pawelec 2017). This latter may already be present before the clinical manifestation of the cancer and has consequently elicited immune reactions and immune memory. Such memory responses may be better preserved with aging than responses to neoantigens which require the presence of naïve CD8+ T cells. These differences may be successfully exploited during the future design of age-specific immunotherapies (Hurez et al. 2017).

Following antigen recognition, even by memory cells, proliferation leading to clonal expansion is required in order to generate and maintain ongoing responses. However, proliferative capacity is in general decreased with aging (Douziech et al. 2002). This is mainly due to the decreased signaling pathways occurring through the entire signaling machinery starting from the early signaling, such as tyrosine phosphorylation of Lck, eventually leading to the translocation of transcription factors such as NFAT (Larbi et al. 2006). There are not only changes in the feed forward signaling but also in feedback signaling (Le Page et al. 2014). At some steps of the signaling pathway, the inhibitory signals will have proven more powerful than the activation signals, and the cascade will be blocked (Li et al. 2012). There are also changes in the lipid rafts, presently referred to as nanoclusters, in terms of lipid composition and function (Fulop et al. 2014; Schamel et al. 2017). There are increases in the cholesterol content of the membrane rendering it more rigid and the coalescence of the nanoclusters more difficult. This renders immune synapse formation more difficult, leading to the signal transduction changes discussed above (Larbi et al. 2006).

The characteristics of immunometabolism are a very important aspect of T-cell function which change with age and influence T-cell differentiation which is also changing with aging (Weyand and Goronzy 2016). For T-cell clonal expansion, vigorous proliferation requires nutrients such as glucose, lipids, and proteins. T lymphocytes must sense these nutrients and adapt their metabolism to their availability. In the quiescent state, the T cells use oxidative phosphorylation (OxPhos) to produce energy in the most efficient way (Michalek and Rathmell 2010)). However, when T cells are activated, they switch to aerobic glycolysis (Warburg effects) resulting in anabolism leading to biomass production for rapid proliferation (MacIver et al. 2013; Liu et al. 2014; Peng et al. 2016; Kouidhi et al. 2017). The master regulators of these metabolic changes are PI3K, Akt, and mTOR complex signaling pathways (Hahn-Windgassen et al. 2005). There are several intermediates which are specific for the various nutrients such as AMPK, SREBP, or the p70S6 kinase. Together these changes converge on the promotion of greater nutrient utilization (glycolysis and amino acids: glutaminolysis) to facilitate T-cell activation and proliferation (Bettonville et al. 2016). These metabolic changes are needed for an effective Th1 response and antitumor immunity (Jiang and Yan 2016). It is of note that T cells and cancer cells both use aerobic glycolysis for ATP production. Thus, immunometabolism

is different in naïve and effector cells as a result of their adaptation to their functional requirements.

Compared to naïve and effector T cells, memory T cells have increased mitochondrial mass and mitochondrial respiratory capacity to spare (van der Windt et al. 2012), leading to their possession of the maximal respiratory capacity available for a living cell. These cells can very rapidly generate the necessary ATP by relying on lipid catabolism, using so-called β-oxidation (FAO), needed for their long-term survival (Pearce et al. 2009). The fatty acids originate from intracellular lipolysis either by autophagy or by metabolizing lipids such as LDL or VLDL. The master receptor in the transformation of effector cells to memory cells is TRAF6 and AMPK for their maintenance through lipolysis (Rolf et al. 2013).

Important means of tumor escape from immunosurveillance increasing with age may be represented by the "exhaustion" of chronically antigen-stimulated T cells as mentioned above (Wherry and Kurachi 2015). Exhausted $CD8^+$ T cells exhibit more marked upregulation of several inhibitory receptors at the cell surface relative to functional memory or senescent $CD8^+$ T cells. These markers include PD-1, CTLA-4, LAG-3, and TIM-3, which suppress the activation of T cells (Hoffmann et al. 2016). It should be stressed that these cells are neither terminally differentiated nor senescent, and by modulating these receptors, anticancer activities may be restored (Topalian 2017). They use the same metabolic pathways as memory cells, depending on PD-1-mediated lipolysis and FAO (Kouidhi et al. 2017). It is of note that CTLA-4 does not modify cell metabolism but rather influences the genes involved in cell cycle control and signal transduction such as the NFAT and JAK-STAT pathways (Jiang and Yan 2016; Ok and Young 2017). The frequency of these cells is generally found to be increased with age (Pera et al. 2015). There are differences in their metabolic pathways, emphasizing the possibility that this may further impair efficient proliferation (Bettonville et al. 2016). Moreover, these metabolic pathways also govern T-cell differentiation, possibly contributing to the perceived shift away from Th1 responses toward Th2 cells and Tregs with increasing age. The latter are mostly $CD4^+CD25^+$ T cells expressing the transcription factor Foxp3, which confers immunosuppressive function (Nishikawa and Sakaguchi 2010). The higher expression of CTLA-4 on stimulated $CD4^+$ T cells also shifts T cells toward Tregs with a different immunometabolism (Bryl et al. 2001; Kouidhi et al. 2017). Although somewhat controversial, as mentioned above, the numbers and functions of Tregs do seem to increase with age (van der Geest et al. 2014; Raynor et al. 2012; Gregg et al. 2005). It is likely that Tregs are pro-tumorigenic by suppressing the cognate immune response (Nishikawa and Sakaguchi 2010). Hence, age-related differences in Tregs may favor cancer development.

Immune changes with aging also affect the innate immune system (Solana et al. 2012). There is a potentially interesting paradox that a certain type of immune paralysis for most of the innate immune cell functions proceeds together with a concomitant hyperactivation (Fulop et al. 2016). The former manifests by decreased chemotactic, phagocytic, and free radical-producing activity (Fulop et al. 2004), while the latter signifies the overproduction of pro-inflammatory cytokines. These changes mainly affect neutrophils and monocyte/macrophages (Molony et al. 2017; Albright et al. 2016). Moreover, increased CD14+/CD16+ pro-inflammatory nonclassical monocyte populations, and macrophage phenotypes, are shifted toward inflammatory phenotypes (Metcalf et al. 2015; Hazeldine and Lord 2015). Molecules originating from the tumor are sensed as danger-associated molecular patterns (DAMPs) via the pattern recognition receptors expressed by several innate immune cells. These activate macrophages and DCs through TLRs and inflammasome signaling (Agrawal et al. 2017). With age, commonly global impairments are seen in pattern recognition receptor signaling through a reduction in toll-like receptor (TLR) expression and in TLR-induced pro-inflammatory cytokine production (Nyugen et al. 2010; Bandaranayake and Shaw 2016). This could lead to lower activation of adaptive immune responses (e.g., through lower secretion of inflammatory cytokines) and hence anticancer responses.

NK cells also manifest lower cytotoxic activity on per-cell basis than their younger counterparts. The expression of NK-activating and inhibitory receptors is also changed with age (Tarazona et al. 2015), mainly the former, such as NKp30 and NKp46, which are decreased (Manser and Uhrberg 2016). Antigen presentation is also decreased mainly due to altered immune proteasome activity, part of the general intracellular proteodynamic changes with aging (Johnston-Carey et al. 2015). At the same time, pro-inflammatory cytokines produced by DCs are increased (Agrawal et al. 2017). These changes are part of the general inflamm-aging process occurring with aging (Franceschi et al. 2000, 2017). This can play a very important role in maintaining immune alertness but also to decrease its efficiency against the invaders.

So, do these changes with aging indeed contribute to the emergence of cancers over the lifetime? Certainly, they may (Fulop et al. 2011). On the one hand, there is the potential problem that there may not be enough naïve cells to recognize all the newly emerging cancer neoantigens or that even if they can recognize them, they cannot proliferate and generate sufficient functional T cells to be able to eradicate them. Additionally, there could also be competition between the tumor and the activated T cells for nutrients which would further reduce T-cell proliferative capacity and differentiation into effector T cells. Different metabolites such as indoleamine 2,3-dioxygenase (IDO) or arginase-1 produced by cancer cells may also further impair the ability of T cells to combat cancer in the elderly (Chang et al. 2001; Eleftheriadis et al. 2014). Furthermore, the inflammatory environment also favors the development of cancers; it facilitates carcinogenesis by triggering initial genetic mutations or via epigenetic mechanisms. It also promotes cancer progression and metastasis, also by impairing T-cell activation as well as increasing the development of myeloid-derived suppressor cells (MDSC) which are increased with age (Verschoor et al. 2013). Finally, the cytotoxic activities of phagocytic cells are also compromised, which may further contribute to the emergence of cancer cells.

Nonetheless, the debate is not yet completely over as to whether these differences are really contributing to negative outcomes or whether they are just "innocent bystanders." The naïve repertoire may still be sufficiently diverse in some patients, such that the low numbers of naïve cells would not necessarily contribute extensively to tumorigenesis. For example, the fact that there is a plateau in the cancer development after the age of 90 appears to militate also against the common belief that immunosenescence contributes substantially to tumorigenesis. However, this may simply be the result of selection against the great majority of people who do not attain such an advanced age. Conceptually, there remains the basic question of whether immunosenescence precedes, is concomitant with, or is the consequence of the nascent cancer.

Some of these issues may be resolved by longitudinal follow-up of immunosenescence biomarkers to explore association with the development of cancer. However, only a few studies have sought such associations and have failed to find anything significant (Turner and Brum 2017) except for some anecdotal data such as IgA in saliva (Phillips et al. 2015). Other circumstantial evidence may come from cross-sectional studies of the associations of potential immunosenescence markers with clinical outcome. Most studies in this context showed that certain cellular marker constellations, such as $CD4^{+}CD28^{-}CD57^{+}$ or $CD8^{+}CD28^{-}CD57^{+}$, were associated with poorer prognosis in some cancers such as lung cancer (Fornara et al. 2015). Other markers indicated certain differences depending on the timing of blood sampling and the stage of disease, which then become extremely important for interpreting these data. It is also known that cancer treatment may induce potentially senescent T cells expressing, for example, $p16^{INK4a}$ (Demaria et al. 2017). However, besides these markers recent research has indicated that the capacity of peripheral blood T cells to recognize and respond to tumor-associated antigens is a better predictor of survival in several malignancies, including breast cancer, colon cancer, and melanoma. This suggests that the dynamic measurement of T-cell functions is a better biomarker for assessing anticancer

immunity and its outcome even in elderly subjects (Bailur et al. 2015).

So, considering the above issues, it can be postulated that elderly patients may also benefit from immunotherapy, which can be conceptualized as an intervention at any level of the immune response that reinforces the body's immune capacity to combat cancer.

What Are the Currently Used Immunotherapies, and How Might Immunosenescence Impact on Their Success?

Immunotherapies are very diversified and when possible can also often be used in combination and/or together with traditional chemo- and radiotherapy (Hurez et al. 2017). They can be specific to one cell type or may target surface molecules or intracellular molecular mechanisms. Some of them are already in clinical use; the others are experimental. In any case our immunotherapeutic arsenal is constantly increasing as we learn more about how interactions between the cancer and the immune system progress.

Regulatory T Cells (Treg)

Tregs play a major role in the induction of anticancer T-cell dysfunction. Thus, targeting either their functions or their number may be an efficient way to reinvigorate helper and cytotoxic T cells to combat cancer. As mentioned above, age-associated changes to Treg function or number is not clearly defined, although most data support their increase with aging (van der Geest et al. 2014; Raynor et al. 2012; Gregg et al. 2005). However, concomitantly, it was also shown that IL-10 production by Tregs from the elderly is decreased. This was shown in mice using an anti-CD25 antibody, but no data support the use of anti-Treg treatment for cancer in elderly (Hurez et al. 2017). The Foxp3 protein is stabilized by acetylation by HDAC9, promoting Treg development and preventing transcription of IL-2, a cytokine produced by $CD8^+$ T effector cells (Beier et al. 2012). Thus, the use of HDAC inhibitors may have beneficial effects on Treg decrease and could enhance anticancer therapies.

Innate Immunity

The targeting of innate immunity either by decreasing immune paralysis or by mitigating pro-inflammatory activity would be a very meaningful immunotherapeutic intervention, especially when combined with other interventions.

Antigen presentation by DC could be increased either in vivo or in vitro. If we would be able to efficiently present major as well as minor tumor antigens to T cells to boost their cytotoxic activity, this would be of major impact. CD40L or agonist anti-CD40 antibodies may boost DC activation (Khong et al. 2012). In the elderly, a vaccine using CD40L linked to specific antigens would have great clinical potential (Tang et al. 2009). In aging, most of the monocytes and macrophages exhibit pro-inflammatory phenotypes (M1) (Metcalf et al. 2015; Hazeldine and Lord 2015). However, there is a great plasticity between the pro-inflammatory and anti-inflammatory (M2) macrophage phenotypes (Mills et al. 2015). In the tumor environment, it seems that most of the tumor-associated macrophages (TAMs) are of M2 phenotype, favoring tumorigenesis. A paradox seems to exist between the circulating macrophages (M1) being able to combat cancer cells and those TAMs (M2) which seem to favor cancer survival. The most important factors secreted by TAMs are TGFβ and IL-10, which have immune suppressor activities, as well as growth factor activities, and as such favor tumorigenesis (Mantovani et al. 2008). Thus, targeting either transformation in the tumor environment of M2 macrophages to M1 which combat tumors, or the factors produced by them such as TGFβ, may become very interesting immunotherapies in the elderly (Geeraerts et al. 2017). Some tentative approaches using IL-12 or poly-(cysteine 5° to guanine: CpG) with anti-IL-10 receptor antibody with the aim of converting M2 to M1 macrophages have been be envisaged (Watkins et al. 2007). Recently, an antagonist of M-CSFR has been designed to block the transformation in the tumor

microenvironment of macrophages to M2 type (Pyonteck et al. 2013; Bonelli et al. 2018).

Like macrophages, neutrophils in the tumor environment may acquire an N2 phenotype, also favoring tumorigenesis (Hurt et al. 2017). N1 neutrophils are efficient at combating cancer, but with aging, there is not only a decrease in the tumor antagonist effector functions of neutrophils, but they become pro-inflammatory. So, the same intervention strategies would apply to neutrophils as for macrophages – but there are no such strategies as these cells are so short-lived that most investigators have not considered them likely to be a valuable target.

Finally, the innate system myeloid-derived suppressor cells have received a great deal of attention recently. These cells are essentially immature myeloid cells of neutrophilic or monocytic origin having immunosuppressive properties (Gabrilovich 2017; Sica and Strauss 2017). There are few data on their status in aging, but one report indicates that they are increased in the elderly (Verschoor et al. 2013). Certainly, they are increased in inflammatory diseases and in many cancers where they suppress antitumor immunity and represent a strong prognostic factor for survival (Sun et al. 2012; Azzaoui et al. 2016). MDSCs secrete factors such as IL-10 and arginases which suppress T-cell antitumor immunity (Marvel and Gabrilovich 2015). They promote the appearance and function of Tregs and also favor the maintenance of the M2 macrophage phenotype (Zhao et al. 2015; Gabrilovich 2017). MDSCs are very likely to make a major contribution to decreasing immune responses in aging and to inhibit antitumor immunity in the aging host (Flores et al. 2017). Thus, targeting these cells would be of the outmost importance (Shipp et al. 2016).

Adoptive Cell Transfers

There is again a great deal of interest in expanding tumor-specific T cells in vitro (e.g., TILs or chimeric antigen receptor (CAR)-bearing T cells) and then adoptively transferring them into patients. In the elderly, there is no report concerning specific CAR-T treatment, but if necessary functionally impaired geriatric CAR-T cells could be rescued supporting the possibility for a successful treatment in elderly in the future (Guha et al. 2017). The findings with active DC-based vaccines were seldom directly correlated to age, so it is difficult to draw direct conclusions on the efficacy of such an adoptive DC-based vaccine transfer. Studies in the future are needed to fill this therapeutic knowledge gap.

Recently, NK cells have also been reconsidered for adoptive immunotherapy, given the realization that cancer cells may escape CTL killing by downregulating HLA molecules, which should render them susceptible to natural killing (Tarazona et al. 2017). NK inhibitory receptors mainly recognize HLA class I molecules and prevent target cell killing. This is already exploited in the control of hematological malignancies after allogeneic stem cell transplantation when inhibitory receptors on NK cells are mismatched with recipient HLA molecules (Ruggeri et al. 2008). The NK cells are also used for adoptive immunotherapy. They are expanded outside of the organism and consequently transfused. This has many potential problems which are difficult to overcome such as the maintenance of the cytotoxic capacity in vivo.

A novel clinical approach is to exploit chimeric antigen receptor-transduced cell transfer. This involves engineering a modified T-cell receptor with (an MHC-unrestricted) antigen recognition portion from an antibody into T cells from the patient, expanding them in vitro and then transfusing them back into the patient (June et al. 2014; Glienke et al. 2015). Preliminary data are showing that the efficiency of CAR T cells from the peripheral T cells of elderly patients is decreased both in terms of decreased efficacy of their generation as well as in their effectiveness against cancer cells. A recent report described a manipulation which could restore effective functioning of CAR T cells in vitro from old T cells (Guha et al. 2017). This technique may hold promise in elderly patients mainly with the acute lymphoblastic leukemia (Huguet and Tavitian 2017). This technique has recently also been used to target NK cells against CD19 and CD20 in B-cell malignancies (Tarazona et al. 2017).

mTOR Inhibitors

Inhibition of mTOR has been shown to increase longevity in mice. Thus, the idea emerged that rapamycin can be used as an antiaging drug (Roth and Ingram 2016). mTOR is also a very important pathway for T-cell immunometabolism as well as for differentiation, and mTOR suppression favors the development of Tregs. Nonetheless, in the clinical setting, the use of a very low-dose mTOR inhibitor rapamycin can boost antitumor immunity (Pedicord et al. 2015). It seems that rapamycin can reduce PD-1 expression on T cells through the modulation of FOXO1 and as such increase T-cell functions. Thus, mTOR inhibitors may increase antitumor T-cell immunity. However due to their numerous side effects, it is unlikely that they will become major adjuncts to immunotherapy in elderly people.

TLR Agonists

TLRs are important pathogen-associated molecular pattern (PAMP) recognition receptors (Satoh and Akira 2016). These receptors, via their signaling pathways, by their by-products may influence the adaptive immune system (Mikulandra et al. 2017). An early effective immunotherapy approach exploited TLR ligation in bladder cancer by bacille Calmette-Guérin (BCG), an attenuated *Mycobacterium bovis* preparation. This treatment clearly increases survival but mainly in people less than 75 years of age (Margel et al. 2011). The exact mechanism of action of this treatment is not known, but increased innate immune responses are likely to be responsible. So, this is an FDA-approved immunotherapy treatment for bladder cancer in elderly individuals.

Immune Checkpoint Inhibitors (ICI)

Following activation, PD-1, a member of the Ig superfamily, transmits inhibitory signals that abrogate T-cell receptor (TCR)-mediated activating signals and downregulate T-cell activation. Ligands of PD-1 include PD-L2, which is primarily expressed on APCs, and PD-L1, expressed on many types of cells including tumor cells, immune cells, epithelial cells, and endothelial cells (Hato et al. 2016; Zou et al. 2016).

A recent breakthrough in immunotherapy is the recognition that exhausted T cells expressing either programmed cell death 1 (PD1, CD279), programmed cell death ligand 1 (PD-L1), or cytotoxic T-lymphocyte antigen 4 CTLA-4 (CD152) or both can be functionally reactivated. These inhibitory coreceptors can be blocked by antibodies designated "checkpoint inhibitors" (Pardoll 2012; Sharma and Allison 2015). These antibodies block the negative signals initiated by these receptors resulting in decreased T-cell killing functions to eliminate cancer cells. The number of these inhibitory receptors on T cells has been shown to increase with age contributing also to their decreased proliferation (Channappanavar et al. 2009). This might explain why data from pivotal studies is discordant, with less efficacy in older versus younger patients for some cancers (head and neck, non-small cell lung cancer (NSCLC), and renal cancer (RCC) and similar for others (melanoma and bladder cancer). This lack of efficacy could also probably be correlated to the small number of elderly patients included in clinical trials (Elias et al. 2017; Daste et al. 2017; Hurez et al. 2017). The high expression of PD-L1 is probably a predictive factor for some tumors; this seems to be independent of age. There are now other immune checkpoint molecules which further identify exhausted T cells such as lymphocyte activation gene 3 (Lag-3) and T-cell immunoglobulin, T-cell immunoreceptor with Ig and ITM domains (TIGIT), and mucin-domain containing 3 (Tim-3). These receptors are also increased with aging and are future targets for ICI therapy (Baitsch et al. 2012; Nguyen and Ohashi 2015; Hurez et al. 2017).

There are presently two clinically exploited immune checkpoint inhibitors. Monoclonal anti-PD-1 antibodies are most successfully used in different cancers such as melanoma, (NSCLC), lymphoma, and head and neck cancer (Wang et al. 2018; Sharma and Allison 2015). PD-1 is expressed preferentially on the surface of effector

memory (exhausted) T cells. Clinically, the impact of age on the immunotherapy response has not been systematically described. However, several meta-analyses confirmed the remarkable efficiency of ICI in elderly subjects too (Elias et al. 2017; Daste et al. 2017). This treatment most likely also affects other cells expressing the PD-1 such as NK cells, B cells, myeloid cells, and DCs (Fanoni et al. 2011). Thus, this treatment not only restores T-cell functions but also influences antibody production, NK cell cytotoxicity, and the suppressive activity of MDSCs (Velu et al. 2009)). Not only PD-1 but also PDL-1 may be expressed by myeloid cells in the tumor microenvironment, and their modulation may also increase antitumor immunity mediated by T cells (Herbst et al. 2014). Recent trials of the anti-PD-1 monoclonal antibody nivolumab demonstrated efficacy for NSCLC (Reck et al. 2016). In that trial, there was a lower efficacy of immunotherapy with nivolumab for patients older than 75 years (Sgambato et al. 2017). However, these results need to be interpreted cautiously due to the small sample size of these subgroups.

CTLA-4 antibodies are also very efficient immune checkpoint modulators most often used for metastatic melanoma. CTLA-4 binds CD80 or CD86 on antigen-presenting cells and abrogates the capacity of T cells to further respond to their specific antigens. When the CTLA-4 receptor is blocked, inhibition is relieved, and the capacity of the T cell to respond is regenerated. In early trials, 10–20% of metastatic melanoma patients showed clinical responses and went on to experience a substantial survival advantage, never achieved before with any other treatment (Hodi et al. 2010). This was a major advance in cancer and especially in melanoma therapy. As a result, the antibody ipilimumab was the first to be licensed by the FDA, in 2011.

Taken together, it appears that neither anti-PD-1 (e.g., pembrolizumab) nor anti-CTLA-4 (e.g., ipilimumab) treatment shows clear patient age-dependent decreases in efficacy and safety (Elias et al. 2017; Daste et al. 2017; Johnson et al. 2017; Pawelec 2017). This further questions how immunosenescence interferes with the application of immunotherapy.

Even more recently, this technique of using immunomodulatory checkpoint antibodies to enhance antitumor immunity has been extended to include NK cell checkpoints. Thus, the inhibitory receptors on NK cells responding to HLA class I molecule such as KIR and NKG2A have been also targeted by specific antibodies, so far only in preclinical trials (Tarazona et al. 2017). However, there are no data from the elderly on the efficacy and toxicity of these treatments. It should be noted that although these treatments are not free of toxicity, it does not seem worse in elderly patients (Daste et al. 2017). Pruritus, rash, diarrhea, nausea, and liver toxicity were the most specific AEs in the older population. Frequencies of these toxicities were similar in younger and older patients, with a slight increase in rash in the latter (10% vs. 7%). Hence, some patients are not responding which can be explained by the decreased immune response with aging, more specifically the decrease in T cells bearing these receptors and the overwhelming presence of senescent cells in a pro-inflammatory milieu.

Thus it can be clearly stated that older age is not a contraindication to immune checkpoint inhibition, and instead functional status may be a more relevant consideration. However, the overall toxicity profile, efficacy, and relative risks and benefits in comparison with other therapies have not been studied comprehensively for tumor types other than melanoma, and they will need further study.

Elderly Participation in Clinical Trials

There are usually very few patients over 70 years of age in the majority of antitumor clinical trials. The FDA has been recommending the inclusion of elderly people in clinical trials for many years. This paucity of trials in the elderly is rendering it difficult to assess the impact of immune changes occurring with aging on anticancer immunotherapy. It is not only age that matters but also comorbidities commonly seen in the elderly, such as renal or hepatic dysfunction (Johnson et al. 2017). Moreover, some of these elderly

subjects are frail or have Eastern Cooperative Oncology Group (ECOG) status >2. The inclusion of these patients is of high importance to assess the effects of immunotherapy in older patients, especially for checkpoint blockade. Thus, it is the outmost importance in general to include elderly in these trials. Of course, this also raises ethical questions regarding survival, cost, and social acceptability, mainly in the context of palliative treatment.

Conclusions and Future Perspectives

Aging is accompanied by many changes in immunity. Neither the extent nor the physiological significance of all of the many differences seen in people of different ages is completely clear thus far or even which of these differences are actually age-associated changes. Most of the data seem to suggest a decrease of immune function with advancing age, but others indicate increases or no change. Most importantly, the significance of these changes for the development of age-associated disease including cancer is not known with any certitude (Fig. 1). The recent success of finally being able to exploit immune surveillance of tumors to cure some patients makes it imperative to determine whether immunosenescence decreases antitumor immunity. It is clear that many additional factors are likely to play a role in the increasing cancer incidence with age, at least up to extreme old age. In the current era of immunomodulatory antibody immunotherapy shown to be dramatically effective in a fraction of mostly younger patients, there is a justified concern that these treatments may be less effective in the elderly because of the aforementioned immune changes with aging. This is presently difficult to establish as most of the elderly cancer patients are not participating in clinical trials. However, when they are included, results so far are similar to those in younger subjects, also with a similar toxicity profile. These mostly anecdotal data suggest that the elderly will be able to benefit from immunotherapy. However, specific trials are needed to confirm and extend these positive results, particularly in the context of directed targeting of neoantigens. It is clear that multimodal and multi-target treatments may become the standard of care for a personalized application mainly in elderly people with their immune history and potential longstanding coexistence with the nascent cancer. New strategies will also emerge with the better understanding of natural anticancer immunology and age-related changes (Table 1).

Table 1 Immunotherapies: present and future for the elderly

Adaptive immunity	
Adoptive transfer	CAR T cells
	DC-based vaccine
	NK cell expansion
Immune checkpoint inhibitors	PD-1/PD-L1
	CTLA-4
	LAG-3
	Tim-3
Tregs	Future
Innate immunity	
Neutrophils	Future
Macrophages	MCSF-R
MDSCs	Future
TLR agonists	Future
NK cells	Checkpoint blockade
Inflammation	Future
Immunometabolism (mTOR pathway)	
Nutrition	Rapamycin
Life style	Exercise
SASP	Senolytics

Cross-References

- Aging and Cancer Biology
- Cellular Senescence and Tumor Promotion
- Chronic Mechanistic Target of Rapamycin Inhibition: Preventing Cancer to Delay Aging or Vice Versa?
- Lung Cancer in Older Adults: Systemic Treatment
- Mitochondria, Oxidative Stress, Cancer, and Aging

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Aging and Cancer Biology

7

Vladimir N. Anisimov

Contents

Abstract

The incidence of cancer increases with age in humans and in laboratory animals alike. There are different patterns of age-related distribution of tumors in different organs and tissues. Aging may increase or decrease the susceptibility of various tissues to initiation of carcinogenesis and usually facilitates promotion and progression of carcinogenesis. Aging may predispose to cancer at least by two mechanisms: tissue accumulation of cells in late stages of carcinogenesis and alterations in internal homeostasis, in particular, disturbances in immune and endocrine system. Increased

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susceptibility to the effects of tumor promoters is found both in aged animals and aged humans, as predicted by the multistage model of carcinogenesis. Aging is associated with number of events at the molecular, cellular/tissue, and systemic/organismal levels that influence carcinogenesis and subsequent cancer growth. The available data on the effects of environmental carcinogens on life span and the aging at different levels of integration are critically analyzed. The exposure to various mutagenic agents, i.e., 5-bromodeoxyuridine, alkylating substances, carcinogenic polycyclic aromatic hydrocarbons, nitroso compounds, and ionizing radiation, decreases the life span of treated animals in direct proportion to dose and was considered as an acceleration of aging. There are significant similarities between normal aging features and effects of environmental carcinogens on DNA, neuroendocrine and immune system, and carbohydrate and lipid metabolism, whereas main difference was observed at cellular level.

Keywords

Carcinogenesis • Aging • Multistage model • Cancer microenvironment • Geroprotectors

Introduction: Aging and Cancer – Two Related Phenomena?

Cancer is a common cause of disability and death in the elderly: Over 50% of malignant neoplasms occur in persons aged 70 and above (Yang et al. 2012; Forman et al. 2013). The relationship between aging and cancer is not clear: Considerable controversy surrounds the mechanisms that lead to increased incidence of cancer in the aged. Two major hypotheses have been proposed to explain the association between cancer and age. The first hypothesis holds this association a consequence of carcinogenesis duration. That is, the sequential carcinogenic steps that are required for the neoplastic transformation of normal tissues develop over several years, and cancer is more likely to become manifest in older individuals by a process of natural selection. Peto et al. (1985) suggested that the high prevalence of cancer in older individuals simply reflects a more prolonged exposure to carcinogens. The incidence of cancer is a power function of the duration of carcinogen exposure, rather than a power function of tumor-host age. According to the second hypothesis, age-related progressive changes in the internal milieu of the organism provide an increasingly favorable environment for the initiation of new neoplasms and the growth of already existent but latent malignant cells (Anisimov 1983, 1987, 2003, 2009; Miller 1991; DePinho 2000). These mechanisms also include proliferative senescence, as the senescent cells lose the ability to undergo apoptosis, and produce substances favoring cancer growth and metastases (Campisi et al. 2001; Campisi 2003; Campisi and Robert 2014). The elucidation of the causes of an age-related increase in cancer incidence may be the key to a strategy of primary cancer prevention (Fig. 1).

Aging and Susceptibility to Carcinogenesis in Different Tissues

Animal experiments seem to confirm that age-related differences in the sensitivity to carcinogen in some tissues do exist. Thus, susceptibility to carcinogens decreases with age in the murine mammary gland, the small intestine and colon, the thyroid, and the ovarian follicular epithelium; it increases, by contrast, in the subcutaneous tissue, the cervix uteri, and the vagina. In other sites (the lung, hemopoietic tissues), it remains stable (for details see Anisimov 1983, 1987, 2009). For instance, female rats exposed to N-nitrosomethylurea (NMU) in doses of 10, 20, or 50 mg/kg at the age of 3 months developed mammary carcinomas and tumors of the kidney, ovaries, and colon. In contrast to young animals, the rats exposed to the same doses of the carcinogen at the age of 15 months showed a higher frequency of tumors of the corpus and cervix uteri following exposure to NMU and a lower frequency of mammary and intestinal adenocarcinomas and tumors of the ovary and kidney (Anisimov 1988). A comparison of the results with data on DNA alkylation, DNA synthesis, and O^6-methylguanine repair obtained in

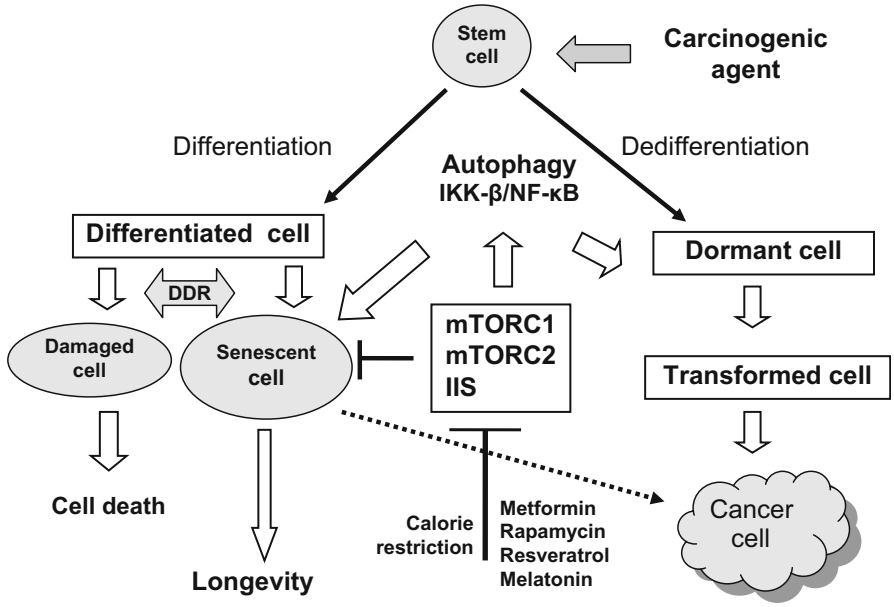

Fig. 1 Relationship between aging and carcinogenesis: the key role of insulin/IGF-1-like signaling (IIS) and mTOR signaling (From Anisimov 2013). DNA damage induced by environmental and endogenous factors (ROS, chemicals, ionizing radiation, ultraviolet, constant illumination, oncogenes, some diets, etc.) may lead to cellular senescence or cellular lesions which could be deleted by apoptosis or autophagy. The same agents can induce damages which are followed by neoplastic transformation thus leading to cancer. Metformin, rapamycin, and some other compounds with mTOR and IIS-inhibitory potential (resveratrol, melatonin) are able to modify both the aging and carcinogenesis

the same model suggests that age-related proliferative activity changes occurring in the target tissues in the mechanism of age play a critical role in modifying the effect on carcinogenesis. Obviously, there are no common patterns of age-related changes in DNA synthesis and repair or in the proliferative activity of different tissues with age.

This wide variation in experimental result can possibly be attributed to several factors, including those related to the experimental model and factors associated with the tumor host. Model-related factors involve the characteristics of different carcinogens (direct or indirect action, chemical structure, and the mechanisms of action), the route of administration, the exposure duration, the presence of local and systemic activity, and the time of observation. Host-related factors involve animal species, strain, sex, and age. The effective dose of an indirect carcinogen, requiring metabolic activation, may vary significantly in old and young animals, because the activity of the enzymes necessary for carcinogen activation in the liver and/or target tissue(s) may significantly decrease with age.

Critical factors that determine the susceptibility of a tissue to carcinogenesis include DNA synthesis and proliferative activity of that tissue at the time of carcinogen exposure and the efficacy of repair of damaged DNA (Tomasetti and Vogelstein 2015). The homeostatic regulation of cell number in normal tissues reflects a precise balance between cell proliferation and cell death. Programmed cell death (apoptosis) provides a protective mechanism from cancer by removing senescent, DNA damaged, or diseased cells that would otherwise potentially interfere with normal function or lead to neoplastic transformation (Hanahan and Weinberg 2011). Apoptosis and autophagy play a substantial role in many other aspects of aging and cancer, including control of the life span of most members of the immune complex and the rate of growth of tumors. P53-mediated apoptosis is suggested to act as a safeguard mechanism to prevent cell proliferation

induced by oncogene activation (Kinzler and Vogelstein 1997).

Being a component of two protein complexes, mTORC1 and mTORC2, serine/threonine protein kinase mTOR (mechanistic target of rapamycin) is a key enzyme of the mTOR-signaling pathway that regulates the maintenance of cellular homeostasis by coordinating transcription, translation, metabolism, and autophagy with availability of amino acids, growth factors, oxygen, etc. The activation of protein kinase mTOR by growth factors and nutrients suppresses autophagy and increases protein synthesis, thus increasing risk of cancer development, whereas mTOR inhibition increases longevity of mammals (Parkhitko et al. 2014; Laplante and Sabatini 2012). Administration of mTOR inhibitors rapamycin, rapalogs, or metformin increased life span of mice and reduced the tumor development (Harrison et al. 2009; Anisimov et al. 2010; Blagosklonny 2014; Anisimov 2015; Leontieva et al. 2015). It was shown that old mice have elevated mTORC1 signaling in hematopoietic stem cells (HSC) and that induction of mTORC1 by *Tac1* loss induces premature aging in HSC (Chen et al. 2009). Reducing mTORC1 with rapamycin restores HSC self-renewal and hematopoietic functions followed by improvement in immunity and increased life span of mice.

Age-related factors that limit susceptibility to carcinogens are tissue specific (Anisimov 1987). This conclusion explains, at least in part, both age-related changes in the susceptibility to carcinogenesis in target tissues and organ and tissue variability in the age distribution of spontaneous tumor incidence. This conclusion generates a critical question: Is aging accompanied by the accumulation of premalignant lesions in target tissues?

Aging and Multistage Carcinogenesis

Both carcinogenesis and aging are associated with genomic alterations, which may act synergistically in causing cancer (Hanahan and Weinberg 2011). In particular, age-related changes in DNA metabolism possibly favor cell transformation and cancer growth: genetic instability, DNA hypomethylation, and the formation of DNA adducts.

Genetic instability involves the activation of genes that are normally suppressed, e.g., cellular proto-oncogenes, and/or the inactivation of some tumor suppression genes (p53, Rb, etc.) (Kinzler and Vogelstein 1997; Hanahan and Weinberg 2011). DNA hypomethylation is a characteristic of aging, as well as of transformed cells. Hypomethylation, a potential mechanism of oncogene activation, may result in the spontaneous deamination of cytosine and consequent base transition, i.e., substituting the pair thymine, adenine. The accumulation of inappropriate base pairs may cause cell transformation by activating cellular proto-oncogenes. The different extent of DNA abnormalities among aging tissues accounts in part for the different susceptibility of these tissues to carcinogens (Catania and Fairweather 1991).

The damage caused by endogenous oxygen radicals is suggested to be a major contributor to both aging and cancer (Shigenaga et al. 1994). Endogenous oxidative damage to lipids and proteins increases with age. The level of one oxidized nucleoside, 8-hydroxy-2′-deoxyguanosine (oh8dG), in the DNA increased with age in the liver, kidney, and the intestine but remained unchanged in the brain and testes of rats. The urinary excretion of the nucleoside, by contrast, decreased in the rats with age. A variety of cellular defense systems are involved in protecting cellular macromolecules against the devastating action of oxygen-based radicals. They include antioxidant enzymes (Cu,Zn-superoxide dismutase (SOD), manganese-containing SOD, catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase), some vitamins (α-tocopherol, ascorbic acid), uric acid, and pineal indole hormone melatonin.

In the last decades, the importance of telomeres in aging has been highlighted. Telomeres are DNA sequences at the end of eukaryotic chromosomes in somatic cells. During cell replication, telomeres are preserved by the enzyme telomerase, a ribonucleoprotein enzyme that adds the telomere sequences TTAGGG to chromosome ends (Campisi et al. 2011; Blackburn et al.

2015). In the absence of telomerase, telomeres are shortened with each cell division. Loss of the distal region of telomeres correlates with the decline of the proliferative life span of cells both in vitro and in vivo. There are well-founded arguments suggesting that telomere shortening and reactivation of telomerase are important components of aging and carcinogenesis, respectively (Hanahan and Weinberg 2011).

There are evidences of an age-related accumulation of spontaneous mutations in somatic and germ cells (Vijg 2000; Adams et al. 2015). The accumulation with age of some spontaneous mutations or mutations evoked by endogenous mutagens can induce genome instability and, hence, increase the sensitivity to carcinogens and/or tumor promoters. Thus, the data available show that some changes in the structure and function of DNA are evolving with natural aging. The character of these changes varies in different tissues, causing uneven tissue aging. In turn, this leads to both age-related increases in spontaneous tumor incidence and age-related changes in susceptibility to carcinogens in various organs.

Carcinogenesis is a multistage process: Neoplastic transformation implies the engagement of a cell through sequential stages, and different agents may affect the transition between continuous stages (Schlessinger and Van Zant 2001). Multistage carcinogenesis is accompanied by disturbances in tissue homeostasis and perturbations in nervous, hormonal, and metabolic factors which may affect antitumor resistance. The development of these changes depends on the susceptibility of various systems to a carcinogen and on the dose of the carcinogen. Changes in the microenvironment may condition key carcinogenic events and determine the duration of each carcinogenic stage, and sometimes they may even reverse the process of carcinogenesis. These microenvironmental changes influence the proliferation rate of transformed cells together, the total duration of carcinogenesis, and, consequently, the latent period of tumor development. There is also evidence of age-related accumulation of cells at the latest stage of the multistage process of carcinogenesis. Numerous experiments support the results of this model.

Of particular impressive are experiments using skin transplants. Skin tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) failed to induce tumors in the skin of 2-month-old mice grafted to syngeneic animals of different ages but caused the same tumor incidence in the skin of 1-year-old donors irrespective of the recipient's age (Ebbesen 1985). These results indicate that the age of the target tissue determines susceptibility to late-stage agents more so than the age of the host.

In Tg.AC transgenic (v-Ha-ras) mice, skin tumor incidence and multiplicity were strongly age-dependent, increasing with advancing age of the experiment animal when first treated with TPA or exposed to wounding by UV light (Battalora et al. 2001). The authors suggest that natural developmental changes in keratinocytes are co-opted by the molecular mechanisms that regulate the induction of transgene expression, thus stimulating tumor formation in older Tg.AC mice.

The age-related accumulation of cells in advanced carcinogenic stages can also be demonstrated by other types of experiments. The mice model of hepatocarcinogenesis is very convenient for this purpose because of the availability of strains of animals with different susceptibility to hepatic carcinogenesis. In the liver of highly susceptible mice, the concentration of hepatocytes in the advanced stages of carcinogenesis increased early in life before exposure to experimental carcinogens. In the liver of F344 rats, the number of spontaneous proliferative foci is proportional to the animals' age. The incidence of proliferative foci and hepatic tumors induced by phenobarbital, carbon tetrachloride, or peroxisome proliferators in rodents is also a function of age (Ward et al. 1988).

Cellular Senescence and Carcinogenesis

In contrast to germ cells and certain stem cells, the majority of somatic cell types have a limited proliferative life span. This restriction may have evolved as a protective mechanism against cancer, although it may also cause the accumulation of cells at the end of their replicative life span that

may be responsible for the aging process and an increase in the susceptibility to carcinogenesis (Campisi 2003). The term "cellular senescence," originally defined as a series of cellular changes associated with aging, now refers more commonly to a signal transduction program leading to irreversible arrest of cell growth, accompanied by a distinct set of changes in the cellular phenotype. Senescence is a potent anticarcinogenic program, and the process of neoplastic transformation involves a series of events that allow cells to bypass senescence (Shay and Roninson 2004; Sicora et al. 2016). Although the relationships between cellular senescence and aging in vivo are not very clear yet, senescent cells were reported to accumulate in aging tissues: in human skin and liver (Dimri et al. 1995), in primate retina, and in some other tissues. Senescent cells were shown capable of stimulating the malignant progression of premalignant keratinocytes and mammary gland epithelial cells (Krtolica et al. 2001). Cellular senescence is controlled by the tumor suppressor proteins p53 and pRb. Inactivation of these proteins results in bypass of senescence. It is worthy to note that due to its essentially irreversible growth arrest and the requirement for p53 and pRb function, cellular senescence is considered a potent tumor suppressor mechanism. Numerous studies, primarily in human fibroblasts, suggest that telomere shortening is the primary cause of replicative senescence (Campisi 2003).

It is important that cellular senescence can be induced by a variety of extrinsic factors, such as X-ray irradiation, UV irradiation, H_2O_2, ectopic expression of certain oncogenes (Ras, Raf, ets2, E2F1), and tumor suppressors (p16, p14, p53). Cellular senescence may be one of the mechanisms by which cancer chemotherapy drugs work in vivo (Schmitt et al. 2002; Shay and Roninson 2004). Thus, the exposure to exogenic carcinogens can lead to accumulation of senescent cells which, in turn, can be anticarcinogenic factor and also can stimulate the malignization of precancerous cells in the target tissue.

Note that senescence is not an inevitable consequence of extended proliferation in a culture. Thus, rat Schwann cells appear to have the capacity for unlimited proliferation in vitro, whereas fibroblasts isolated from the same nerves undergo the classic replicative senescence seen in rodent fibroblasts. Some other normal rodent precursor cells (e.g., oligodendrocytes) have an unlimited proliferative capacity if cultured in conditions that avoid both the differentiation and activation of checkpoint responses that arrest the cell cycle. In contrast to fibroblasts, human mammary epithelial cells spontaneously escape senescence and generate genomic abnormalities that are required for the initiation of carcinogenesis.

Aging and Cancer Microenvironment

An important question related to the integral model of carcinogenesis concerns age-related changes in tissue microenvironment as these changes may favor or limit carcinogenesis in different circumstances (Liotta and Kohn 2001). Should aging tissues alter the environment in which tumor develops, the growth rate of transplantable tumors may vary with the age of the tumor recipient. These experiments bypass the effect of age on carcinogenesis itself and explore the role of age-related changes in the organism on the growth and progression of transformed cells. Evaluation criteria for such experiments should include tumor transplantability, the rate of tumor growth, and the survival time of tumor-bearing animals. The natural history of spontaneous tumors in humans (the rate of tumor doubling, metastazing potential) and the survival of cancer patients newly diagnosed at different ages provide information on the effects of age on tumor growth in humans. Available data both in experimental animals and in humans are contradictory and support different effects age has on tumor development (Anisimov 2006b). In general, an "age effect" is possible both in experimental and human malignancies. Tissue origin (histogenesis) and tumor immunogenicity are the principal factors determining age-related differences in tumor growth.

McCullough et al. (1994) observed that transformed rat hepatocytic cell lines were only weakly tumorigenic following transplantation into the livers of young adult rats. The tumorigenicity of

these cell lines increased progressively with the age of the tumor recipients. These results suggest strongly that the tissue microenvironment represents an important determinant in the age-related tumorigenic potential of transformed cells.

In recent years, it has become increasingly apparent that the senescence response is a complex phenotype, which has a variety of cell nonautonomous effects (Campisi et al. 2011). The senescence-associated secretory phenotype, or SASP, entails the secretion of numerous cytokines, growth factors, and proteases. The SASP can have beneficial or detrimental effects, depending on the physiological context. Among the detrimental effects, the SASP can disrupt normal tissue structures and function and, ironically, can promote malignant phenotypes in nearby cells. These detrimental effects in many ways recapitulate the degenerative and hyperplastic pathologies that develop during aging. It is worthy to note that many features of SASP are very similar with the cancrophilia syndrome proposed by Dilman (1994).

It is important to stress that in every tissue, the number of events occurring in the stem cell before its complete transformation is variable and depends on many factors, in particular the rate of aging of the target tissue and its regulatory system (s) (Anisimov 2009). This model is consistent with the analysis of the age-related distribution of tumor incidence in different sites in humans and laboratory animals. It must be emphasized also that old animals can be used as an adequate model for long-term assays for carcinogenicity of suggested weak carcinogens and/or tumor promoters.

Among most critical points in the mechanisms underlying the molecular and cellular basis of age-related cancer, an important role is played by the stroma (Elkhattouti et al. 2015). It was stressed that some components of senescent stroma, such as fibroblasts, contribute to create a tumor-promoting microenvironment through mechanisms including SASP and another stroma-derived factors. It was stressed that the ectopic expression of such transcription factors as OCT4, SOX2, KLF4, and cMYC (OSKM) in vivo, apart from inducing the reprogramming of a small population of cells, also induces damage and senescence in sufficient number of neighboring cells, with IL-6 being a critical mediator (Mosteiro et al. 2016). Thus, aging induces changes in molecular pathways that contribute in the initiation and/or clonal dominance of mutations in stem and progenitor cells. Cell-extrinsic factors affect stem cell maintenance and the selection of mutant stem cells and progenitor cells during aging of an organism (Adams et al. 2015).

Premature Aging Promotes Carcinogenesis

It is well known that some syndromes of untimely aging (progeria) are associated with an increased incidence of cancer (Lehmann 1985). Alongside with the classical progeria syndromes, some diseases are accompanied by disturbances that may be regarded as signs of intensified aging. For instance, the Stein-Leventhal syndrome (sclerocystic ovaries syndrome) occurs during puberty and is characterized by a bilateral sclerocystic enlargement of the ovaries, associated with a pronounced thickness of the ovary capsule. The enlargement forms a mechanical obstacle for the ovulatory rupture of a mature follicle. In these ovaries, follicular cysts and hyperplasia of theca tissue can be found. Patients have anovulation, sterility, hirsutism, hyperlipidemia, lowered glucose tolerance, hyperinsulinemia, obesity, hypertension, and increased incidence of breast and endometrial cancer (Dilman 1994). In rodents, the syndrome of persistent estrus, which normally completes the reproductive period of life, can be induced by several methods, including neonatal administration of sex steroids, exposure to some chemical carcinogens or to ionizing irradiation, housing under constant illumination, subtotal ovariectomy, orthotopic transplantation of an ovary into castrated animals, electrolytic lesion of anterior and/or mediobasal hypothalamus, etc. (Anisimov 1987). Regardless of the induction method, premature aging and a rise in tumor incidence have been observed in rats with persistent estrus (Anisimov 1987).

The induction of persistent estrus in rats exposed to chemical carcinogens (DMBA,

NMU) was associated with increased tumor incidence when compared to animals without persistent estrus exposed to a carcinogen alone (Anisimov 1987). These observations highlight the promoting effect of the persistent estrus syndrome on carcinogenesis.

Effect of an Exposure to Environmental Carcinogens on Aging and Life Span

The potency of carcinogenic and mutagenic agents to accelerate aging has been discussed for many years (Larionov 1938; Alexander and Connel 1960; Dilman 1971, 1994; Alexandrov 1982 Anisimov 1987, 2009). There are available data on the effects of carcinogens on aging at different levels of an integration: molecular, tissue, systemic, and organismal.

Exposure to various mutagenic agents, i.e., 5-bromodeoxyuridine, alkylating substances, carcinogenic polycyclic aromatic hydrocarbons, nitroso compounds, ionizing radiation, and light at night, decreases the life span of treated animals in direct proportion to dose and was considered as an acceleration of aging (Anisimov 2009).

Neonatal 7,12-dimethylbenz(a)anthracene (DMBA) administration decreased the mean life span of female mice from 608 to 297 days. Premature cessation of estrus function, graying of hairs, loss of weight, etc. were observed (Ohno and Nagai 1978). Dunjic (1964) noticed shortening of rat life span proportional to dose of Myleran and accompanied by such manifestations of old age as cataract and testicle atrophy. Female rats exposed to 3-methycholanthrene (MCA) manifested early discontinuation of estrous function and a number of hormonal shifts which have suggested intensified aging induced by the carcinogen (Anisimov 1987). There are data on smoking-induced life shortening of life span and acceleration of aging both in rodents and in human (Teramoto et al. 1993; Watanabe 2016). In mice exposed to radiomimetics (nitrogen mustard or triethylenemelamine), a decrease of life span was observed which correlated with all types of diseases associated with old age (Conklin et al. 1963). Acceleration of aging by ionizing radiation could serve for explanation of results obtained in studying "dose-effect" dependence in the action of irradiation (Alexandrov 1982).

DNA Damage in Aging and Carcinogenesis

One of the most advanced theories of aging is free radical theory proposed in 1956 by D. Harman (1998). This theory postulated that various oxidative reactions occurring in the organism (mainly in mitochondria) generate free radicals as by-product which cause multiple lesions in macromolecules (nucleic acids, proteins, and lipids), leading to their damage and aging. This theory explains not only the mechanism of aging per se but also a wide variety of age-associated pathology, including cancer. There are evidence that key mechanisms of both aging and cancer are linked via endogenous stress-induced DNA damage caused by reactive oxygen species. They include oxidative nuclear and mitochondrial DNA damage and repair and telomere shortening and telomere-driven cellular senescence and have been intensively discussed in a number of comprehensive reviews (von Zglinicki et al. 2001; Blackburn et al. 2015). It is worthy to note that chemically and radiation-induced carcinogenesis also are critically involved in the free radical processes.

The intensity of natural damages in DNA is very high, e.g., in a human cell, spontaneous depurinization takes place at a rate of up to 10,000 acts per day and spontaneous deamination of adenine and cytosine at a rate of hundreds of events per day. As a result, permanently working mechanisms of DNA repair have evolved. It turns out that in both of the most intensive natural mutation processes (depurinization and deamination), thymine is not present (mutations related to it are significantly more rare), and therefore the reparation schemes for thymine may have evolved less intensively (Lindahl 1993). Hence, if we want to induce uniformly distributed point mutations (and simultaneously to minimize damages in other structures) in laboratory animals, then it is meaningful to use analogues of thymine as a mutagen.

Some "in vitro" and "in vivo" effects of the thymidine analogue, 5-bromodeoxyuridine (BrdUrd), suggest that BrdUrd may be used to investigate the role of selective DNA damage both in carcinogenesis and in aging. BrdUrd is incorporated into replicating DNA in place of thymidine, and this effect is mutagenic (Morris 1991). In addition to the usual keto form, BrdUrd may assume an enol tautomeric form, which forms hydrogen bonds with guanine instead of adenine, the normal pair for thymidine and 5-bromouracil. In the absence of 5-bromouracil repair in rat DNA (Lindahl 1993), if BrdUrd is incorporated into DNA as the enol tautomer, base-pair substitution mutations are expected to occur (GC→AT and AT→GC transitions) during subsequent DNA replication (Morris 1991). Unlike purine analogues, BrdUrd is not involved in energy production or in cell signaling and interactions and hence can reach required levels of mutations while being less toxic than in the case of "spoiled" analogues of purines. This ability to induce uniformly distributed point mutations with a chosen intensity using BrdUrd is based on the fact that the number of mutations is linearly dependent on the concentration of BrdUrd. Assuming a fairly even level of BrdUrd incorporation, into the DNA of various tissues of neonatal rats and long-term persistence in them (Ward et al. 1991), cells with highest proliferative activity would be more likely to undergo malignant transformation. Exposure to BrdUrd had dramatic effects on cellular functions including cell differentiation, inactivation of regulatory genes or master switch, and proliferation. These changes in cellular function may favor tumor development.

In a series of experiments (Napalkov et al. 1989; Anisimov and Osipova 1992; Anisimov 1994), rats received subcutaneous injections of BrdUrd at 1, 3, 7, and 21 days of postnatal life at the single dose of 3.2 mg per rat. BrdUrd persisted for up to 49 weeks in all tissues studied immunohistochemically, especially in tissues with normal or low cell turnover. For cells with high turnover, few or no BrdUrd-labeled cells remained at 49 weeks (Ward et al. 1991). The exposure to BrdUrd was followed by the decrease in the mean life span of the animals of 38% in males and 27% in females and by the increase in the rate of aging (calculated according to Gompertz equation) in comparison with controls. The monitoring of estrus showed an acceleration of natural age-related switching off of reproductive function in female rats, due to disturbances in central regulation of gonadotropic function in the pituitary. The exposure of rats to BrdUrd was followed by signs of immunodepression, by increase in the incidence of chromosome aberrations and spontaneous tumors. The latency of these tumors was decreased. In offspring of rats neonatally treated with BrdUrd, the increased incidence of congenital malformation and of spontaneous tumors and accelerated aging were both observed. Neonatal exposure of rats or mice to BrdUrd was followed by the initiation of the neoplastic process and, consequently, by increased tissue susceptibility to "late-stage" carcinogens such as N-nitrosomethylurea (NMU), X-irradiation, urethane, estradiol benzoate, and persistent estrus syndrome. These data provided the evidence that a sole perturbation of DNA induced by BrdUrd contributed substantially to the initiation of tumorigenesis and to the acceleration of aging.

BrdUrd was found to induce in vitro flat and enlarged cell shape, characteristics of senescent cells, and senescence-associated beta-galactosidase in mammalian cells regardless of cell type or species (Suzuki et al. 2001). These results suggest that BrdUrd induced senescence-like phenotypic resemblance in both mortal and immortal mammalian cells and, possibly, activated a common senescence pathway present in both types of cells. It is important to stress that BrdUrd immediately induces premature senescence in normal cells and the senescence-like phenomenon in any type of immortal cells. It was shown also that BrdUrd immediately and dramatically induces senescence-associated genes in human cells.

The mathematical model of processes of aging and carcinogenesis in tissue based on the experimental data on in vivo exposure to BrdUrd has been considered (Butov et al. 2001). Modeling was carried out on the basis of the recurrent algorithms constructed on the stochastic equations in terms of semimartingale characteristics of the processes. The results confirm the conclusion that under BrdUrd treatment there is an accelerated

aging in tissues with proliferating cells and an increment of death from tumor growth. These results can serve as an indirect validation of the hypothesis about the influence of levels of tissue damages during mutagenesis and oxidative stress both on the rates of aging and on the rate of carcinogenesis. The abovementioned observation on in vitro effects of BrdUrd is in agreement with this conclusion.

Effect of Carcinogens on the Neuroendocrine System

It should be stressed that the most significant aftereffects induced by carcinogenic agents on supracellular levels are those produced on the central chains of the neuroendocrine system, the hypothalamus in particular. In certain hypothalamic nuclei, cells synthesize and secrete releasing or inhibiting hormones, which control secretion of pituitary hormones. In turn, hypothalamic peptidergic neurons are controlled by humoral signals and neurogenic stimuli, which enter the hypothalamus with blood and via afferent nervous tracts. Important roles of mediators and modulators between these signals are played by the biogenic amines (catecholamines, norepinephrine and dopamine, serotonin, γ-aminobutyric acid, etc.) in which the hypothalamic area is rich. With the information from internal and external media of the host, the hypothalamus coordinates the functions of the nervous and endocrine systems and eventually maintains constancy of the internal medium (homeostasis) of the host. The significance of the hypothalamus is so great that it is considered by some researchers as the "biologic clock" of aging (Dilman 1971, 1994).

Hypothalamic nuclei develop relevant morphological, biochemical, and functional changes in aging which tell eventually on the function of the endocrine and some of the other integrating systems of the organism. These changes result in an age-related increase of the threshold of sensitivity of the hypothalamus to inhibition by steroids (sex hormones, in the system of reproductive homeostasis, and glucocorticoids, in the system of adaptation to stress). According to Dilman (1994), this disturbance is a key one in the process of realization of the neuroendocrine program of development, aging, and formation of age-related pathology, including cancer.

Adult rats, exposed to single administration or chronic treatment with a variety of carcinogens, showed an elevated threshold of sensitivity of the hypothalamus to homeostatic inhibition via the mechanism of negative feedback (Anisimov 1987). Being noncarcinogenic for rats, anthracene or benzo(a)anthracene did not possess such property.

An age-related decrease of catecholamine level and amount of receptors to estrogens in hypothalamus as well as disturbances in the ratio of activity of adrenergic and serotoninergic brain structures plays a leading role in the mechanism of age-related elevation of hypothalamic threshold of sensitivity to inhibition by estrogens (Dilman and Anisimov 1979).

It is well known that hormonal imbalance, which develops in the first hours and days after carcinogen administration, is an important factor determining the appearance of mammary gland neoplasms under polycyclic aromatic hydrocarbon influence. In fact, ovariectomy performed immediately after DMBA administration suppresses mammary tumor development, while conducted 1 week after it, the ovariectomy does not prevent mammary carcinogenesis. Already in the first hours after DMBA or MCA administration to rats, an activation of neurosecretory elements in the hypothalamus nuclei was observed. Soon after the administration of polycyclic aromatic hydrocarbons, rats developed pronounced shifts in the function of the ovaries, adrenal glands, and thyroid gland. These data convincingly suggest an immediate influence of carcinogenic polycyclic aromatic hydrocarbons on the neuroendocrine system in rats, a possible triggering mechanism of which is their influence on the level of biogenic amines in the hypothalamus. There are data on different effects of chemical carcinogens on the level of biogenic amines in the hypothalamus of rats. Some of them effect predominantly the noradrenergic and dopaminergic structures (DMBA, DMH, and NMU), while others effect the serotoninergic (MCA) (Anisimov

1987). There could be a supposed influence of some carcinogens on the activity of MAO (2-AAF and NEU). It should be noted that such hepatocarcinogens as N-nitrosodimethylamine (DENA) and 2-AAF differently influence adrenoreceptors (Gurkalo and Pliss 1978). Despite the fact that the tested carcinogens produced different effects on the level of biogenic amines in the hypothalamus, practically all of them induced a general physiological shift – an increased level of hypothalamic threshold of sensitivity to homeostatic inhibition by estrogens.

Hypothalamic shifts, which develop in animals exposed to carcinogenic agents, lead to significant morphological and functional changes in the reproductive system. Thus, rats develop follicular cysts of the ovaries and persistent estrus in distant terms after irradiation or MCA treatment (Anisimov 1987). Similar changes on the hypothalamic level regularly switch off the reproductive period in female rats during natural aging (Dilman and Anisimov 1979; Aschheim 1976). Signs of accelerated development of age-related disturbances in the system hypothalamus-pituitary-adrenal glands of animals exposed to irradiation and some carcinogens have been described in numerous works (Alexandrov 1982).

Effect of Carcinogens on Carbohydrate and Lipid Metabolism

Hormone-metabolic shifts which develop in the organism during natural aging play an important role in the development of the tumor process. Among these shifts great importance is attributed to decreased tolerance to glucose, hyperinsulinemia, hypercholesterolemia, and hypertriglyceridemia (Dilman 1994).

Decreased glucose utilization, hyperinsulinemia, delayed rise of insulin level, and no elevation of serum IGF-I activity was observed in 14–16-month-old rats after glucose loading as compared to 3-month-old rats. At the same time, decreased sensitivity to insulin and low response of the level of free fatty acids to glucose loading were revealed in female rats of this age (Anisimov 1987).

In series of experiments, carbohydrate and lipid metabolism in rats exposed to different carcinogenic agents have been studied. A single or weekly administration of DMH during 1, 4, or 6 months did not cause changes in the blood basal glucose level. However, pronounced decrease of glucose utilization has been detected in a glucose tolerance test in 3 days after a single carcinogen injection (Anisimov 1987). Decreased tolerance to carbohydrates was revealed in rats in 1, 4, and 6 months after beginning weekly DMH administrations. A trend to elevated levels of serum cholesterol and triglycerides was traced in all experimental groups. The level of immunoreactive insulin in the serum of rats exposed to DMH during 6 months was observed to be higher than in the control group being investigated both after 18-h starvation and in 20 min after i.v. glucose loading. In rats subjected to chronic DMH administration (15 mg/kg of body weight × 15 times with weekly intervals), triglyceride level in the serum in 16 and 24 weeks of experiment was decreased by 18% and in 48 weeks when animals had developed colon tumors was increased by 33% (Windle and Bell 1982).

In the other experiment parameters of carbohydrate and lipid metabolism were studied in rats submitted to two i.v. administration of NMU in a dose of 50 mg/kg of body weight with a weekly interval (Anisimov 1987). Insulin level in the serum was significantly higher than other parameters in comparison with control 1 month past carcinogen administrations. However, in glucose tolerance tests, these rats manifested pronouncedly decreased glucose utilization and reactive hyperinsulinemia**.** The value of glycemia index was 1.4 times larger in rats exposed to carcinogen in comparison with control ones 1 h past glucose loading. Twice normal serum IGF-I activity was observed by that time in female control rats. In rats treated with NMU, the rise in somatomedin activity was not traced. Glucose tolerance tests revealed in rats submitted to NMU i.v. administrations disturbances of carbohydrate tolerance by latent diabetes mellitus typical of the old aged. Since this disturbance was found in the period prior to tumor appearance, it could be supposed to have been

conditioned by carcinogenic action and not by tumor influence on the organism (Anisimov 1987).

Considerable shifts in carbohydrate and lipid metabolism were revealed in rats exposed to DMBA or X-ray irradiation as well as in progeny of rats subjected to NMU or DES administration during pregnancy. In all the experiments, these disturbances were found in the period prior to neoplasm appearance. First of all there are disturbances in tolerance to carbohydrates, revealed in glucose tolerance tests, more or less pronounced hyperinsulinemia, and disturbances in regulation of the serum somatomedin activity. The level of serum cholesterol and triglycerides does not vary in some cases (Anisimov 1987).

Comparative evaluation of disturbances in neuroendocrine regulation occurring in the organism during aging and due to carcinogens gives an impression of earlier development and stronger pronouncement of age-related changes in radiation and carcinogenic effect without significant quality differences. Carcinogenic factors (irradiation included) are shown to cause in the organism a sharp transition to an older level and not acceleration of age-related changes (Alexandrov 1982). This transition is asynchronous and has different latent periods in various components of biological objects.

Effect of Carcinogens on Immune System

The tumor immunosurveillance hypothesis, first raised by P. Erhlich in 1909 and then refined by Burnet (1974), postulated that the immune system constantly surveys the newly developing tumors and, as long as it is effective, prevents the development of neoplastic disease. It was assumed that clinically evident tumors represent exceptions that slipped through the immunological net. At present it seems that immune defense mechanisms form the last barrier in organism natural mechanisms of protection against cancer and are probably less effective as compared with some other mechanisms operating at earlier stages of malignant tumor formation (Jakobisiak et al. 2003). The immunologic theory of aging, proposed 50 years ago by Walford (1969), suggests that the normal process of aging in man and in animals is pathogenetically related to faulty immunological processes. Since that time, research on immunological aging has undergone extraordinary expansion, leading to new information in areas spanning from molecular biology and cell signaling to large-scale clinical studies. Investigation in this area has also provided unexpected insights into HIV disease, many aspects of which represent accelerated immunological aging (Jakobisiak et al. 2003). It is worthy of note that the majority of chemical carcinogenic agents and ionizing radiation are immunosuppressors (Blankenstein and Qin 2003). It seems that metabolic immunodepression is one of the mechanisms of immunosuppressive effect of carcinogenic agents (Dilman 1994). Nikitina (1997) reported that an exposure to modulated electromagnetic fields induced by marine radio transmitters accelerated aging in seamen. Maintaining rodents at the constant illumination was followed by accelerated aging in reproductive, adaptation, and energy homeostases, development of metabolic syndrome, and other age-associated diseases, including cancer (Vinogradova et al. 2009; Vinogradova and Anisimov 2012).

Carcinogens as Promoters of Spontaneous Carcinogenesis

The data discussed above provide evidence that carcinogenic agents are able to accelerate aging. If this is the case, apart from the induction of neoplasms in target tissue(s), carcinogenic agents must increase the incidence of the tumors peculiar to a given strain of animal. Total incidence of spontaneous neoplasms (mammary fibroadenomas and fibromas, endometrial polyps, thyroid adenomas, adrenal cortex, and pituitary adenomas) in intact female outbred rats was 26%, and the mean latent period was equal to 738 days. Female rats aged 3 months were injected with NMU four or two times. As a result, apart from mammary adenocarcinomas and kidney, colon, and ovarian tumors, the benign tumors pertinent to control females not treated with the carcinogen were developed by

experimental animals in 38% and 25% of cases, respectively. The incidence of these tumors was the same as in control animals, but their mean latent period was equal to 295 days and 406 days, respectively. In other words, NMU-treated female rats developed benign tumors in endocrine glands and hormone-dependent organs much earlier than control ones (Anisimov 1981). Similar results were obtained in experiments involving a single injection of N-methyl(acetoxymethyl)-nitrosamine into 3-month-old female rats. Mean latent period of benign tumor development in the intact control and carcinogen-treated animals was 844 days and 516 days, respectively. It was shown the enhancement of spontaneous carcinogenesis in F344 rats treated with low (less than 10 ppm) dosages of NMU (Maekawa et al. 1984). Thus, there is some evidence on the promoting effect of intensified aging on carcinogenesis.

Effect of Geroprotectors on Aging and Carcinogenesis

The effects of factors or drugs that increase life span (geroprotectors) on spontaneous tumor development may provide important clues to the interactions of aging and carcinogenesis. About 20 substances were suggested as life span extension means (Anisimov 1987, 2006b; Spindler 2012; Blagosklonny 2014; Longo et al. 2015). The term *geroprotector* was introduced for such kind of substances. It seems rather fortunate because it means "defending from aging." Contrary to geriatric drugs which are prescribing to the elderly people, the treatment with geroprotectors should be used at young and adult age. Being suggested on the current knowledge on factors and mechanisms or theories of aging, these interventions in the aging process sometimes were followed some unfavorable effects.

The question of the safety of long-term use of these preparations including not only adverse effects but also the late effects, including cancer, is one of the priorities in this field. Other aspects of the problem related to observations on the age-related increase in cancer morbidity directly connected with the population aging (Anisimov 1987, 2009). That is why the evaluation of possible risk of the increase in cancer incidence should be taken into account when means of life extension will be recommended to practical use. The comparison of the data on the mechanisms of action of geroprotectors with its influence on the development of spontaneous and experimentally induced tumors permits to deepen our understanding of interactions between two fundamental biological processes – aging and carcinogenesis.

There are geroprotectors that extend the life span equally in all members of the population (these substances postpone the beginning of population aging), geroprotectors that decrease the mortality of long-living subpopulation leading to a rise in maximal life span (these substances slow down the population aging rate), and geroprotectors that increase the survival in short-living subpopulation without change of the maximal life span (in this case aging rate increases). Available data show a good correlation between the type of geroprotectors and the pattern of tumor development in the same population of animals. Geroprotectors of the first type do not influence the incidence of tumors but do prolong tumor latency. Geroprotectors of the second type are effective in inhibiting spontaneous carcinogenesis, prolonging tumor latency, and decreasing tumor incidence. Drugs of the third type can sometimes increase the incidence of cancer (Anisimov 1987, 2006).

The comparison of the data on the type of the slowing of mortality rate and the character of the antitumor effect of geroprotectors permits to suggest that the tumor incidence of a certain age is the function of the rate of aging (Anisimov, 1983, 1987, 2004). The calculations revealed a highly significant positive correlation between the rates of mortality of the rat populations studied and the rates of age-related increase of tumor incidence in these populations, while no positive correlation between mean life span and tumor incidence was found. These results led to the conclusion that the incidence of tumors and the rate of their age-related increase directly depend upon the rate of mortality of a population no matter if the animals were exposed to geroprotector or not. This dependence together with the data that

environmental factors which promote tumor growth (overfeeding, constant illumination, chemical carcinogens, ionizing radiation, etc.) may cause an acceleration of aging (Anisimov 1987, 2004, 2006b) suggests that the rate of mortality in these cases may be a function of the dose of carcinogenic agent.

In the framework of a multistage model of carcinogenesis, geroprotectors may both inhibit and enhance the passage of transformed cells through sequential carcinogenic stages. In general, the efficacy of geroprotectors in preventing cancer development decreases inversely with the age of exposure to the carcinogen. It is important to emphasize that geroprotectors of the second type delay aging by influencing the "main" regulatory systems of the organism (nervous, endocrine, immune). These effects delay the development of age-related changes in the microenvironment of cells exposed to carcinogens.

Geroprotectors may also be classified into two main groups according to their mechanism of action. The first group includes drugs that prevent stochastic lesions of macromolecules. The theoretical basis for using these drugs is provided for by variants of the "catastrophe error" theory, which regards aging as a result of the accumulation of stochastic damages. The second group includes substances that appear to delay intrinsic aging, i.e., programmed cellular aging.

Antioxidants are the most typical representatives of the first class of geroprotectors. Age of initial administration and doses of environmental carcinogens influence the geroprotective and tumor-preventing effects of antioxidants. The effectiveness of these substances increases when the initial administration occurs early in life and decreases with the dose of environmental carcinogen(s) to which the organism was exposed.

The second class of geroprotectors includes antidiabetic biguanides (phenformin and metformin), melatonin, and calorie-restricted diet. These factors influence the hormonal, metabolic, and immunological functions of the body, delaying age-related changes in these functions (Anisimov 1987, 2006, 2015). It was shown that melatonin is the most potent endogenous scavenger of free radicals in vitro and in vivo. Melatonin inhibits production of DNA adducts in carcinogen-exposed animals, protects chromosomes of human lymphocytes from radiation damages, enhances gap junctional intercellular communications in vitro, and prevents metabolic syndrome and spontaneous tumor development in rodents (Anisimov et al. 2006b).

The survival curves of human populations were noted to be more and more "rectangular." This is caused first of all by the decrease in infant and early mortality which is connected with tuberculosis and other infectious and non-infectious diseases. As a result, a significant increase in the mean life span of the human population occurred. Maximum human life span, however, has stayed the same for centuries. Thus, the changes in the shapes of the survival curves of human populations respond to the third type of aging delay according to the above-discussed classification. The changes of this type were shown experimentally and epidemiologically to be associated with an increase in tumor incidence. In other words, for the increase in mean life span achieved by the decrease in the mortality at early ages, mankind pay at later ages by an increased risk of having cancer or some other diseases of civilization like atherosclerosis or diabetes.

There are two strategies of development of the stem cell in an organism which could be realized in an organism. One strategy is the cellular differentiation and aging, and at least, in its individual death (apoptotic or necrotic). When factors of antiaging reach some limit of their compensatory possibilities to support tissue and functional homeostasis in life-important organs, the death of an organism as a whole has taken place. Another strategy of the stem cells in the circumstances of influence of exogenous or endogenous harmful factors could lead to its dedifferentiation, immortalization, and formation of a clone of neoplastic cells (Anisimov 1987, 2004, 2009). The simplified scheme presented allows to understand why drugs which prevent effects of some factors accelerating aging or, contrary, stimulate the antiaging factors, in a different way affecting homeostasis in tissues and in an organism as a whole, may promote or inhibit tumor development.

Further progress in preventive medicine is impossible without radical changes in the approaches to public health and to the prolongation of the human life span. In the burst of industrialization, urbanization, and increasing environmental pollution (including light pollution), one may hope only for a partial alleviation of the unfavorable effects on human health. The achievement of significant results in this field will require the solution of very complex scientific and technical problems as well as considerable economic expenses. It is probably true that even at present, changes in the life style, i.e., in dietary and sexual habits and in smoking and alcohol consumption, may be the most promising approach to achieving a decrease in cancer incidence and, hence, an increase in life span. It seems to become more clear that means which normalize the age-related changes in the hormonal status, metabolism, and immunity and thus slow down the realization of the genetic program of aging (not postpone aging, but slow down the rate of it) must be most effective in the protection from both premature aging and cancer. Among these means are mimetics of calorie restriction (e.g., metformin), melatonin, and some pineal peptides. The influences which protect from the initiating action of damaging agents (antioxidants and antimutagens) may be important additional means of accelerated aging prevention especially under conditions of an increased risk of exposure to environmental harmful agents.

Conclusion

Table 1 summarizes the data available in literature and obtained in experiments on some hormonal metabolic shifts in the organism and disturbances at tissue and cellular levels observed during natural aging and during carcinogenesis in vivo. It can be seen that there is a similarity between the shifts in aging and carcinogenesis. Carcinogens could be supposed to initiate a normal cell, interacting with its elements on the molecular level, on the one hand, and to produce diverse changes in the organism facilitating promotion and progression of tumor growth, on the other hand.

Table 1 Patterns of changes observed in an organism during natural aging and carcinogenesis at molecular, cellular/tissue, systemic/organism, and population levels of integration

Parameters	Aging	Carcinogenesis
Molecular level		
Free radical generation	Increases	Increases
DNA adduct formation	Increases	Increases
DNA repair efficacy	Decreases	Decreases
DNA hypomethylation	Increases	Increases
Genomic instability	Increases	Increases
Telomere length	Decreases	Increases[a]
Error protein synthesis	Increases	Increases
Mutation rate	Increases	Increases
Oncogene expression	Increases	Increases
p53 mutations	Increases	Increases
mTOR activity	Increases	Increases
Cell/tissue level		
Oxidative stress	Increases	Increases
Chromosome aberrations	Increases	Increases
Growth factor production	Deceases	Increases[a]
Proliferative activity	Decreases	Clonal proliferation[a]
Focal hyperplasia	Increases	Increases
Apoptosis	Increases	Decreases[a]
Autophagy	Increases	Decreases[a]
Angiogenesis	Decreases	Increases[a]
Bioenergetics	Decreases	Anaerobic glycolysis[a]
Cell-to-cell communication	Decreases	Decreases
Number of senescent cells	Increases	Increases
Latent (dormant) cell number	Increases	Increases
Systemic/organism level		
Melatonin circadian rhythm	Disrupted	Disrupted
Serum melatonin level	Decreases	Decreases
Hypothalamic biogenic amine level	Decreases	Decreases
Hypothalamic threshold of sensitivity to homeostatic inhibition by steroids	Increases	Increases

(*continued*)

Table 1 (continued)

Parameters	Aging	Carcinogenesis
Tolerance to glucose	Decreases	Decreases
Serum insulin level	Increases	Increases
Susceptibility to insulin	Decreases	Decreases
Insulin-like growth factor-1 (IGF-1) level	Decreases	Increases[a]
Low-density lipoproteins and cholesterol level	Increases	Increases
Serum glucocorticoid level	Increases	Increases
Fertility	Decreases	Decreases
T-cell immunity	Decreases	Decreases
Inflammoaging	Increases	Increases
Cancer risk	Increases	Increases
Population level		
Cancer incidence	Exponential pattern	Exponential pattern
Progeria	Acceleration	Increases
Exposure to 5-bromodeoxyuridine	Acceleration	Increases
Exposure to ionizing radiation	Acceleration	Increases
Exposure to constant illumination	Acceleration	Increases
Treatment with geroprotectors	Postponement	Prevents
Rate at the oldest age	Decreases in mortality	Decrease in incidence

[a]Related to clonally proliferating malignant cells

The incidence of cancer increases with age in humans and in laboratory animals alike, but the patterns of the age-related distribution of tumors are different for different tissues and different tumors. Aging may increase or decrease the susceptibility of different tissues to tumor initiation and usually facilitates promotion and progression of carcinogenesis. Aging may predispose to cancer by two mechanisms: tissue accumulation of cells in the late stages of carcinogenesis and alterations in internal homeostasis, in particular alterations in the immune and endocrine systems. Increased susceptibility to the effects of tumor promoters is found both in aged animals and aged humans, as predicted by the multistage model of carcinogenesis. Old animals should be included in standard protocols for the long-term assay for carcinogenicity, in particular, of compounds with suggested tumor-promoting activity. Strategies for cancer prevention must include not only measures to minimize exposure to exogenous carcinogenic agents but also measures to normalize age-related alterations in the internal milieu.

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Chronic Mechanistic Target of Rapamycin Inhibition: Preventing Cancer to Delay Aging or Vice Versa?

8

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Abstract

Caloric restriction prolongs lifespan and healthspan in all model systems tested so far, including yeasts, worms, flies, mice, rats, and monkeys (Rhesus macaques). Caloric restriction also improves healthspan, including reducing cancer development in mice and Rhesus macaques. Nonetheless, chronic caloric restriction to prolong life or healthspan, including cancer prevention, is unlikely to be popular or widely adopted for human clinical use. As caloric restriction inhibits mTOR, the pharmacologic mTOR inhibitor, rapamycin, was tested in lifespan extension and clearly prolonged lifespan and healthspan in mice even when started late in life. Although the types and prevalence of cancer in control and rapamycin-fed mice were similar, cancer-related deaths were delayed in mice fed rapamycin, demonstrating potential cancer prevention. Rapamycin and related pharmacologic mTOR inhibitors, collective dubbed "rapalogues," are considered too dangerous for chronic human use for longevity extension or cancer prevention. Nonetheless, these data raise the interesting possibility that a pharmacologic intervention to suppress mTOR, or more specifically mTORC1, could prolong lifespan or healthspan in humans, including through cancer prevention, provided that a safe and effective agent for these purposes were identified. Many questions remain, including the specific mTOR-related pathway most appropriate for targeting, doses and schedules of specific agents for such purposes, and understanding specific mechanisms of action. The question arises as to whether rapalogues prolong life or delay aspects of aging by preventing cancer. This chapter will examine evidence to date and provide suggestions for major areas of needed research and possibilities for clinical trials and applications.

Keywords

Cancer prevention · Rapamycin · mTOR · DNA repair · Longevity

Introduction

Cancer treatments are generally less effective for advanced stage and metastatic cancers, and despite recent successes with cancer immunotherapy agents (Topalian et al. 2016), most advanced and metastatic cancers remain incurable. Thus, primary cancer prevention is an important cost-effective alternative to treatment and likely to be better tolerated compared with traditional treatment regimens in cancer-prone, aged hosts. Further, efficacious cancer prevention strategies will reduce the prodigious health impact of cancer based on the foregoing data and therefore could reasonably be expected to prolong human lifespan. Recent advances in understanding the contributions of mammalian target of rapamycin (mTOR) signaling pathway in longevity extension and cancer prevention have demonstrated the potential for concomitant lifespan extension and reduction in age-related debilities, defined as the healthspan. This chapter will provide evidence for mTOR suppression as a bona fide, feasible cancer prevention approach, which could also afford improved healthspan and longer lifespan. Improved healthspan could potentially help mitigate the cost impact of lifespan extension. However, because of the legitimate concerns for

potential adverse effects of mTOR inhibition in large, relatively healthy populations (Lamming et al. 2013), many aspects of this approach require careful and detailed consideration. Despite challenges, the potential to target mTOR signaling or related pathways as a cancer prevention strategy appears tractable and worthy of additional investigations.

Aging Is the Principal Risk Factor for Cancer

In some countries in Europe, 21% of the population is older than 60 years. This 60+ year old population is predicted to account for ~34% of the population by 2050 (United Nations 2011). Cancer is largely a disease of the elderly, and the primary risk for cancer is advancing age (Siegel et al. 2017; Hiller et al. 2017). Therefore, healthcare, long-term care, and welfare systems sustainability in many developed and developing nations hinge on outcomes of attempts to develop safe interventions to slow aging, compress overall morbidity/disability and increase healthspan in humans, as approximately 2 billion people on the planet are anticipated to be age 65 years old or older by 2050. It is currently estimated that worldwide cancer incidence will nearly double from 14.1 million cases per year in 2012 to 22.2 million cases per year by 2030, a projection based in large measure upon the growing elderly demographic (Bray et al. 2012). Approximately 60% of new cancer diagnoses occur in people 65 years or older with a staggering 70% of total cancer-related deaths occurring in this group (Berger et al. 2006). The total economic impact of cancer is hundreds of billions of dollars annually in the United States alone (Society 2012). Cancer is the second leading cause of death in the United States, just barely behind heart disease (https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm) and a leading cause of death worldwide in 2012, the date of most recent comprehensive statistics (http://onlinelibrary.wiley.com/doi/10.3322/caac.21262/full). Please also see ▶ Chap. 1, "Population Trends in Aging and Cancer."

Caloric Restriction Prolongs Life and Healthspan

It has been known since the 1930s that reducing caloric intake without engendering malnutrition can prolong life (Hursting et al. 2003; Mccay et al. 1989). The phenomenon of longevity extension from caloric restriction has been validated in yeasts, worms, flies, rodents, and Rhesus macaques as described in detail in ▶ Chap. 7, "Aging and Cancer Biology". Mechanistically, caloric restriction of 30–40% without malnutrition impairs accelerants of aging, including decreased metabolism, circulating serum hormones, growth factor levels, and the central energy-regulatory adenosine monophosphate-activated protein kinase/mTOR pathway. Recent analysis of the 2-year CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) trial conducted by the National Institute of Aging in young, nonobese adults demonstrated that chronic caloric restriction (11.7% on average) slowed biological measures of aging (Belsky et al. 2017). This trial employed multiple algorithms using pre-, middle-, and posttrial biomarkers including serum albumin, alkaline phosphatase, and C-reactive protein, among others, to compare chronological versus biological age. Of note, the authors found that the extent of caloric restriction was positively correlated to the slowed rate of biological age, both in participants experiencing $<10\%$ caloric restriction and in those experiencing $\geq 10\%$ caloric restriction versus the ad libitum dietary arm. Please see ▶ Chaps. 20, "Pharmacology of Aging and Cancer" and ▶ 23, "Biomarkers of Aging (With a Clinical Potential in Oncology)" for more details. Aside from providing longevity extension, there are many health benefits from moderate caloric restriction, such as increased physical capabilities and reduced chronic or age-related diseases and including reduced cancer incidence (Kenyon 2010; Brandhorst and Longo 2016; Colman et al. 2014; Hursting et al. 2003) (see ▶ Chap. 7, "Aging and Cancer Biology").

Caloric Restriction Prevents Cancer

A consistent and notable observation is that chronic caloric restriction specifically reduces cancer incidence across model systems, suggesting a conserved cancer prevention mechanism (Brandhorst and Longo 2016; Colman et al. 2014; Fontana et al. 2010; Hursting et al. 2003). The overall cancer-preventive effects of caloric restriction likely owe to the multitude of cellular changes that include metabolic adaptions in insulin-like growth factor-1, cortisol, Sirtuin1, and inflammatory signaling, as well as molecular alterations in phosphoinositol-3 kinase/Akt/mTOR, mitogen-activated proteiern kinase, and adenosine monophosphate-activated protein kinase signaling (Longo and Fontana 2010). One mechanism by which caloric restriction is thought to prevent tumorigenesis is through the reduction in insulin and insulin-like growth factor 1 signaling, which converges downstream at the metabolic regulatory sensor mTOR complex 1, or mTORC1 through insulin receptor substrate 1-mediated phosphoinositol-3 kinase/Akt activation. Decreased mTORC1 activity limits protein, DNA, and lipid synthesis, slows cellular proliferation, and stimulates the canonical autophagy pathway. Thus, caloric restriction could directly limit cellular transformation by reducing the increased cellular metabolic activity required for cancer progression. Other mechanisms involved in aging include the impact of oxidative stress which results from the aforementioned deregulated pathways and is described in more detail in ▶ Chap. 13, "Mitochondria, Oxidative Stress, Cancer, and Aging."

Notably, two independent studies conducted by the University of Wisconsin National Primate Research Center and the National Institute of Aging discerned different healthspan and lifespan outcomes from caloric restriction in the non-human primate model of Rhesus macaques. The 23-year National Institute of Aging study initially reported that caloric restriction did not improve survival in primates, By contrast, the University of Wisconsin study demonstrated that caloric restriction significantly improved both lifespan and healthspan in Rhesus macaques (Colman et al. 2009). A subsequent analysis comparing the two studies showed that although monkeys in the studies at the National Institute of Aging and University of Wisconsin were initiated on a 30% caloric restriction diet, there was a significant decline in food intake as the animals aged (Mattison et al. 2012). A conserved finding now appreciated is that a 30% caloric restriction diet in adult primates reduces age-related and all-cause mortality (Colman et al. 2014; Mattison et al. 2012). In the University of Wisconsin study, calorically restricted monkeys experienced a 50% reduced cancer incidence along with significantly decreased cardiovascular disease, brain atrophy, and glucose regulatory impairment. Further, the mortality rate due to age-related disease was 13% in the caloric restriction cohort versus 37% in the control group, suggesting that caloric restriction improves healthspan by preventing many age-associated pathologies. The biology underlying the prevention of such pathologies can be found in greater detail in ▶ Chaps. 15, "Respiratory Organ Aging and Cancer," ▶ 16, "Digestive Organ Aging and Cancer," and ▶ 17, "Musculoskeletal Aging, Sarcopenia, and Cancer."

Partial fasting is a less severe form of caloric restriction yet nonetheless protects against toxicities of chemotherapy, reduces cancer progression, and improves immune functions (Cheng et al. 2014; Parrella et al. 2013; Fontana et al. 2010; Levine et al. 2014). However, the overall health including immune state and diet of the elderly patient must be carefully considered before, during, and after cancer therapy regimens as these patients could be at increased risk for cachexia. See also ▶ Chaps. 26, "Frailty in Cancer Patients," ▶ 56, "Digestive Symptoms Control and Nutrition Issues in Older Cancer Patients," and ▶ 60, "Decision Making and Safety Issues in Older Cancer Patients." Fasting-mimicking diets vary in caloric composition and duration but can involve periods of fasting from 2 to 21 days and longer in some cases. The positive impact of partial fasting on human health parallels that of caloric restriction and includes reductions in cardiovascular disease, weight, neurodegenerative disorders, and cancer

incidence (Mattson et al. 2016). In particular, fasting cycles that restrict protein have shown much success in limiting aging-associated diseases such as Alzheimer's disease and multiple types of cancer, attributed in many studies to reductions in the insulin-like growth factor-1 signaling pathway that inhibits Ras/MAPK and phosphosinositol-3 kinase/Akt, and ultimately mTORC1. Fontana et al. demonstrated that diets ranging from 7% to 21% protein-restricted effectively inhibited castration-resistant prostate cancer and breast cancer growth in multiple mouse models through decreased serum insulin-like growth factor-1 and mTORC1 activity (Fontana et al. 2013). See also ▶ Chap. 20, "Pharmacology of Aging and Cancer."

Interestingly, a fasting-mimicking diet of 5 days per month for 3 months elicited profound improvements in healthy human participants, as the fasting-mimicking diet reduced body mass index, blood pressure, and serum insulin-like growth factor-1 and cholesterol among other biomarkers for aging and cancer (Wei et al. 2017). The fasting-mimicking diet alone or in combination with the chemotherapy drug doxorubicin delayed syngeneic 4T1 breast cancer and B16 melanoma progression in vivo in mouse models (Di Biase et al. 2016). This antitumor effect depends on stress-responsive heme oxygenase-1, which was decreased in fasting-mimicking diet cohorts compared with control diet-fed mice, resulting in increased lymphoid progenitor cells and $CD8^+$ T cells. Moreover, the fasting-mimicking diet, alone or in combination with chemotherapy, sensitized breast and melanoma tumors to increased cytotoxicity by $CD8^+$ T-cells.

Nonetheless, caloric restriction is not universally preventive, as cancers less responsive to this approach have been defined. For example, in a murine model of lung cancer, tumors with an activating *PIK3CA* mutation (and thus constitutive phosphoinositide-3 kinase signaling) were resistant to preventive effects of caloric restriction (Kalaany and Sabatini 2009). In this same study, similar lack of efficacy of caloric restriction was seen in a *PTEN*-null murine model of prostate cancer, where there was no reduction in the incidence of prostate intraepithelial neoplasia lesions in calorically restricted versus ad libitum-fed mice. Thus, activating phosphoinositide-3 kinase pathway mutations such as *PIK3CA* or loss of tumor-suppressive *PTEN* might not be prevented by caloric restriction. The type and intensity of caloric restriction also directly influence the amount of cancer prevention engendered in mouse models (Lee and Longo 2011). Thus, it could be possible to develop dietary regimens that effectively reduce cancer risk and which could be acceptable to large human populations. In contrast to caloric restriction, in vitro and in vivo studies demonstrate that presence of phosphoinositol-3 kinase pathway activating mutations (*PIK3CA*, *PTEN*) actually confers sensitivity to rapamycin and rapalogue everolimus except when *KRAS* mutations are present (Di Nicolantonio et al. 2010).

mTOR Promotes Signals Through Distinct mTORC1 and mTORC2 Complexes

The mTOR pathway has been linked to longevity extension in every organism model studied (Johnson et al. 2013), and health and longevity benefits of caloric restriction derive at least in part from mTOR suppression (Miller et al. 2014). mTOR signals integrate diverse and numerous internal and environmental cues (e.g., growth factors, nutrients, stress, energy) to regulate fundamental cellular processes (e.g., biosynthesis of macromolecules including lipids and proteins, autophagy, the cell cycle, and cell differentiation fates) (Laplante and Sabatini 2012). mTOR is the central catalytic protein present in two distinct complexes, mTORC1 and mTORC2, into which additional complex-specific proteins are integrated for full activation and downstream signaling specific to each complex (Laplante and Sabatini 2012). mTORC1 signaling is the pathway generally considered to extend longevity (Johnson et al. 2013) but likely also cooperates with other pathways and factors. For example, insulin and insulin-like growth factor signals, also related to longevity, can modulate mTORC2 which directly activates Akt by phosphorylation

of serine 473 and ultimately activates mTORC1. Further, Raptor knockout to ablate TORC1 signals extends *C. elegans* lifespan, while RNAi-mediated downregulation of the Rictor homolog *rict-1*, which inhibits TORC2 signals, will either increase or decrease *C. elegans* lifespan depending on the diet composition (Vellai et al. 2003; Soukas et al. 2009).

Rapamycin Extends Life in Mice

As caloric restriction inhibits mTORC1, in 2005, David Sharp at the University of Texas Health Science Center at San Antonio proposed to the Interventions Testing Program of the National Institute of Aging that the pharmacologic mTORC1 inhibitor rapamycin might also extend lifespan by replicating essential signals of caloric restriction without the actual dietary modulation. Rapamycin was selected as the proof-of-concept mTORC1 inhibitor because of its high mTORC1 specificity that has been validated in an extensive body of published literature, including in human clinical trials (Kennedy and Pennypacker 2014; Lamming et al. 2013), despite some known adverse effects (Soefje et al. 2011). See also ▶ Chap. 20, "Pharmacology of Aging and Cancer."

Pharmacologic mTOR inhibitors are characterized by distinct mechanisms of action, which include small-molecule inhibitors and second-generation mTOR kinase/dual mTORC inhibitors. Rapamycin and rapalogues are small molecule mTOR inhibitors that complex with the FK506-binding 12 kDa protein (FKBP12) through methoxy group crosslinking (Marz et al. 2013; Brown et al. 1994; Sabatini et al. 1994). The rapamycin-FKBP12 complex subsequently binds to the FKBP-rapamycin-binding domain on mTOR, itself already complexed with Raptor and mLST8, to block substrate access to the mTOR kinase active site cleft, rather than directly inhibiting the mTOR active site (Yuan and Guan 2016).

Thus, although rapamycin-bound FKBP12 disrupts mTORC1 kinase activity to inhibit mTORC1 (Zoncu et al. 2010), long-term rapamycin can inhibit mTORC2 signals depending on specific cells and conditions in vitro and in vivo (Sarbassov et al. 2006). Recent studies attempting to decipher the molecular and structural basis of rapamycin's differential inhibitory potential on mTORC2 have found that differences in signaling effects are related in part to the duration of treatment. Specifically, both short-term and long-term rapamycin treatments potentiate dephosphorylation of cytoplasmic complex 2 components Rictor and Sin1 but only long-term rapamycin exposure impairs assembly of the mTORC2 complex (Rosner and Hengstschlager 2008).

Aging biologist Randy Strong at the University of Texas Health Science Center at San Antonio suggested improving rapamycin delivery in mouse chow by encapsulating rapamycin in edible polymers for ease of chronic oral administration and enhanced bioavailability. This microencapsulated rapamycin formulation was developed as eRapa in mouse chow and used to deliver ~2.42 mg/kg/mouse/day of rapamycin for initial longevity studies (Harrison et al. 2009; Dao et al. 2015). The proprietary eRapa formulation has been used to deliver low, intermediate, and high doses of rapamycin for dose-response studies and have been shown to have improved tolerability in mice over unencapsulated rapamycin (Harrison et al. 2009; Miller et al. 2014). Chronic eRapa administration prolongs lifespan up to 30% in mice even when given late in life and improves healthspan with a dose dependence and propensity to extend female over male lifespan (Harrison et al. 2009; Miller et al. 2014). At present, rapamycin and related pharmacologic mTORC1 inhibitors, collectively dubbed "rapalogues," are considered too dangerous to be given widely to general human populations for health or longevity extension (Lamming et al. 2013). Nonetheless, these data raise the interesting possibility that a pharmacologic intervention to suppress mTOR, or more specifically mTORC1 signals, could be used in humans, provided that a safe and effective agent for this purpose were identified, and/or that specific at-risk populations could be identified to justify the risk of adverse effects. Please also see ▶ Chaps. 7, "Aging and Cancer Biology" and ▶ 21, "Drug Interactions in Aging and Cancer."

Pharmacologic mTOR Inhibition and Cancer Prevention

Recent data demonstrating that caloric restriction reduces cancer incidence through mTORC1 suppression has led to considerable interest in evaluating pharmacologic mTOR inhibitors for cancer prevention. In addition to known longevity extension effects of rapamycin, there is a compelling rationale to use pharmacologic mTOR inhibitors as anticancer agents as many cancers have oncogene-driven phosphoinositol-3 kinase/Akt/mTOR activation. However, the clinical efficacy of rapalogues as monotherapy for cancer treatment is modest in all cancers evaluated, due to their cytostatic rather than cytotoxic effects (Zoncu et al. 2011) among other considerations, which could result from multiple mechanisms of phosphoinositol-3 kinase pathway reactivation including phosphoinositide dependent kinase 1-mediated phosphorylation of Akt tyrosine 308 (Zou et al. 2016). Some of these limitations and off-target effects have been addressed by evaluating efficacy of combinatorial strategies of rapalogues plus chemotherapies and autophagy inhibitors, in addition to the development of second-generation dual mTORC inhibitors that inhibit both mTORC1 and mTORC2 and that have moved into human cancer treatment trials (Gupta et al. 2012).

As mTORC1 promotes protein translation and tumor cell growth through translational machinery proteins including 4EBP1 and S6K, inhibiting mTORC1 blunts tumor growth through metabolic and protein synthesis impairment (Laplante and Sabatini 2012). These actions therefore suggest consideration for mTORC1 inhibitors as plausible cancer prevention drugs.

In the seminal 2009 multisite study by Harrison et al., rapamycin delivered in eRapa markedly extended median and maximal lifespan in genetically diverse UM-het 3 mice, an effect attributed by authors to limiting the incidence or lethality of age-associated neoplasms (Miller et al. 2011). A median of 10% and 18% were increased in male and female lifespan, respectively. Cancers are the leading cause of death in UM-het 3 mice, accounting for 66–70% of all deaths, with lymphoma, hemangiosarcoma, and lung carcinoma the most common, and approximately equally represented in eRapa-fed and control-fed mice (Miller et al. 2011). However, in some cancers, such as liver, lung, and mammary carcinomas, time of death was delayed in eRapa fed versus control mice (841 versus 1006 days, 755 versus 1004 days, and 826 versus 1142 days, respectively) suggesting that eRapa could either delay cancer onset, reduce growth of cancers, or make the cancer more tolerable as potential longevity mechanisms. See also ▶ Chaps. 54, "Principles of Cancer Targeted Therapy in Older Adults" and ▶ 64, "Research Methods: Translational Research in Geriatric Oncology."

It has now been convincingly demonstrated that eRapa inhibits tumor development in distinct mouse models of spontaneous cancer in the setting of specific predisposing genetic defects. In $Apc^{Min/+}$ mice, their defect in Wnt/β-catenin promotes colon tumorigenesis. eRapa delivering 2.42 mg/kg rapamycin daily potently suppressed intestinal neoplasia in this model and extended the survival of these mice from a median of 174 days to that of normal BL6 mice at 974 days (Hasty et al. 2014). In another study, eRapa potently suppressed neuroendocrine tumors in $Rb1^{+/-}$ mice with heterozygous loss of the Rb tumor suppressor gene. $Rb1^{+/-}$ mice were fed eRapa delivering rapamycin at 2.42 mg/kg/mouse/day starting at 9 weeks of age had significant lifespan extension from 377 days to 411 days in females and 369–420 days in males as compared with the control-diet cohort. eRapa-fed mice had a significantly decreased incidence of thyroid tumors common in the $Rb1^{+/-}$ mice that could have improved their survival (Livi et al. 2013). See also ▶ Chap. 43, "Colorectal Cancer in Older Adults: Systemic Treatments."

In $p53^{+/-}$ male mice with heterozygous loss of the p53 tumor suppressor gene, 1.5 mg/kg/day rapamycin in drinking water reduced spontaneous cancer incidence and effectively extended mean lifespan by 10% (Komarova et al. 2012). By contrast, in a different study of $p53^{-/-}$ mice null for p53, eRapa delivering rapamycin at 2.42 mg/kg/mouse/day afforded no cancer prevention or survival extension (Christy et al.

2015), suggesting that rapamycin requires functional p53 for some of its cancer prevention activities. However, these two studies also differed in the specific mice tested and the type and dose of rapamycin used.

Rapamycin has been evaluated for efficacy in two murine models of Human papilloma virus E6/E7 gene-expressing anal cancer. Rapamycin 5 mg/kg/day in slow release pellets for 17 weeks effectively slowed tumor growth 2.5 fold in K14E6/7 mice (Stelzer et al. 2011). In another model of human papilloma virus E6/E7-driven squamous cell skin carcinoma, rapamycin treatment before topical skin application of the carcinogen dimethylbenz(a) anthracene resulted in robust decrease in squamous cell carcinoma development (Callejas-Valera et al. 2016). In a study of female A/J mice, lung adenocarcinoma was induced with the nicotine-associated carcinogen nitrosamine ketone (Patlolla et al. 2015). Early intervention (3 weeks postnitrosamine ketone) or late intervention (20 weeks postnitrosamine ketone) with diets containing 0, 8, or 16 parts per million rapamycin reduced lung adenocarcinoma development and also reduced adenomas that could progress to cancers. In early intervention, rapamycin prevented 26% (low dose) and 42% (high dose) of nitrosamine ketone-induced lung tumor formation. In late intervention, rapamycin prevented 31% (low dose) and 44% (high dose) of nitrosamine ketone-induced lung tumor formation. The authors observed a robust inhibition of p-mTOR, p-S6 K, PCNA, and other proteins. See also ▶ Chaps. 49, "Lung Cancer in Older Adults: Systemic Treatment" and ▶ 21, "Drug Interactions in Aging and Cancer."

Since many cancers arise in chronic inflammation (Demaria et al. 2010), rapamycin was tested as a cancer prevention agent in a model of carcinogen (dimethylbenz(a) anthracene) plus inflammation (12-O-tetradecanoylphorbol-13-acetate)-induced squamous cell skin cancer. BL6 mice were fed eRapa delivering rapamycin at 2.42 mg/kg/mouse/day or Eudragit control for 1 month. DNA damage was then initiated with 100 μg dimethylbenz(a) anthracene and tumors were promoted with 12-O-tetradecanoylphorbol-13-acetate, 25 μg/week for 24 weeks. In this model, initially benign skin papillomas eventually undergo malignant degeneration into squamous cell carcinomas after about 4 months. eRapa significantly reduced the development of benign papillomas and fully protected against their malignant degeneration. eRapa did not affect $CD45^{-}CD34^{+}CD49f^{mid}$ cancer initiating stem cells or affect major, known immune mediators of malignancy in this model, suggesting alternative cancer protective mechanisms (Dao et al. 2015).

Anecdotal evidence suggests that rapalogues could be safe and tolerable for effective cancer prevention in a high-risk population. For example, in human transplant recipients, mTOR inhibitor use correlated with reduced postkidney transplantation cancer rates (De Fijter 2017). However, these data derive from observational studies without defined mechanisms. These interesting observations merit additional follow up. See also ▶ Chap. 37, "The Evolving Role of Transplant for Older Adults."

Rapamycin and rapalogues are thought to blunt tumor growth by inhibiting mTOR signals, particularly mTORC1 directly in the cancer cells (Riaz et al. 2012). Nonetheless, in dimethylbenz (a) anthracene/12-O-tetradecanoylphorbol-13-acetate dermal carcinogenesis, eRapa did not affect p-mTOR serine 2448 in skin despite its potent capacity to inhibit benign skin neoplasia and malignant degeneration. There was evidence that eRapa inhibited mTORC1 signals as detected by Western blots for p-4E-BP1 and p-rpS6 in tumors and skin of dimethylbenz(a) anthracene/12-O-tetradecanoylphorbol-13-acetate-treated mice. Further, eRapa appeared to inhibit mTORC2 as detected by reduced p-Akt serine 473 (Dao et al. 2015). mTORC1 could be suppressed specifically in the skin cancer-initiating cell that drives carcinogenesis in this dimethylbenz(a) anthracene/12-O-tetradecanoylphorbol-13-acetate model (Affara et al. 2006), but this explanation is not supported by the finding that mTORC1 was not suppressed in

the benign papillomas and the numbers and proliferation of cancer initiating cells were not affected by eRapa (Dao et al. 2015). A different group of investigators used four applications of topical rapamycin prior to 12-O-tetradecanoylphorbol-13-acetate in dimethylbenz(a) anthracene/12-O-tetradecanoylphorbol-13-acetate carcinogenesis and found reduced p-mTOR and p-rpS6 (evidence for reduced mTORC1), and increased p-Akt serine 473 (evidence for increased mTORC2) in skin (Checkley et al. 2011), which could be due to effects of short-term rapamycin in this work versus chronic rapamycin in the prior study, or differences in oral versus topical rapamycin effects or rapamycin versus eRapa effects, among other considerations. The authors ascribed mTORC1 suppression as the mechanism of cancer prevention in this work.

In the $Apc^{Min/+}$ intestinal neoplasia model (Hasty et al. 2014), the rapamycin concentration in intestine after eRapa was ~7000-fold higher than skin rapamycin concentrations after the same eRapa dose in dermal dimethylbenz (a) anthracene/12-O-tetradecanoylphorbol-13-acetate carcinogenesis (Dao et al. 2015). Low skin rapamycin concentrations suggest that either these low levels suffice to suppress skin tumorigenesis, or that higher rapamycin concentrations in some other anatomic compartments affect immunity or other factors that control dermal carcinogenesis. Thus, more work on tissue delivery of mTOR inhibitors are needed, particularly to define the lower limits of drug that are still effective in cancer prevention, as such knowledge could help develop protocols using rapalogues with minimal adverse effect potential. See also ▶ Chap. 60, "Decision Making and Safety Issues in Older Cancer Patients."

mTOR Mediates Significant Immune Effects

mTOR has many notable immune effects such as controlling differentiation and function of conventional αβ T cells (Delgoffe et al. 2011; Powell et al. 2012) and regulatory T cells (Delgoffe et al. 2009), and rapalogues are generally considered immunosuppressive through reducing T cell interleukin-2 production that then blunts T cell activation. Nonetheless, recent reports show that rapalogues can improve -antigen-specific B cell (Keating et al. 2013) and T cell (Araki et al. 2009) immunity in virus infections in mice and improve vaccine responses in elderly humans (Mannick et al. 2014). See also ▶ Chap. 6, "Immunosenescence and Cancer Immunotherapy at Old Age: Basics."

eRapa was given to young (6 months old) or aged (19–22 months old) BL6 mice for 6 months without other interventions to assess immune effects of chronic mTOR suppression (Hurez et al. 2015). Many notable immune effects were seen in mice fed eRapa, but effects in young and aged mice, and between males and females were surprisingly similar for most immune outcomes studied. There was no major eRapa effect on regulatory T cell numbers or function in spleen, although regulatory T cell numbers were increased in Peyer's patches. There were few changes in myeloid cell and B cell numbers or composition. T cell numbers and Th1 immunity, which produces interferon-γ and is associated with anticancer immunity were reduced by eRapa. Some changes were also noted in Th2, Th9, Th17, Th22, Treg, and T-follicular helper T cell differentiation pathways. Notably, Th17 $CD4^+$ T cells producing IL-17, generally considered to be proinflammatory, were increased by eRapa. T cell PD-1 is a marker of poorly functional, exhausted T cells. eRapa reduced PD-1 expression in $CD4^+$ and $CD8^+$ T cells, and functional tests showed the $PD\text{-}1^+$ T cells from eRapa-fed mice were more functional than their counterparts from control-fed mice. eRapa also reduced expression of the Lag3 exhaustion marker in both $CD4^+$ and $CD8^+$ T cells. These changes are generally consistent with improved cancer immune surveillance and with the concept that rapamycin could prevent cancer through immunomodulation.

Immune Effects of Rapamycin in Cancer Prevention

Based on potential for rapamycin to boost cancer immune surveillance that prevents cancer, studies of potential immune effects of rapamycin in cancer were investigated. In the dimethylbenz (a) anthracene/12-O-tetradecanoylphorbol-13-acetate dermal carcinogenesis model, eRapa increased γδ T cell numbers and functions but not conventional αβ T cell numbers or functions in skin of BL6 mice. Despite almost 100% protection from cancer by eRapa in wild-type mice, δ TCR knockout mice specifically lacking only γδ T cells were entirely unprotected from dimethylbenz(a) anthracene/12-O-tetradecanoylphorbol-13-acetate dermal carcinogenesis by eRapa, demonstrating an important role for γδ T cells in eRapa protection against dermal carcinogenesis, at least in this model. Moreover, intratumoral injection of γδ T cells recovered from eRapa-treated but not control treated mice resulted in regression of established dimethylbenz (a) anthracene/12-O-tetradecanoylphorbol-13-acetate cancers. eRapa-mediated γδ T cell perforin was shown to be required to mediate tumor regressions. Cancer protection also required interferon-γ that induced the chemokine CXCL10 to recruit $CXCR3^+$ γδ T cells into the tumor. Thus, eRapa-mediated cancer protection depends on specific immune factors including γδ T cells, their perforin and host IFN-γ to recruit γδ T cells to skin (Dao et al. 2016). Such data suggest that underlying host immunity or rapamycin-induced immune effects can contribute to rapamycin cancer prevention, which could affect populations considered for potential trials, or suggest novel means to improve cancer prevention effects through other immune boosting agents. These investigators further showed that eRapa affected distinct γδ T cell subsets in mice. Human γδ T cell subsets differ from those in mice, so direct comparisons to humans cannot be made, but like mice, γδ T cells in humans are also tissue-specific, suggesting that rapamycin immune effects could differ in distinct organs or in distinct cancer types. Further, this study only examined young mice, and thus age effects on cancer prevention were not tested. As immune functions change with age (Mirsoian et al. 2014; Hurez et al. 2012; Hurez et al. 2015) (and see rapamycin has been shown to improve immune functions in age (Hurez et al. 2015), this concept bears further investigations.

Low-dose rapamycin also improved a cancer vaccine in a mouse cancer model (Pedicord et al. 2015) and improved T cell activation and immunotherapy in a mouse model of lymphoma and melanoma (Liu et al. 2017). Thus, rapamycin at low doses has significant antitumor effects through immune modulation, which could be useful in cancer prevention. However, rapamycin or caloric restriction could face limitations as effective immune interventions for the elderly if used at too high a dose (rapamycin) or intensity (caloric restriction) (Goldberg et al. 2015). The impact of either antiaging intervention was evaluated in BL6 mice for 60 days, following infectious challenge with West Nile Virus. Interestingly, rapamycin and caloric restriction have differential effects on thymic cellularity. Calorically restricted mice had a higher proportion of naive peripheral $CD8^+$ T cells but that did not translate into improved immune response to West Nile virus infection and could reduce survival in infection. Older mice on caloric restriction were more prone to West Nile virus infection and had reduced T cell function and thus an increased mortality rate compared with age-matched controls. Distinct mechanisms for caloric restriction versus mTOR inhibition to impair adaptive immunity in aged mice were found in this work.

Age-related adiposity promotes detrimental inflammation generally, and specifically in anticancer immunotherapy including through tumor necrosis factor-α-related pathways. Caloric restriction in aged mice reduced adiposity and tumor necrosis factor-α-driven inflammation during cancer immunotherapy that decreased immune treatment toxicity or anti-CD40 antibody plus interleukin-2 (Mirsoian et al. 2014). These data suggest that antitumor necrosis factor-α strategies could be used to mitigate potential toxicities of immunotherapies in aged humans or mitigate mTOR-driven cancer immune surveillance to prevent cancer. Limitations of this nicely done study are that while immunotherapy effects were

studied, more commonly used immunotherapy approaches (antibodies against PD-1, PD-L1, and CTLA-4) were not studied, nor were tumor-bearing mice studied. See also ▶ Chaps. 6, "Immunosenescence and Cancer Immunotherapy at Old Age: Basics" and ▶ 29, "Predictive Tools for Older Cancer Patient Management."

T cells and interferon-γ are major mediators of cancer immune surveillance (Mittal et al. 2014). Strikingly, RAG knockout mice lacking T or B cells and interferon-γ knockout mice derived very significant improvement in lifespan and healthspan when eRapa delivering rapamycin at 2.42 mg/kg/mouse/day was given from 2 months of age (Hurez et al. 2015), demonstrating that eRapa can improve lifespan in the absence of major cancer defense mechanisms and can improve health span even in the absence of major inflammation mediators.

Cancer Prevention Effects of Other mTOR Inhibitors

In addition to the demonstrated cancer prevention properties of mTOR inhibition through caloric restriction or rapalogues, metformin and aspirin also have noteworthy cancer prevention properties that might include mTOR inhibition as a mechanism. The widely used antidiabetic agent metformin inhibits hepatic glucose production through activation of the energy regulator adenosine monophosphate-activated protein kinase, which inhibits downstream mTORC1 signaling and thus mimics caloric restriction and rapalogues in this respect. In addition to its obvious utility for treating type 2 diabetes, metformin has therapeutic potential against human age-related pathologies by combatting inflammation, oxidative stress, and premature senescence (Novelle et al. 2016). These effects suggest that it could help prevent cancer (and other disorders, including Alzheimer's disease and Parkinson's disease (Markowicz-Piasecka et al. 2017)). See also ▶ Chap. 5, "Cellular Senescence and Tumor Promotion."

Recently, chronic low-dose dietary metformin was demonstrated to mimic caloric restriction or rapalogue administration and to extend both lifespan and healthspan in multiple mouse models. One study show a dose-dependent difference in metformin effects, where B6C3F1 and BL6 male mice were given either 0.1% (10.6 mg/kg/mouse/day, defined as low-dose) or 1% (high-dose) metformin for 30 weeks (Martin-Montalvo et al. 2013). Both cohorts of mice given lose-dose metformin had a 4 to 6% increase in mean lifespan, while the high-dose cohorts had an unexpectedly shortened lifespan associated with renal toxicity and lactic acidosis. The low-dose metformin-fed mice had improved healthspan evident by increased physical performance and body weight maintenance, and reduced ocular lens opacity, insulin, and cholesterol levels. Further, transcriptome analysis in this same study showed that low-dose metformin-fed mice had gene expression changes similar to calorically restricted mice in stress-response pathways, mitochondrial bioenergetics, glycolysis, and fatty acid metabolism. In particular, similar trends in decreased gene expression of serum amyloid protein expression (*SAA1*, *SAA2*) was found in livers of both metformin and calorically restricted mice, consistent with a reduced inflammatory response.

In a study of metformin as a cancer prevention agent, 9-week-old $Apc^{Min/+}$ mice received daily dietary metformin (250 mg/kg) or control chow for 10 weeks. Although there was no difference in the total number of intestinal polyps between metformin versus control diet mice, metformin significantly decreased polyp size and cell proliferation as assessed by BrdU staining. Moreover, metformin inhibited mTORC1 signaling as seen in blunted mTOR and S6K phosphorylation, leading to reduced protein synthesis, which could help explain reduced polyp size but not numbers.

The analgesic and nonsteroidal anti-inflammatory agent acetylsalicylic acid (aspirin) is a mainstay for prevention of multiple age-associated pathologies including colorectal cancer, cardiovascular disease, and stroke (Richman and Owens 2017). Salicylate, a plant-derived natural product from which aspirin is synthesized, allosterically activates adenosine

monophosphate-activated protein kinase by preventing dephosphorylation of T^{172} (Hawley et al. 2012). Aspirin is one of the most potent cancer prevention agents for colorectal cancer known and was recently shown to reduce 20-year risk of colorectal, stomach, gastrointestinal, and prostate cancers among other cancers – a benefit that increases proportional to the duration of aspirin intake (Rothwell et al. 2011). Salicylate activates adenosine monophosphate-activated protein kinase signaling, leading to inhibition of mTOR inhibition and induction of autophagic flux (Din et al. 2012). Additional studies are required to understand how aspirin prevents cancer to optimize its clinical uses.

Potential mTOR-Related Targets

Many life-extending interventions in model organisms including calorie restriction, adenosine monophosphate-activated protein kinase activation, insulin/insulin-like growth factor signaling inhibition, and possibly sirtuins work by reducing mTORC1 signaling (Johnson et al. 2013; Kennedy and Pennypacker 2014). These data suggest that these interventions are at least partially dependent on mTORC1 signals. However, downstream signaling consequences are not fully defined. 4E-BP1 and S6K are each downstream of mTORC1 and each have longevity extension effects. S6K deletion in yeast, flies, worms, and mice improves longevity (Johnson et al. 2013), and increased 4E-BP1 activity (a consequence of mTORC1 suppression) improves longevity in flies. Interestingly, rapamycin is generally unable to reduce mTORC1-mediated inhibition of 4E-BP1 phosphorylation as effectively as its capacity to inhibit other downstream mTORC1 targets. Thus, either 4E-BP1 activation is not a major longevity extension mechanism for rapamycin, or rapamycin longevity effects could be further improved by adding an agent specifically to activate 4E–BP1. Of note, 4E-BP1 is phosphorylated at multiple residues through mechanisms that could be both mTOR-dependent (at tyrosine 36/45) and mitogen-activated protein kinase pathway-dependent (at serine 64 and threonine 69) depending on the stimulus (Herbert et al. 2002). The cross-talk between the mitogen-activated protein kinase pathway and phosphoinositol-3 kinase/Akt/mTOR pathway has resulted in understanding that the mitogen-activated protein kinase pathway is activated in response to rapamycin or rapalogues in multiple preclinical and clinical studies (Mendoza et al. 2011). In particular, the mitogen-activated protein kinase pathway promotes mTORC1 activation independent of phosphoinositol-3 kinase/Akt signaling through multiple mechanisms, including activating eIF4B phosphorylation at serine 422 (Shahbazian et al. 2006) and mTORC1-activating Raptor phosphorylation at serine 8, serine 696, and serine 863 (Carriere et al. 2011). The impact of this alternative mTORC1 activation by mitogen-activated protein kinase pathway signaling has potential for evaluation of biomarkers to predict rapamycin efficacy or could become future drug targets in combination with rapamycin therapy. See also ▶ Chap. 54, "Principles of Cancer Targeted Therapy in Older Adults."

The details of eRapa-mediated signaling downstream of mTOR in cancer prevention are little reported. In studies of skin cancer prevention using eRapa in dimethylbenz(a) anthracene/12-O-tetradecanoylphorbol-13-acetate-induced dermal carcinogenesis, mTORC1 was not clearly inhibited in skin or the tumors there as detected by Western blotting for S6K and 4E-BP1phosphorylation (Dao et al. 2015). By contrast, topical rapamycin suppressed both mTORC1 and mTORC2 in this model (Checkley et al. 2011). At least in *C. elegans*, intact autophagy is also required, though not sufficient, for lifespan extension in response to TOR complex 1 inhibition (Hansen et al. 2008). Little is known in this regard for life extension in other models or in cancer prevention.

Finally, upstream mTOR modulators such as adenosine-monophosphate activated protein kinase (discussed above), the tuberous sclerosis complexes 1 and 2 and Rheb (Martin and Hall 2005) could be considered as druggable targets for cancer prevention.

Other mTOR Effects in Cancer Prevention

eRapa reduced the DNA damage that is critical to dimethylbenz(a) anthracene/12-O-tetradecanoylphorbol-13-acetate-induced carcinogenesis as demonstrated by reduced phosphorylation of H2AX, an indicator of double-stranded DNA breaks, and reduced mutation of the *HRAS* codon 61 that promotes carcinogenesis in this two-stage skin model (Digiovanni 1992). Thus, eRapa could prevent some cancers by reducing DNA damage. In this dermal carciongenesis model, when eRapa was delayed until after tumor initiation (DNA damage) with dimethylbenz(a) anthracene, protection from cancer was abolished, consistent with the concept that some eRapa protection in tis model could be from reducing DNA damage. Langerhans cells in skin promote carcinogenesis in the dimethylbenz (a) anthracene/12-O-tetradecanoylphorbol-13-acetate model by metabolizing dimethylbenz (a) anthracene to its active carcinogenic metabolite, but eRapa did not alter numbers of skin Langerhans cells (Modi et al. 2012). Nonetheless, it is possible that rapamycin could prevent cancer by altering the metabolism of carcinogens. See also ▶ Chap. 4, "Role of Cell Cycle Control, Checkpoints, and DNA Repair Mechanisms in Stem Cells and Changes with Aging and Cancerogenesis" A detailed understanding of metabolic effects and other cancer prevention effects of mTOR inhibition or of rapalogues will help define optimal patient populations most likely to benefit from cancer prevention using mTOR inhibitors.

Adverse Effects of mTOR Inhibitors

Rapalogues can generate significant adverse effects in murine models and humans, including but not limited to metabolic dysfunction (e.g., insulin resistance, hyperinsulinemia, hyperglycemia), hematopoietic lineage defects (e.g., defective proliferation of specific bone marrow cells) interstitial pneumonitis, and other adverse toxicities including mucositis and rash (Soefje et al. 2011). The majority of human data on rapamycin adverse effects have been obtained in sick patient populations, not from healthy individuals. Thus, data on adverse rapalogue effects in generally health populations as would be studied in longevity extension or cancer prevention trials are largely unknown. Everolimus (RAD001) is a rapalogue with mTORC1 inhibitory properties similar to rapamycin but with better pharmacokinetics. In addition to its use as an immunosuppressant for transplant patients, everolimus is FDA-approved to treat kidney, breast, and neuroendocrine tumors of gastrointestinal or lung origin and is being evaluated in a multitude of cancer treatment clinical trials. In a study of everolimus in elderly humans to improve influenza vaccine efficacy, low doses (about 20% of typical pharmacologic doses) were relatively well-tolerated, with relatively few adverse effects (Mannick et al. 2014). The primary endpoint of improving influenza vaccine efficacy was achieved in this study, demonstrating the potential for improved immune function during aging. See also ▶ Chap. 27, "Geriatric Interventions in Oncology."

Further, as rapamycin adverse metabolic effects are largely attributed to inhibiting mTORC2 (Lamming et al. 2012), it could be feasible to mitigate adverse metabolic effects by specifically inhibiting mTORC1, without loss of clinical efficacy. RTB101 is a drug developed by resTORbio that inhibits S6K and 4E-BP1 activation but not the whole mTORC1 pathway when used at low doses. Everolimus plus RTB101 synergistically inhibits mTORC1 without inhibiting mTORC2. In a trial of influenza vaccine efficacy in the elderly, RTB101 at 10 mg/day plus everolimus at 0.1 mg/day, both given orally, improved influenza vaccine efficacy better than either agent alone. Significant adverse events of the drug combination included diarrhea, nausea, mouth ulcers, and rash. Hyperglycemia and hyperlipidemia were worse with everolimus alone versus everolimus plus RTB101. Nonetheless, the combination was generally well tolerated and is moving forward clinically.

A recent panel of longevity experts met in Erice, Sicily, to discuss moving specific agents into human longevity trials. After much discussions that culminated in vetting an extensive list of

gene targets and drugs, the group selected dietary mimetics of chronic dietary restriction (e.g., fasting cycles, protein restriction), drugs to inhibit the growth hormone/insulin-like growth factor-1 axis or the mTOR-S6K pathway and drugs to activate adenosine monophosphate-activated protein kinase and sirtuins or anti-inflammatory agents as most promising for human trials on healthspan extension (Longo et al. 2015). Many of these approaches also have cancer prevention potential. Thus, clinical data on cancer prevention from these trials is possible.

Closing Thoughts

Much data suggest that the mTOR signaling pathway is a drug discovery target not only for longevity extension but also to prevent cancers, which could secondarily improve lifespan or healthspan. Rapamycin is a proof-of-concept agent for this concept and might not ultimately be optimal for general cancer prevention in humans owing to toxicity concerns (Lamming et al. 2013). Notably, there has been concern for immunosuppression. However, rapalogues are often combined with other immunosuppressive agents and therefore its specific effects in humans are not fully understood. However, rapalogue cancer prevention benefits in selected high-risk populations (such as those with familial adenomatous polyposis at extremely risk for early colon cancer) could outweigh risk concerns and justify use in such selected populations.

Currently, studies of rapamycin effects in normal humans are not reported in detail. There is new data showing that rapalogues augment immunity to pathogens (Havenith et al. 2013; Keating et al. 2013) and boost vaccine immunity in elderly humans (Mannick et al. 2014), consistent with beneficial immune effects. Work showing that eRapa prevents cancer in spontaneous tumor models (Hasty et al. 2014; Livi et al. 2013; Komarova et al. 2012) and in models of inflammation-driven cancer (Dao et al. 2015, 2016; Saha et al. 2015), extends lifespan to normal in $Apc^{Min/+}$ mice (Hasty et al. 2014) and greatly improves lifespan and healthspan in highly immunodeficient RAG KO, and interferon-γ KO mice (Hurez et al. 2015) is inconsistent with rapamycin mediating detrimental immunosuppression and supports further studies of rapalogues and agents targeting mTOR signals as cancer prevention agents.

Mechanisms for rapamycin-mediated cancer prevention are likely complex and multifactorial and could include improved cancer immune surveillance, immunostimulation, delayed biological aging, increased autophagy, or reduced DNA damage, among other considerations. See also ▶ Chap. 6, "Immunosenescence and Cancer Immunotherapy at Old Age: Basics." As mechanistic details are better understood, additional drugs or targets could be identified for cancer prevention. Such information will help determine optimal use of agents and optimal populations for clinical testing. eRapa longevity extension effects also include sex differences (females generally derive greater longevity benefits versus males), and mechanisms are shown to differ from those mediated by caloric restriction (Miller et al. 2014). Thus, the hunt for additional drugs to intervene in mTOR-mediated effects on longevity and cancer prevention continues.

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Calpain-Calpastatin System in Lymphoid Neoplasm of the Aged

9

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Abstract

Two ubiquitous calpains (extremely calcium-dependent, neutral, cytoplasmic cysteine proteases) and their endogenous inhibitor – calpastatin – form the calpain-calpastatin system (CCS). Activity of the CCS is implicated in the processes of proliferation and apoptosis of many human cell types. We have demonstrated a necessity of resting activity of the CCS for adequate proliferative response of nonmalignant T lymphocytes, as well as the reduction of amounts and activities of the CCS proteases in the elderly. On the other hand, we have also shown that hyperactivity of the CCS protects chronic B-cell leukemia (B-CLL) cells from apoptosis and possibly

induces their excessive proliferation. As the B-CLL is the typical leukemia of old age, and relatively frequently transforms into the tumor (lymphoma) growth, it was interesting to analyze the existing data on overall role of the CCS in the processes of proliferation, apoptosis, aging, and malignant transformation of human lymphoid cells. This chapter summarizes these data.

Keywords
Aging · Lymphocytes · Lymphoid malignancy · Leukemia · Lymphoma · Cell proliferation · Apoptosis · Limited proteolysis · Calpain · Calpastatin

Introduction: Basic Characteristics of Lymphoid Malignancies

Any malignancy derived from cells belonging to whatever stage of lymphopoiesis, whether in the bone marrow or in periphery, is considered to be a lymphoid neoplasm. These lymphoid neoplasms in general, as well as those more typical for the elderly, are clinically divided into lymphoid leukemias and lymphomas. While the first are delocalized, i.e., growth of malignant cells occurs initially in the bone marrow from which they may spread via blood to organs which they infiltrate, the latter are more typical tumors, which can develop in the lymphatic organs or elsewhere. In fact, the malignancy belonging to lymphoid neoplasms' group is now considered a leukemia if it tends to affect circulating cells only, a lymphoma if it tends to produce tumors, and a lymphoma/leukemia if it exhibits both these features together (Swerdlow et al. 2016).

Lymphomas are broadly divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHLs) while leukemias – mostly for clinical reasons – into the acute lymphoblastic leukemias (ALLs) and chronic lymphocytic leukemias (CLLs).

HL is now considered (despite its variegated clinical and pathomorphological forms) to be derived from some developmental stage of the B lymphocyte (likely from the germinal center (GC) lymphocytes), which not only proliferates but also differentiates into disease-characteristic cells, namely, Reed-Sternberg and LP cells. Agewise, the peak incidence of Hodgkin lymphomas is observed in 15–35-year-olds, and a secondary incidence peak is seen around the age of 55 (Caporaso et al. 2009).

On the other hand, NHLs form a large group of lymphoma subtypes, which substantially differ in both their clinical features and cellular origin and in susceptibility to therapy. They can be broadly divided into B-cell and T-cell lymphomas and other, not specified, lymphoproliferative disorders. Lymphopoiesis is very complex, and multiple stages are distinguished in the development of each phenotypically distinct form of lymphocytes. Thus, B-cell lymphomas can be further divided into five main types: diffuse large B-cell, mantle cell, marginal zone, follicular, and Burkitt lymphomas. What makes the NHLs more relevant to the topic of this chapter is their incidence rates, which rise steeply from age 50 to 54, and peak in the 85–89 age group for both sexes (Smedby and Hjalgrim 2011; Fisher and Fisher 2004).

Common characteristics of all lymphoid leukemias and lymphomas have on one hand very high proliferation rate corresponding to high mitotic indexes and resulting in potential tumor/total cell mass doubling time between 40 and 100 h; this indicates that most cells in these tumors are cycling at any time (Lang et al. 1980). This was long ago confirmed by quantitation of cells expressing the Ki-67 antigen characterizing the non-resting (i.e., dividing) cells; depending on the clinical grade of lymphoma, proportion of Ki-67-positive blasts may reach even 70% (Baird 1993; Cooperman et al. 2004). Similar proportions of Ki-67+ lymphocytes are only seen in the germinal centers of reactive lymph nodes and undergo reduction with pathogen elimination.

On the other hand, growing of each lymphoid neoplasm does not stem from higher-than-healthy proliferation rates only. Another reason for their rapid accumulation is decreased or even fully eliminated susceptibility to undergo apoptosis. This finding is true for Hodgkin lymphomas,

non-Hodgkin lymphomas, and lymphoid leukemias (Mani and Jaffe 2009; Kunkalla et al. 2013; Packham et al. 2014; Mikosik et al. 2015; Witkowski et al. 2002). Major molecular mechanisms involved in apoptosis abrogation in lymphoid neoplasms include increased expression of anti-apoptotic and pro-survival molecules on one hand and decreased expression of pro-apoptotic species on the other (Tacke et al. 2004; Ito et al. 2004; Dadi et al. 2012).

Calpains, Calpastatin, and Their Roles in Cellular Survival, Proliferation, and Apoptosis

Every eukaryotic cell possesses multiple proteolytic enzymes either freely floating in cytoplasm or attached to or embedded in intracellular organelles (lysosomes) or forming specific macromolecular machines (proteasomes). Their roles range from total degradation of proteins and peptides to amino acid "building bricks" through limited cleavage into smaller and larger peptides with specific functions to a limited modulating proteolysis, where only a (usually regulatory) part of a protein is clipped off to change the substrate properties and functions. Ultimate "scissors" yielding free amino acids can be found as amino- and carboxypeptidases in the cytoplasm as well as in lysosomes. The enzymatic activities contained in the lysosomes mostly deal with the extracellular substrates brought inside the cell by the process of endocytosis (in the innate immune cells culminating as phagocytosis of bacteria and certain own cells); another facet of lysosomal activities is their participation in autophagy – a process where intracellular organelles (e.g., mitochondria) are contained in actively formed intracellular vesicles which then fuse with lysosomes, allowing for recycling of molecules building an organelle and recuperation of some energy (Anding and Baehrecke 2017). Also the proteasomes, which require "tagging" of the proteins to be targeted and degraded by their binding with a number of ubiquitin molecules (polyubiquitination), serve to degrade the intracellular proteins (including obsolete, used-up, and misfolded). However, they do not convert the digested proteins to their amino acid components. Rather, the product of intraproteasomal proteolysis is the range of peptides with the length from 3 to 22 amino acids which, in order to yield free amino acid "bricks," require further proteolysis by cytoplasmic peptidases. Still, proteasome function, as well as that of derived immunoproteasomes, is indispensable, as they provide each cell with the capability to present antigenic epitopes to the cytotoxic lymphocytes. Thus, some of these proteasome-derived peptides (typically 8–10 aa long) may directly be loaded onto MHC Class I complexes and serve as epitopes to be recognized by the T-cell receptors on CD8+ cells. Stimulation with gamma interferon leads to exchange of certain components within the proteasomes which converts them to immunoproteasomes, capable to manufacture the presentable epitopes at much higher rate than proteasomes and with average lengths more suited for binding in the MHC Class I "groves" (McCarthy and Weinberg 2015; Neefjes et al. 2011).

Calpains: General

Calpains (calcium-dependent, neutral, cytoplasmic cysteine proteases) form a (currently) 15-member family of cytoplasmic endopeptidases with very specific properties and list of intracellular substrates. Since their discovery in 1964, they draw broad attention of scientists as the only protease group so strongly dependent on contact with Ca^{2+} (Ono and Sorimachi 1824; Ono et al. 2016). Some of these enzymes are relatively ubiquitous (including calpains numbered 1, 2, 5, 7, and 10), while the activity of others is apparently limited to specific tissues (Potz et al. 2016; Baudry and Bi 2016). Another evolutionary approach divides the calpain family into typical or classical (1, 2, 3, 8, 9, 11, 12, 13, 14) and atypical (5, 6, 7, 10, 15, 16); this approach is based on structural similarities within both groups and differences between them (Baudry and Bi 2016). Major structural difference between the classical and nonclassical calpains is their structural elements required to bind Ca^{2+}, so-called EF-hands; while the classical

calpains exhibit a penta-EF-hand type of calcium binding domain, it is lacking in atypical calpains. Of the former, calpains 1 and 2, also known as μ- and m-calpain, respectively, and sometimes called "conventional," were so far detected in practically all vertebrate (including human) tissues tested, so they are the most ubiquitous of the whole family (Ono et al. 2016). Catalytic subunits of the conventional calpains are coded by the CANP1 and CANP2 genes, respectively. Unlike the rest of the family, conventional calpains are uniquely characterized by one more feature: they contain common, small (30 kD) regulatory subunit coded by a separate gene *CAPNS1*.

Calpain Substrates

As mentioned above, calpains act by cleaving the substrate proteins at (or in coordination with) specific, relatively unique sites. For a relatively long time, these sites were described as enriched in proline, glutamic acid, serine, and threonine, otherwise known as PEST sequences, flanked by the arginine and lysine (Perrin and Huttenlocher 2002; Tompa et al. 2004). In fact, predictions of proteins to be the calpain substrates were made based on the abundance and location of the PEST domains. One such example is the IκB molecule, which contains such PEST domain and is degraded by calpain (Shumway et al. 1999). More recently, deeper analysis of calpain chemistry, structures of catalytic sites, as well as novel bioinformatics approaches including the machine learning had yielded many more potentially cleaved amino acid sequences (Sorimachi et al. 2012; DuVerle et al. 2011). Interestingly enough, the authors of the cited paper suggest that in the biological settings, that less probable sites may actually be cleaved with equal or even more effectiveness than the "strong" ones. This observation would greatly increase the list of potential and real targets of the proteolytic activity of calpains in the cells. Indeed, it was recently stated that the conventional calpains alone are capable to cleave more than 40% of the peptide bonds of most polypeptides, at least when their proteolytic activities are studied in vitro.

Currently there are about 200 of them known (Piatkov et al. 2014). However, based on the abovementioned machine learning and other analyses, it is suggested that the total number of cellular substrates for calpains 1 and 2 may exceed 1000 (Ono and Sorimachi 1824). The list includes many proteins that are involved in transduction of signals leading to either proliferation or apoptosis of many cell types. Thus, it includes cyclins (especially cyclin D1, found to be increased in centrocytic lymphomas), surface growth factor/mitogen receptors including the Egfr, membrane (receptor), and cytoplasmic kinases, including PKCα and PKCγ, as well as calmodulin kinase IV (CAMK-IV), calcineurin inhibitor DSCR1, IGF-binding protein Igfbp2, and proto-oncogenes (e.g., c-myc and ras) (Piatkov et al. 2014; Moretti et al. 2014; Choi et al. 1997). An interesting group of calpain substrates are the transcription factors and their regulators, notably c-fos, c-jun, p53, β-catenin, and IκB. The latter is a very well-known negative regulator of NFκB, preventing it from entering the nucleus and releasing it after being phosphorylated by a specific activation-dependent kinase IKK. Discovery of susceptibility of IκB to calpain cleavage suggests an alternative path to NFkB activation in the cells responding to stimulation by building an appreciable calcium signals (Lopatniuk and Witkowski 2011). Also cohesin, a protein necessary for maintenance of the fidelity of chromosome cohesion and segregation during mitosis, is on the calpain substrates' list (Rao et al. 2001).

Movement of the cells, including the lymphocyte transmigration from the vessels and into the tissues, requires calpain-mediated, spatially and temporally controlled cleavage of cytoskeletal proteins, including ankyrin, talin, vimentin, cortactin, troponin T2, and dystrophin (Piatkov et al. 2014; Franco and Huttenlocher 2005). Proteolysis by calpains plays many other roles as well, including their major functions in the brain and muscle (Piatkov et al. 2014; Lopatniuk and Witkowski 2011; Sorimachi and Ono 2012).

Excessive calpain-dependent cleavage of activator of Cdk5 cyclin-dependent kinase occurring in the neurons activates the kinase which in turn hyperphosphorylates the tau protein leading to its misfolding and formation of

neurofibrillary tangles, typical for tauopathies including Alzheimer's disease.

Calpains cleave calcium channels, including the ryanodine receptor and the NMDA receptor, as well as voltage-gated Ca^{2+} channels (Piatkov et al. 2014). On the other hand, they do cleave also the membrane calcium-dependent ATPase (calcium pump, PMCA) molecules.

Also the list of known calpain substrates directly involved in the positive or negative regulation of apoptosis is relatively long and includes both the pro-apoptotic proteins like Bak, Bid, caspases 3, and 9 and the anti-apoptotic proteins including Bcl-2, Bcl-XL, and Bfl-1 (Piatkov et al. 2012, 2014; Lopatniuk and Witkowski 2011). Interestingly, at least in the case of Bcl-XL, the actual target of calpain-dependent destruction is its deamidated form; this happens upon DNA-targeting chemotherapy, e.g., of follicular lymphoma (Dho et al. 2013).

Calpain Action on Target Proteins

Calpains belong to the group of proteases which can be characterized as modulative, rather than hydrolytically degrading their targets. As was said above, calpains cleave their targets in relatively specific, predefined sites. The result of such limited (modulative) cleavage may be either inactivation of target protein (e.g., IκB, above) or its activation (e.g., PKC) (Sessoms et al. 1992).

It was recently demonstrated that calpain activities yield protein fragments that bear destabilizing N-terminal residues. By recognizing proteins that are having these structurally destabilizing N-terminal residues, calpains generate their fragments tagging them for further proteasomal destruction (Piatkov et al. 2012, 2014; Brower et al. 2013; Varshavsky 2012). In this way, calpains may protect the cellular proteome from errors (improperly constructed proteins) that could affect cell functions by decreasing intracellular concentration (and thus activities) of properly built ones. This would be pro-survival, both in the case of normal and malignant cells.

On the other hand, some target proteins may be variably cleaved and initially "only" modulated in order to yield them active or inactive in a specific intracellular context but later finally degraded. This double-edged activity includes, for instance, the caspase 3. Thus, "initial" events of calpain-dependent cleavage activate the caspase but at the same time yield it more prone to further calpain-dependent, now degrading, events or to proteasomal degradation. That way calpain activity may be pro-apoptotic or anti-apoptotic, depending on spatiotemporal considerations of this activity in a specific cell type.

A Puzzle Regarding Calpain Activity In Vivo

It was shown that calpains are activated (at least in vitro) solely by relatively high (micro- to millimolar for calpain-1 and -2, respectively) concentrations of calcium ions and by presence of (membrane) phospholipids which, in fact, reduce their need for Ca^{2+} (Ono and Sorimachi 1824; Lopatniuk and Witkowski 2011; Saido et al. 1992).

The limiting factor, potentially preventing them from being constantly active in the cells, was considered to be the intracellular concentration of Ca^{2+} ions which in most resting cells remains at around 100 nM, only to be brought to a few μM during activation. This is also true for the lymphoid cells where "calcium signals" observed within seconds to minutes of the onset of stimulation by a mitogen or antigen rarely exceed 1–2 μM. This should be sufficient for activation of calpain-1 (μ-calpain), but clearly not m-calpain, described as requiring millimolar Ca^{2+} for activity. Still, both calpains were found in the lymphocytes and their activities demonstrated (Lopatniuk and Witkowski 2011; Mikosik et al. 2007, 2013, 2016). One explanation that was proposed was that contact with membrane phospholipids decreases the calpains' need for Ca^{2+} (Saido et al. 1994; Tompa et al. 2001). Also, while the *average concentrations* of Ca^{2+} in resting and activated lymphocytes, usually measured by flow cytometry with the use of calcium-sensitive fluorochromes, are as mentioned above, the *local concentrations*, e.g., in the vicinity of periodically opening CRAC channels, may be much higher and approach multi-micromolar at least for the short moments. This way also a necessary

condition of calpain activation in the lymphoid cells, i.e., relatively high concentration of Ca^{2+} available for binding by the enzyme molecules, would become possible not only during early moments of stimulation as proposed earlier but also in resting state. In fact, we have recently demonstrated a significant activity of both μ- and m-calpain in resting human peripheral blood lymphocytes (Mikosik et al. 2016). This proteolytic activity was coupled with equally conservative transcriptional activities of both calpains (CANP1 and CANP2, respectively). This finding seems understandable if one considers that the *resting*, at least semipermanent calpain activity in unstimulated lymphocytes, serves some physiological purpose. In fact we have demonstrated in the same paper that specific inhibition of calpains prevents the T cells from proliferation and cytokine secretion upon stimulation in vitro and shown that these effects may be at least in part due to modified (decreased) levels of phosphorylated NFκB, p56lck, and phospholipase Cγ in the cells in which the calpains were inhibited before the beginning of stimulation (Mikosik et al. 2016). Our interpretation of these findings is that the observed, constitutive activity of calpains is necessary to maintain a non-zero level of T-cell readiness for the rapid initiation of the immune response (proliferative and secretory) to antigens.

Considering the above, including the ubiquitous calpain substrates' list encompassing multiple molecules of extreme importance for cellular proliferation, apoptosis, and other functions, as well as their permanent constitutive activity in the human lymphoid cells at rest, one can easily perceive that this activity must be in a very precarious, dynamic balance. Otherwise such an activity, if unleashed, would greatly affect multiple functions of the lymphoid cells, ultimately leading to two possible outcomes. One would be their early apoptotic death, especially during early response to activation. It is tempting to say that possibly the well-known activation-induced cell death (AICD) happening to many stimulated T cells in vitro and possibly in vivo is dependent on this pro-apoptotic calpain activities, especially because the dependence between AICD extent and Ca^{2+} concentration in stimulated lymphocytes was observed (Sarin et al. 1994; Ruiz-Vela et al. 1999). The second one, more to the topic of this chapter, would be the calpain activity-dependent pro-survival, anti-apoptotic activities which could in principle lead to either accumulation of excessive numbers of active T cells, possibly leading to some autoimmune reactivity and pathology, or to the promotion of lymphoid malignancy. Along with the latter notion, we have repeatedly shown that excessive activity of calpains protects malignant lymphocytes from apoptosis, both in the case of acute lymphoblastic leukemia typical for children and for chronic B-cell leukemia of the elderly (Mikosik et al. 2015; Witkowski et al. 2002).

Thus, if allowed to, the calpains would either cleave the proteins that are necessary for adequate pre-proliferative signaling and for mitosis itself or induce apoptosis by cleaving-off, e.g., the inhibitory parts (peptides) of the effector caspases or, eventually, prevent apoptosis by cutting these caspases and other relevant proteins to non-functional pieces. In fact, all these activities are seen in some clinically relevant conditions, like muscular dystrophy and Alzheimer's disease, where the main problem is cell degeneration, or, on the other hand, protection from apoptosis by the token of removing the effector caspases and possibly other pro-apoptotic factors mentioned above, as in case of ALL and B-CLL leukemias.

What is maintaining the precarious and so important balance between the necessity of some calpain activity in the lymphocytes even at rest, and the danger of its excess? It is now accepted that due to their involvement in cellular life-and-death decisions, the activity of calpains requires multiple safety valves. One of these is the requirement for really high (near-millimolar) Ca^{2+} concentration for the activity of m-calpain, as without it the active site of the enzyme assumes an inactive conformation and is inaccessible for potential targets (Ono et al. 2016). Although we did see it even in resting T cells, and interpreted as occurring in the close vicinity of the opening CRAC channels, it was never as potent as that of μ-calpain, despite the fact that the actual cellular amounts of both proteases were comparable (Mikosik et al. 2016). Another "safety valve" feature is the existence of the unique, specific, equally ubiquitous

cytoplasmic inhibitor of calpain activity, the calpastatin (Wendt et al. 2004; Goll et al. 2003; Friedrich and Bozoky 2005). Calpastatin accompanies the calpains in all human cells tested so far, including the lymphocytes, and their relative concentrations seem to be in a stoichiometric equilibrium. Calpastatin is activated (and starts performing as an inhibitor of calpain activity) only upon modulative cleavage by active calpain, for which it is a substrate; in this way some activity of the enzyme can occur before calpastatin is activated (Lopatniuk and Witkowski 2011; Piatkov et al. 2014; Wendt et al. 2004; Goll et al. 2003; Friedrich and Bozoky 2005). Finally, both active and resting (inactive) calpains 1 and 2 are the substrates for their own activity; thus initially the activation of some calpain molecules makes possible the activation of others by cleaving some parts of both the large and small (regulatory) subunits; later, autodegradation takes over and amounts of active enzymes are reduced (Ono and Sorimachi 1824; Lopatniuk and Witkowski 2011; Piatkov et al. 2014). So, there is strong built-in mechanism modulating the CCS complex. It is becoming clear now why we had observed constitutive transcription of the genes for both calpains (CANP1 and 2) and for calpastatin (CAST) in resting T cells. On one hand, the appreciable activity of calpains in the resting cells was likely evolutionarily selected for as beneficial for the speed of the response, and so, on the other, it had to be maintained in the system where active enzymes are disappearing "from own hands."

Calpains and Aging

By the token of being modulatory for so many important cellular proteins involved in proliferation and apoptosis, i.e., the two major cellular functions greatly affected by advanced age, calpains must have been perceived as potential element of the cellular aging machinery. Considering that in most if not all aging and senescent cells, their proteostasis, i.e., maintenance of functionally relevant proteins at adequate qualities and quantities, is impaired, calpains became one of the master molecules of interest for cellular gerontologists. However, so far the papers studying their role in human aging concentrate on their involvement in aging-associated neurodegeneration (especially Alzheimer's and Parkinson's diseases), sarcopenia (muscular wasting of the old), and some chronic inflammatory states, notably atherosclerosis and its consequences – the cardiovascular problems (Pinto et al. 2017; Nixon 2003). On the other hand, the involvement of calpains in aging of human immune (lymphoid) cells, with their dwindling bursts of proliferative and secretory activities upon antigen stimulation and long periods of rest, is so far studied only fragmentarily. At the beginning of this century, our group had shown that the amount and total activity of both μ- and m-calpains decrease in the peripheral B lymphocytes of old individuals (Witkowski et al. 2002). We had extended these observations more than a decade later, demonstrating that amounts of all three members of the calpain-calpastatin system, i.e., μ- and m-calpain and calpastatin, decrease significantly in peripheral blood T and B cells of elderly in their 60s and 70s and remain high in these cells coming from the oldest old, i.e., centenarians (Mikosik et al. 2013). These quantitative changes were not associated with known shifts of the proportions of major subpopulations within the T cells (including the naïve and memory, as well as these expressing CD28 versus these that did not). As we did show recently in a paper already cited above, at least for the peripheral blood T cells, the resting (constitutive) calpain activity is necessary for adequate buildup of proliferative response to stimulation and cytokine production (Mikosik et al. 2016). Our as yet unpublished data suggest that the actual calpain activities (measured by flow cytometry in living cells, rather than total available activities in cell lysates) are also changing in the lymphocytes of old individuals, albeit differentially for various populations. Maintenance of sufficient resting calpain and calpastatin amounts in old lymphoid cells requires increased levels of transcripts of all three genes, CANP1, CANP2, and CAST (Witkowski, unpublished), which stresses the

importance of calpain activity in the lymphocytes for supporting their functioning in the aging environment.

Complex Relations Between CCS Hyperexpression and Hyperactivity as Likely Mechanisms of Apoptosis Escape and Increased Proliferation in Lymphoid Neoplasms

Ubiquitous calpains' activity is implicated in multiple human pathologies, including atherosclerosis, Alzheimer's disease, cardiovascular disorders, Parkinson's, muscular dystrophies, cataracts, and many others; the effect of – presumably excessive – calpain activity is described as at least aggravating, or even causative, to the extent that calpain inhibitors are presently contemplated and tested as therapeutic candidates (Ono et al. 2016). Cancers are no different, and excessive calpain activity is proposed as causative or aggravating for a score of them (Ono et al. 2016). This activity prevents apoptosis and increases basic autophagy levels in cancer cells, helping their survival under stress (including chemotherapy) (Shi et al. 2013). By interfering with cytoskeleton and adhesion molecules, as well as by stimulating neovascularization, calpain activity facilitates cancer cell migration and invasiveness. However, both the cited paper and other ones bring up that calpain activities may also act as preventive, by stimulating cancer cell apoptosis and/or inhibiting their protective autophagy (Ono et al. 2016; Moretti et al. 2014; Tan et al. 2006). In the latter case, calpains do it by cleavage of G protein Gsα, which leads to high levels of cAMP inhibiting the autophagy (Williams et al. 2008).

As was mentioned above, calpains affect the amounts and activities of multiple proto-oncogenes and transcription factors. On the other hand, their own activity is augmented by activation of Src, Jun, Fos, Myc, k-Ras, and other oncogenes during oncogenic transformation of many cell types. While this may be pro-survival, the increase of calpain activities in v-Myc – transformed cells – is the strongest and pro-apoptotic (Carragher et al. 2004). On the other hand, more recently Li et al. had reported that in model transgenic E1-myc B-cell lymphoma cells, activation of c-Myc is parallel with constitutive activation of (mostly) μ-calpain and pro-survival or anti-apoptotic, thus promoting or sustaining the tumorigenesis (Li et al. 2012). One possibility is that calpains can cleave and degrade c-Myc, defusing its pro-apoptotic action in these cells (Small et al. 2002; Conacci-Sorrell et al. 2010, 2014; Conacci-Sorrell and Eisenman 2011). In the cited paper, caspase 3/7 inhibitors protected cells from death induced by calpain inhibitor, suggesting that calpain activity generated a pro-survival signal for this lymphoma and its lack resulted in caspase-dependent apoptosis (Li et al. 2012).

Interestingly enough, we did see the constitutive activity of both μ- and m-calpains in perfectly normal human peripheral blood T cells; it is possible then that also in these cells the pro-proliferative effect is associated with calpain-dependent decrease in c-myc activity; transition from normal to malignant (lymphoma) lymphocyte would – in this case – be hypothesized more as a continuum (Fig. 1) (Mikosik et al. 2016).

As already cited in this chapter, we have demonstrated increased amounts and activities of both (especially μ-) calpains in the malignant cells of acute B-lymphoblastic leukemia (B-ALL) and in chronic B-cell leukemia of the aged. Inhibition of calpains in these cells in vitro induced their significant apoptosis (Witkowski et al. 2002). In fact, induction of apoptosis of multiple human B-cell and T-cell lines, including RAMOS, DAUDI, NALM-6, JURKAT, and MOLT-3 by in vitro treatment with calpain inhibitors, was already demonstrated in the year 2000 (Zhu and Uckun 2000). However, other authors who assessed the activity of calpains in adult **T**-cell leukemia (one of the very severe forms of leukemia) found that m-calpain was significantly downregulated in these cells (Ishihara et al. 2013). Still, one cannot just suppose that B-cell-derived malignancies exhibit increased calpain activities, and T cell-derived malignancies do not. An example (and proposed mechanistic, molecular explanation) of the reciprocal situation (effects of calpain activity in T-cell lymphomas) is described below.

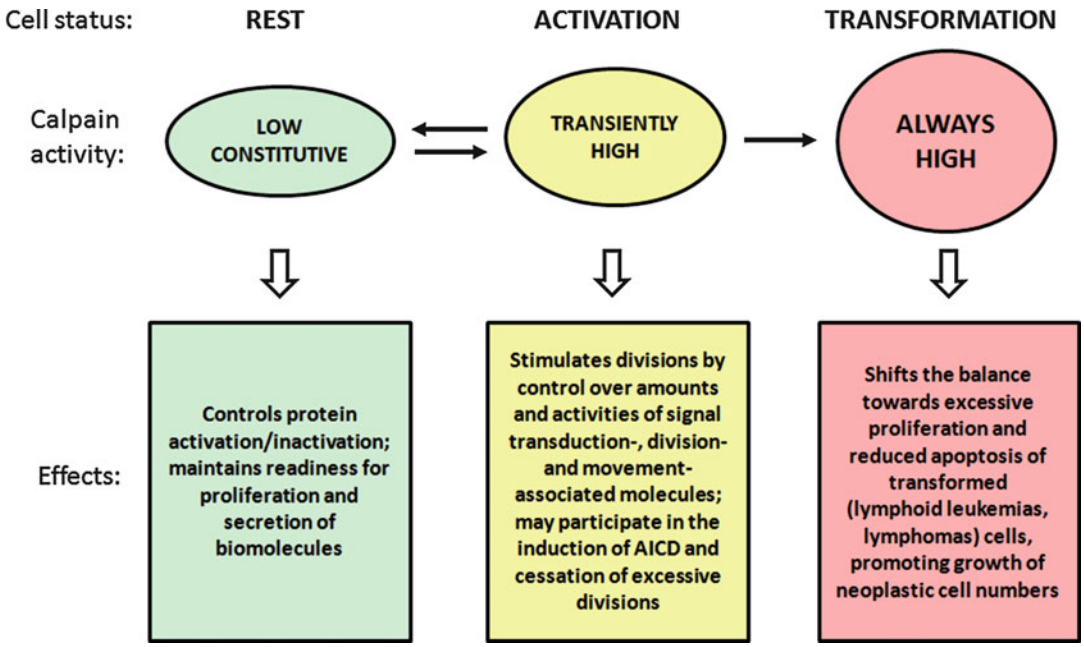

Fig. 1 Hypothesis: Continuity and roles of various activities of calpains in lymphoid cells depending on cell status (rest, activation, transformed (leukemic, lymphomatic)). *AICD* activation-induced cell death

Thus, primary cutaneous T-cell lymphomas (CTCL) form a heterogeneous group of non-Hodgkin lymphoma (NHL). Mycosis fungoides (MF) is the most common form of CTCL and is usually of relatively benign nature. A less common variant of indolent CTCL is the CD30-positive anaplastic large cell lymphoma. Finally, the Sezary syndrome (SS) is an aggressive, leukemic form of CTCL (Mitchell and John 2005).

It is known for some time that cutaneous T-cell lymphoma cells exhibit the aberrant expression of so-called Stat-3γ and Stat-5γ proteins (Hendry and John 2004). These two proteins are nothing more than the C-terminally truncated Stat-3 and Stat-5 transcription factors. At the time of writing the cited paper (2004), it was not known that calpains are in fact producing such C-terminal fragments, which now is an established knowledge, pertinent also for truncated, C-terminal fragments of Stat-3 and Stat-5 (Piatkov et al. 2014; Mitchell and John 2005). In fact the latter was demonstrated already in 2002 but only for human blood platelet STATs (Oda et al. 2002). These fragments may be constitutively activated and provide pro-survival, anti-apoptotic signals (Hendry and John 2004). Constitutive activation of Stat-3 and Stat-5 was demonstrated for both the mycosis fungoides and Sezary syndrome cells (Mitchell and John 2005; Zhang et al. 1996).

Also in human B-cell lymphomas (e.g., Burkitt lymphoma), the activity of calpain is proposed to be anti-apoptotic due to interfering with the amount and activity of the effector caspase 3. These lymphomatic cells can be induced to apoptosis by calpain inhibition, similarly to our observations of acute and chronic B-cell leukemias (Li et al. 2012). Activated, membrane phospholipid-bound calpains were also found in the cells of active mantle cell lymphomas (MCL), especially in their leukemic phase (Boyd et al. 2009). Authors of this paper suggest that this calpain activity in MCL is elevated and constitutive and likely provides the pro-survival or pro-proliferative and anti-apoptotic signals.

Finally, earlier studies on immortalized B cells in vitro (WEHI-231) had shown that they maintain constitutively active NFκB (p50-c-Rel heterodimer) due to continual degradation of

IκBα, sensitive to calpain inhibition (i.e., executed by calpain) (Shumway and Miyamoto 2004).

Conclusion

Concluding, very unique properties of ubiquitous calpains, including their substrate list predisposing them for regulation of proliferation and apoptosis of practically every cell type studied as well as their actual pro-proliferative, anti-apoptotic activity observed even in resting normal lymphocytes and augmented in leukemic/lymphomatic ones, put calpains high on the list of known and potential therapeutic targets in lymphoid leukemias and lymphomas. Still, published data concerning the role of modified calpain activities in the lymphoma pathogenesis are fragmentary and warrant necessity for more thorough and detailed studies.

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The Biologic Interconnections Between Aging and Lymphoma

10

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Abstract

Lymphoma and aging interplay may be firstly considered from an epidemiologic point of view, as the incidence of lymphoma – and notably diffuse large B-cell lymphoma (DLBCL) – increases with age. In addition, its histopathogenic subcategories develop an age-dependent repartition – with less frequent germinal center-derived DLBCL and more activated B cell ones. Finally, some specific entities have been specifically described in an aged population, like EBV DLBCL, leading to specific biologic explanatory hypotheses.

This review aims at summarizing current data (i) on the impact of age on the mutation burden leading to lymphomagenesis, (ii) on defects in cancer surveillance associated with age, (iii) on the impact of clonal restriction in the hematopoietic system, (iv) on the specific lymphoma entities associated with age and particularly EBV DLBCL of the elderly, and finally (v) on the treatment perspectives based on this interplay.

Keywords

Lymphoma · Aging · Senescence · Immunosenescence · Telomere · EBV DLBCL of the Elderly

Abbreviations

3′UTR	3′ untranslated region
ABC	Activated B-cell-like (lymphoma)
AID	Activation-induced deaminase
ATLL	Adult T-cell leukemia/lymphoma
BCR	B-cell receptor
DDR	DNA damage response
DLBCL	Diffuse large B-cell lymphoma
DSB	Double-strand breaks
EBV	Epstein-Barr virus
FL	Follicular lymphoma
GC	Germinal center
GEP	Gene expression profiling
HR	Homologous recombination
hTERT	(Human) telomerase reverse transcriptase
MCL	Mantle cell lymphoma
MLBCL	Mediastinal large B-cell lymphoma
MZL	Marginal zone lymphoma
NHEJ	Nonhomologous end joining
RAG	Recombination-activating gene
SHM	Somatic hypermutation
TCR	T-cell receptor
VH	Variable locus of Ig heavy chain

Introduction

Lymphoma – and particularly diffuse large B-cell lymphoma – can be partly considered as age-related, since its incidences increase with age until 90 years, reaching at this age 0.45‰ in men compared to 0.12‰ at the age of 60 in women (Monnereau et al. 2013). The cumulative incidence of DLBCL increases from 0.13% (in men) and 0.09% (in women) before 39 years to, respectively, 1.77% in men and 1.4% in women after 70 years (Maartense et al. 1998; Siegel et al. 2012; Edwards et al. 2005; Howe et al. 2001). Around half of DLBCL cases occur after 60 years and 40% after 70 years (Morton et al. 2006). Considering other histologic forms of lymphoma, median age at diagnosis is 65 years for FL and 70 years for MCL.

Aside from epidemiologic relationships, some biologic pathways have been proposed to explain the link between lymphoma development and aging.

Indeed, lymphoma pathogenesis is at the crossroads of physiologic processes at high risk of mutagenesis (e.g., B-cell processing itself) and depends on alterations of genetic and immune surveillance and microenvironmental dysfunctions, all being correlated with age (Sarkozy et al. 2015).

This review aims at summarizing current data (i) on the impact of age on the mutation burden leading to lymphomagenesis, (ii) on defects in cancer surveillance associated with age, (iii) on the impact of clonal restriction in the hematopoietic system, (iv) on the specific lymphoma entities associated with age and particularly EBV DLBCL of the elderly, and finally (v) on the treatment perspectives based on this interplay.

Lymphomagenesis and Age: The Role of the Mutation Burden

Lymphomagenesis Process Is Long and Implies Several Steps

B-cell NHL development is closely related to normal B-cell development and maturation. Each lymphoma entity corresponds to a normal cell counterpart in the B-cell lineage. Balanced translocations that involve the immunoglobulin genes (Ig) and an oncogenic partner are frequent and often correspond to the primary oncogenic events resulting in the overexpression of oncogenes. Nevertheless, such events are not sufficient since multiple additional mutation hits may be needed to induce the lymphoma phenotype, according to a multistep process. As such successive mutation hits need time, they are expected to accumulate with aging.

Mutations Related to B-Cell Processing

During normal B-cell development, in the pro-B cell, the V(D)J Ig segment recombination into the variable region of the BCR is mediated via RAG 1 and 2 recombinases leading to DNA double-strand breaks (DSB) at specific recombination signal sequences in the bone marrow. These breaks lead to the activation of the DNA damage response (DDR) pathway, notably the non-homologous end-joining (NHEJ) system. RAG 1/2 is also able to produce DSB in "off-target" sites as oncogenes. Experiments in mice showed that errors in NHEJ can lead to translocation, as t(11;14) or t(14;18) (Guidos et al. 1996). However, full development of a cancer phenotype depends on the blockade of *p53*. Nevertheless, these events are not sufficient: mice bearing only t(11;14) as single mutation do not develop lymphoma (Lovec et al. 1994). In the human context, almost 70% of healthy individuals present normal circulating B cell with t(14;18), and only few will transform into true lymphoma (Roulland et al. 2006). Thus additional mutations are necessary for lymphoma development and may depend on other steps of B-cell processing, as class switch recombination (CSR) and somatic hypermutation (SHM). SHM and CSR correspond to programmed DNA damage occurring in the germinal center (GC), depending on activation-induced deaminase (AID) (Stavnezer et al. 2008). Recent data showed that AID is induced by exogenous DNA damage, leading to enhanced base excision repair (Tepper et al. 2016). Moreover AID can lead in vitro and in vivo to off-target mutations, notably in oncogenes, as well as lymphoma-associated chromosome translocations (Robbiani et al. 2009). Finally, AID was shown to be expressed at high levels in lymphoma subtypes with an ongoing mutation process (Lenz et al. 2007; Roulland et al. 2011).

Nevertheless, in spite that time may impact the accumulation of mutations related to B-cell processing, the exact impact of age on RAG1/2 function and on AID off-target mutations is currently unknown.

The Mutation Burden Is Time-Dependent and Leads to Aging and Cancer

According to the Nobel laureate Peter Medawar mutation burden theory (1952), natural selection does not delete mutations with no detrimental effect on species reproduction (Medawar 1952). Such mutations can accumulate with time and participate to aging phenotype. As the development of lymphoma requires multiple mutational events to deviate from normal B-cell development, age-related genomic and epigenomic instability may participate to this multistep process.

Accordingly, experimental data suggest age induces DNA damage accumulation, notably in the stem cell compartment, in turn leading to dysfunctions in different mechanisms regulating genomic integrity (Rossi et al. 2007; Rübe et al. 2011). Age-related accumulation of reactive oxygen species (ROS) might accelerate DNA damage. In addition, the genetic instability associated with the B-cell processing might synergistically promote DNA abnormalities leading to

lymphomagenesis (Gosselin et al. 2009). Blood-derived sequence data of 2728 individuals from the Cancer Genome Atlas showed that 2% of blood cells contain mutations, the rate reaching 5–6% in patients over 70 years. In 83% of these cases, these mutations implied 19 hematological cancer-associated genes (as *ASXL1, DNMT3A, JAK2, TET2, TP53*, etc.). Blood-specific mutations increase with age, some of them being able to initiate hematopoietic stem progenitor cell clonal expansion. Such clonal expansions are proposed to be a contributing factor to the development of hematological malignancies in the elderly (Xie et al. 2014).

In another large-scale whole-exome sequencing analysis of peripheral blood from 17,182 persons without overt hematological malignancies, 160 genes known to be recurrently mutated in hematological cancers displayed a high rate of somatic mutations, with a frequency significantly rising with age. Interestingly, the presence of somatic mutations correlated both with an increased risk in future development of hematological cancer and with all-cause mortality (Jaiswal et al. 2014).

Thus the accumulation of mutation appears both as an age-related event and as premalignant events that may preclude clonal hematological expansion and overt hematological malignancy.

The Epimutation Burden

During cell differentiation, gene expression is regulated by both transcription factors and chromatin architecture. Classically the chromatin is called euchromatin when it is open to transcription and heterochromatin when it is silenced. Heterochromatinization's main characteristics imply cytosine methylation and histone H3 trimethylation. Genome-wide analysis of DNA methylation showed that age is associated with a general hypomethylation, the hypermethylation of CpG islands, an accumulation of heterochromatin, and its mislocalization. The concept of epigenetic drift has been proposed to describe the accumulation of small changes in DNA methylation during aging. These marks correspond to stochastic errors appearing during the transfer of epigenetic marks during replication (Issa 2014). Such errors accumulate in the most proliferative organs as hematopoietic stem cells and spleen but also the gastrointestinal tract (Maegawa et al. 2010; Beerman et al. 2013). Mutations arising in aging stem cells predominantly affect the epigenetic regulation machinery and may participate to clonal HSC expansions with aging and therefore in hematological malignancy development (Welch et al. 2012).

Similarly, some lymphoma mutation hotspots affect chromatin protein genes (Xie et al. 2014): histone methyltransferases such as *EZH2* and *MLL2*, histone demethylases including *UTX* and *JMJD2C*, and histone acetyltransferases including *CBP* and *p300*. Thus, large-scale modifications of DNA methylation and histone acetylation pattern have been proposed as specific hallmarks of NHL (Shaknovich and Melnick 2011). For example, in a RNA-sequencing study (Morin et al. 2010), 32% of DLBCL and 89% of FL cases had somatic mutations in *MLL2*, a histone methyltransferase, and 11.4% and 13.4% of DLBCL and FL cases, respectively, had mutations in *MEF2B*, a calcium-regulated gene that cooperates with CREBBP and EP300 in acetylating histones.

The Impact of Telomere Shortening

During normal aging, the gradual loss of telomeric DNA in dividing somatic cells due to the "end replication problem" contributes to replicative senescence (Gilson and Géli 2007). Importantly, this telomere length dynamics plays an important signaling role in determining cell fate during aging and cancer (Ye et al. 2014). Indeed, telomere shortening contributes to a mitotic clock leading to replicative senescence, considered an important tumor-suppressive mechanism. Moreover, recent data demonstrated that dysfunctional telomeres induce p53-dependent and p53-independent apoptosis to compromise cellular proliferation and inhibit tumor formation (Wang et al. 2016). At the same time, it contributes to tissue exhaustion and loss of heterogeneity

in organs with a high proliferative rate, and particularly in the hematopoietic system, contributing to age-related dysfunctions and finally to expansions of dysfunctional clones (Falandry et al. 2014a). During cancer development, on one hand, telomerase activation in precancerous cell may lead to their immortalization and is shown in 90% of solid tumors (Kyo et al. 2008). On the other hand, telomere shortening may lead to the induction of DNA damage response (DDR) that may induce pathologic chromosomal recombination through homologous recombination (HR) and/or nonhomologous end-joining (NHEJ) pathways (Hackett and Greider 2002). Any defect in the telomere-binding protein complex (containing TRF1, TRF2, POT1, TIN2, TPP1, and RAP1), also known as the shelterin complex, may also lead to DDR signaling. In aging mice, a gene dosage reduction of Trf1 and/or Tin2 telomere-binding proteins induced DNA damage, precancerous hyperplastic nodules, and T- and B-cell lymphoma (Hartmann et al. 2016).

In the specific context of hematologic malignancies, a recent review has synthetized the different telomeric pathways dysregulated during hematologic malignancies, depending on the oncogenic triggers (Ropio et al. 2016). When telomerase activation is an early event, cancer cells are characterized by long telomeres, as in virus-driven malignancies. In other cases, telomere activation may be a late event, and cancer cells may have short telomeres. Telomerase activation depends mainly on hTERT expression, the reverse transcriptase enzymatic subunit of telomerase as it is its limiting factors, the other subunits being generally produced in excess. Increased expression of hTERT may be driven by genetic mechanisms (*hTERT* amplification, translocations, or point mutations in *hTERT* gene or promoter) as well as epigenetic ones (methylation of DNA, demethylation of CpG islands, acetylation or methylation of histones) or posttranscriptional regulation (mutation of 3′UTR of hTERT gene, action of micro-RNAs). During virus-driven lymphoid malignancies, telomerase is precociously activated either directly (like Tax in HTLV-1-driven ATLL) or indirectly (like HBZ in HTLV-1- or LMP-1 for EBV-driven malignancies) by viral oncoproteins. However, little is known about the impact of age on these regulation pathways.

Age-Related Dysfunction of Anticancer Surveillance

Age is associated with a decline in different organ functions. Among these, the decline in immune surveillance against tumors, but also against infectious diseases, shown to participate to the expansion of some lymphomas, as well as the decline in microenvironment-associated functions or in DNA damage response pathways may participate to hematological malignancy triggering.

Immunosenescence Links Chronic Infection to Cancer Development

Immunosenescence corresponds to the different changes in the immune system associated with age (Franceschi et al. 2000). It includes dysfunctions in B cells and T cells (less naive CD8+ cells, decrease in T-cell repertoire and functionality, less regulatory T cells, more memory T cells) (Maue et al. 2009) as well as dysfunctions in innate immunity associated with a pro-inflammatory profile called inflammaging. The observed phenotype associates a decrease in adaptive immunity and a chronic stimulation of innate immunity (Franceschi et al. 2000). It affects immune responses to infection and to cancer cells and leads to a decrease in vaccine response (Goodwin et al. 2006; Goronzy and Weyand 2013). Thus aging induces an increase in infectious disease (Hadrup et al. 2006), chronic inflammation disorders and autoimmunity, as well as cancer (Fulop et al. 2013). T-cell populations are unbalanced, leading to a "restricted T-cell response" in which mature and senescent CD8+ T cells proliferate instead of naive T cells. In elderly patients T-cell responses are often restricted (9–20%) or monoclonal (15–50%) (Dojcinov et al. 2011). Such epitope-specific repertoires promote sensitivity to infections (Hakim and Gress 2007; Messaoudi

et al. 2006) and consequently infection-linked diseases. In the elderly EBV promotes clonal reactive B-cell hyperplasia and specific forms of DLBCL called EBV + −DLBCL (see below). In turn, Wang reported that chronic infection with CMV and EBV altered the B-cell immune repertoire (Wang et al. 2014a). Such age-related decrease in B-cell repertoire is associated with a decreased survival in older patients (Gibson et al. 2009). Moreover, an "immune-risk profile" has been described in epidemiological studies, which is characterized by deep hallmarks of immunosenescence related to a chronic CMV infection and correlates with a poor outcome in older patients (Pallis et al. 2014).

Considering NHL pathogenesis, chronic infections were shown to promote B lymphomagenesis either directly – via lymphotropic oncogenic viruses (EBV, HHV8, HTLV1; Suarez et al. 2006) – or indirectly via a chronic inflammation. Indeed, epidemiological correlations have been demonstrated between chronic inflammation and MALT MZL (mucosa-associated lymphoid tissue marginal zone lymphomas): *Helicobacter pylori* in the stomach, *Campylobacter jejuni* in the small intestine, *Chlamydia psittaci* in the ocular adnexal gland, or *Borrelia burgdorferi* in the skin. Moreover, chronic HCV infections lead to an increased risk to develop MZL or DLBCL (Zucca et al. 2014). A pathophysiologic scenario has been proposed, involving a chronic antigenic stimulation by microbial pathogens and/or autoantigens. In HCV, the nonstructural viral protein NS3/4A induces BCR activation (Dai et al. 2016).

In spite of the absence of any specific correlation between age and infection-related lymphomageneses, one might consider immunosenescence as one of the drivers of the relationship between age and lymphoma.

Microenvironment and Immunity Change with Age

Most NHL display a biased *IGVH* repertoire, supporting the concept of an antigen-driven BCR selection and stimulation (Hadzidimitriou et al. 2011). Some NHL exhibit restricted or "stereotyped" *IGVH* complementarity-determining region 3 (CDR3) sequences within the BCR suggesting a specific antigen (Ag) stimulation (Darzentas and Stamatopoulos 2013). Thus, as raised in the context of chronic infection, continuous exposure to specific antigens in a specific microenvironment seems to trigger lymphomagenesis.

Senescence Modifies Tumor Cells and Their Microenvironment

Cellular senescence induces, in response to DNA damage signaling, a permanent growth arrest and resistance to apoptosis. Senescent cells display specific properties, both intrinsically via cell-autonomous pathways and extrinsically via cell-nonautonomous pathways. At the cell-autonomous level, they are characterized by a cessation of proliferation and cell cycle arrest. At the cell-nonautonomous level, they display a specific secretory pattern, including pro-inflammatory cytokines and growth factors, also called SASP (senescence-associated secretory phenotype).

Senescence may be activated in response to telomere shortening either due to replication after a stereotyped number of divisions (replicative senescence) or to DNA damage (premature senescence). Such DNA damages may be due to inappropriate expression of oncogenes, exposure to endogenous or exogenous toxins, or oxidative stress. Thus, senescence acts as a tumor suppressor mechanism and as the first barrier to malignant transformation and proliferation. Senescence is also associated with the induction of quiescence in some tissue compartments, as the hematopoietic system, thus allowing a genome protection by minimizing DNA replication-induced errors and the accumulation of mutations (Rossi et al. 2005). Two major tumor suppressor pathways participate to this phenotype, p53 and p16INK4a-pRB (Campisi 2005), and are frequently dysfunctional in different lymphoma subtypes.

The oncosuppressive properties of senescence are raised by the existence of a high number of senescent cells in preneoplastic lesions (Falandry

et al. 2014b). In Hodgkin lymphoma, the expression of p16INK4a and p21CIP1/WAF is correlated with a better prognosis (Calio et al. 2015).

Nevertheless, senescence also contributes to the aging phenotype and paradoxically to lymphoma development by inducing inflammatory background.

Indeed, senescent cells also display a specific secretion pattern known to have both auto- and paracrine properties and able to impact their microenvironment through an increased expression of secreted proteins including pro-inflammatory cytokines and growth factors (Bavik et al. 2006). This secretion profile, called senescent-associated secretory phenotype (SASP) or senescence-messaging secretome (SMS), was reported in fibroblast and epithelial cells (Coppé et al. 2008). This cell-nonautonomous mechanism induces changes in the neighboring cells with increase proliferation and degenerative defects on non-senescent cells (Liu and Hornsby 2007). All these phenomena play a dual role in oncogenesis by promoting tumor clearance with the activation of innate immunity against cancer cells but also by favoring cancer development and invasiveness of premalignant cells, thanks to this pro-inflammatory phenotype (Coppé et al. 2008; Xue et al. 2007). Finally, the pro-inflammatory phenotype induced by senescence can also provoke an increase in chronic inflammatory diseases and autoimmune disorders, considered as an important risk factor for lymphoma (Zucca et al. 2014; Morton et al. 2014).

Age Induces Defects in the DNA Damage Response Pathway

In response to DNA damage, the repair mechanisms are known to induce errors, with a level depending on the proofreading pathways, and introduce both mutations and epimutations. The increased burden of (epi)mutations in aged tissues favors cellular degeneration and participates to the aging phenotype. Moreover, it may induce uncontrolled cell proliferation and finally both a progressive decline in organ function and an increased cancer risk (Campisi 2003). For example, many progeroid syndromes such as ataxia-telangiectasia, Werner syndrome (Cheng et al. 2008), Hutchinson-Gilford progeria syndrome, and restrictive dermopathy (Pereira et al. 2008) have defective DDR and genomic instability and induce a premature aging phenotype and an increased frequency of cancer and lymphoma.

During B-cell commitment, the mutational load is heavy. Lymphomagenesis is closely related to DDR pathway and more particularly to NHEJ since RAG and AID induce either on- or off-target mutations that induce the activation of DDR pathway. Errors in this DDR may promote the accumulation of genetic abnormalities and/or translocations.

Therefore, age-related decline and dysfunction in DDR participate to the accumulation of genetic abnormalities in B cell and the development of lymphoma.

Age-Related Clonal Restriction

During aging, stem cell capacities for proliferation and differentiation are impaired, eventually leading to defects in the clearance of damaged cells and ultimately to cancer progression. Indeed, two cell extrinsic properties of stem cells participate to the protection against cancer: on one hand, proliferative competition allows the selection of undamaged cells from the global pool of stem cells; on the other hand, damaged clones are inhibited (Bondar and Medzhitov 2010). Aging is associated with both a loss of proliferative competition and an impaired immune clearance of senescent cells (Ju et al. 2007; Wang et al. 2014b; Janzen et al. 2006). The accumulation of DNA damage restricts the stem cell pool, thus contributing to the enhanced selection of premalignant clones (Porter et al. 2011).

According to Issa's model of aging, epigenome effects on stem cell function (Issa 2014), toxic exposures, environment, and chronic inflammation can favor stochastic errors in DNA methylation that play a key role in the progressive restriction of the HSC pool, resulting in a growth advantage of some stem cell and exhaustion of others. This stem cell pool restriction may favor

both clonal proliferation/expansion of premalignant clones and exhaustion of normal differentiated cells. Finally, HSC-bearing mutations will be selected, and their clonal advantage will contribute to lymphoma development.

Thus, in HSC, the systematic elimination of defective germinal cells during aging leads to tissue exhaustion and eventually to loss of proliferative selection and finally to clonal selection.

Considering lymphopoiesis, aging is associated with low-grade inflammatory processes. The chronic stimulation of effector T cells and memory T cells induces both a restriction of repertoire diversity and a progressive expansion of oligoclonal T cells, particularly CD8+, CD27-, CD28-, CD45RA+, and CD57+ (Monnereau et al. 2013). B-cell receptor repertories also dramatically decline with age in parallel with clonal expansion of B cells in vivo.

Specific Entities of Lymphoma in the Elderly

Age-Related Molecular Specificities in DLBCL

Even if DLBCL histological characteristics do not differ significantly between age groups, their molecular abnormalities display age-related specificities. With age, the repartition between the three different prognostic molecular signatures identified in gene expression profiling (GEP) studies – namely, the germinal center (GC), the activated B-cell (ABC) lymphoma, and the mediastinal large B-cell lymphoma (MLBDL) – is changing (Rosenwald et al. 2002). The MLBCL, which has a profile similar to Hodgkin lymphoma (Savage et al. 2003), is mostly seen in younger patients; patients developing GC-DLBCL are 8 years younger than patients developing ABC-DLBCL (Mareschal et al. 2011). Elderly patients present more frequently unfavorable genetic features (Klapper et al. 2012): more frequent ABC-DLBCL subtype, BCL2 expression, and an increased genomic complexity. The relationship between age and genetic complexity appears more as a continuum corresponding to the "age evolution model" concept: whatever being their molecular subtype, older patients' lymphomas bear a higher mutation load, related to the stochastic risk of acquiring genetic aberrations with age. A logistic regression analysis revealed a significant association between increasing age and some molecular characteristics: the ABC signature; the BCL2 protein expression; the absence of IRF4 translocations; gains in 1q21, 18q21, 7p22, and 7q21; as well as changes in 3q27 including abnormalities affecting the BCL6 locus. In this cohort, ABC subtype, BLC2 expression, and age were independent prognostic markers. In contrast and after adjustment on age, other genetic markers associated with age such as IRF4 break; 1q21+, 18q21+, 7p22+, 7q21+, and 3q aberrations; or genetic complexity lost their significant prognostic impact. Interestingly, a ATMKO.CD3εKO mouse model reconstituted the phenotypic characteristics of ABC-DLBCL, leading to the hypothesis that ATM pathway defects could participate to these aggressive lymphomas.

EBV DLBCL of the Elderly

In 2008, an additional entity was included in the WHO classification of tumors of hematopoietic and lymphoid tissue: "EBV-positive DLBCL of the elderly" is defined as an EBV-positive clonal B-cell proliferation in a patient older than 50 years and in the absence of any other primary or secondary immune disease. Except these characteristics, no single morphological or phenotypical feature was identified to distinguish them from other lymphoproliferations (Balague Ponz et al. 2009; Oyama et al. 2003; Park et al. 2007; Oyama et al. 2007). The spectrum of EBV+ B-lymphoproliferative disease is wide, from simple reactive hyperplasia and nodal and extra-nodal polymorphic lymphoproliferative diseases to real DLBCL. Most EBV+ DLBCL cases have a post-GC phenotype, an aggressive evolution with poor OS, on the contrary to classical Hodgkin lymphoma also encountered in the elderly (Asano et al. 2009). The postulated pathogenic mechanism

implicates immunosenescence and the reduction in T-cell repertoire that may contribute to decreased immune surveillance (Dojcinov et al. 2011). The GEP of EBV+ versus EBV- DLBCL of the elderly have been compared (Kato et al. 2014), and the prominent gene characteristic of EBV+ DLBCL included inflammation and inflammatory-related genes, particularly the activation of Janus kinase-signal transducer and activator of transcription (JAK-STAT) and NF-kB pathway activation. This activation seems to be based on the EBV+ tumor cells and not on the inflammatory background (Montes-Moreno et al. 2012).

Lymphoma, Senescence, and Therapeutic Options

Future therapeutic targets may include senescence pathway modulation. Cumulative data favor the use of immunomodulation in lymphoma. Lenalidomide therapeutic effect acts through the antilymphoma T-cell response. Therapeutic immunomodulation of the T-cell response can also be achieved by inhibition of the PD-1/PD-L1/2 receptor/ligand axis or the KIR-HLA matched inhibitory axis in NK cells.

Therapy-induced senescence (TIS), known to be a major contributor during antilymphoma treatment, illustrates how premature senescence can have anticancer properties. However and as aforementioned, senescent cells may also promote cancer proliferation and invasion. Consequently, the elimination of the senescent cells should be integrated in future therapeutic strategies. Based on this rationale, Dörr (Dörr et al. 2013) developed a mouse lymphoma model exploiting senescence-related metabolic reprogramming. This model is more sensitive to blocking glucose utilization or autophagy that induces a caspase-mediated apoptosis also called senescence-induced hypercatabolic targeting or synthetic lethal metabolic targeting.

Finally, telomerase represents another pathway for future therapeutic interventions: gene expression differs between normal cells and lymphoma cells, suggesting that targeting telomerase could be envisioned with manageable side effects. This possibility is in development in solid tumors (Harley 2008).

Conclusion

Accumulating time has a major impact on the hematopoietic lineage, explaining the very complex interplay between age and lymphomagenesis. It favors the accumulation of mutations and epimutations, related both to the high proliferative turnover of these cells and also to their high sensitivity to exogenous as well as endogenous mutational events, related to BCR and TCR processing. It induces the accumulation of senescent cells, both through replicative and premature senescence. It favors, during time, clonal restriction, leading both to tissue exhaustion and an immunologic dysfunction and eventually to the selection of pre-tumoral clones. It favors the accumulation of memory B and T cells, contributing to the immunosenescence and to the inflammaging phenotypes, both contributing to chronic infection and inflammation. These pathways contribute to an increased incidence of lymphoproliferative disorders in the elderly, with specific genetic characteristics. They are also good candidates for the development of future therapies.

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Aging of Natural Killer Cells in Acute Myeloid Leukemia

11

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Contents

Abstract

Aging is associated with changes in the immune system involving both adaptive and innate immunity. Immunosenescence refers to the deterioration of the immune system function associated with aging. Natural killer (NK) cells are innate lymphoid cells specialized in killing tumor cells as well as virus-infected cells without the requirement of prior sensitization. NK cells are also involved in regulating immune function as they produce several cytokines and chemokines. NK cell immunosenescence affects the frequency,

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phenotype, and subset distribution of human NK cells. A decreased expression of activating receptors is observed in the elderly that may contribute to the decline of NK cell function. It has been proposed that the failure of tumor immunosurveillance may be partly responsible for the age-associated increase in cancer incidence.

Acute myeloid leukemia (AML) is a disease of older adults with a median age at diagnosis usually over 65 years old. NK cells in AML patients show a reduced expression of several activating receptors that impair NK cell function. Low level of expression of activating receptors such as NKp46 has been correlated with disease progression and patient survival.

KIR-HLA class I receptor-ligand mismatch is associated with a graft versus leukemia effect in haploidentical hematopoietic stem cell transplantation supporting the role of NK cells in AML control. Thus, NK cell-based immunotherapy emerges as a novel treatment for AML patients. However, a better understanding of age-associated changes on NK cell phenotype and function is required to delineate adequate therapeutic strategies in older AML patients.

Keywords

Aging · AML · Cancer · Immunosenescence · NK cells

Abbreviations

ADCC	Antibody-dependent cell cytotoxicity
AML	Acute myeloid leukemia
BiKE	Bispecific killer engager
CAR	Chimeric antigen receptor
CMV	Cytomegalovirus
DNAM-1	DNAX accessory molecule-1
Gal-9	Galectin-9
GVHD	Graft versus host disease
GVL	Graft versus leukemia
HLA	Human leukocyte antigen
HMGB-1	High mobility group protein B1
HSCT	Hematopoietic stem cell transplantation
IFN	Interferon
IL	Interleukin
ILC	Innate lymphoid cells
KIR	Killer cell immunoglobulin-like receptors
LAG-3	Lymphocyte activation gene 3 protein
MHC	Major histocompatibility complex
MICA/B	MHC class I-related chain A/B
MLL5	Mixed-lineage leukemia-5
NCRs	Natural cytotoxicity receptors
NEACT	Nonengrafting alloreactive cellular therapy
NK	Natural killer
PD-1	Programmed death protein 1
TcR	T cell receptor
TGF	Tumor growth factor
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIM3	T-cell immunoglobulin domain and mucin domain 3
TNF-α	Tumor necrosis factor-α
TriKE	Trispecific killer engager
ULBP	UL-16 binding protein

Introduction

Acute myeloid leukemia (AML) is a hematologic disorder usually diagnosed in older adults (Klepin et al. 2014; Thomas 2015; Isidori et al. 2013). Age-associated changes in the immune system, referred to as immunosenescence, are observed in both the adaptive and the innate immune system. Immunosenescence limits the immune response to pathogens or tumor cells. Age induces changes in the frequency, phenotype, and function of different subpopulations of immune cells, including natural killer (NK) cells (Gayoso et al. 2011; Solana et al. 2014). NK cells belong to the family of innate lymphoid cells (ILC). ILC contribute to tissue repair, lymphoid homeostasis, and defense against infections. NK cell are cytotoxic ILC specialized in monitoring cell transformation by virus and tumors and exert different effector functions such as natural cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC), and cytokine production (Vacca et al. 2016).

AML patients frequently show changes in the phenotype and function of NK cells that compromise NK cell recognition and killing of leukemic blasts. These alterations are even more important in elderly AML patients because of age-associated immunosenescence (Sanchez-Correa et al. 2011, 2012).

Recently, immunotherapy is showing remarkable potential against cancer. NK cell-based immunotherapy is becoming a promising approach for the treatment of AML patients. Adoptive therapy using autologous or allogeneic NK cells expanded in vitro and checkpoint blockade of inhibitory receptors together with the use of agonist antibodies to stimulate activating receptors or NK cells engagers binding an activating receptor and a tumor antigen are emerging areas of research for the design of new therapeutic strategies based on NK cells (Shin and Ribas 2015; Chester et al. 2015; Borrego et al. 2016). In this context, a better understanding of the effect of age on NK cell function is necessary to improve the efficiency of NK cell-based immunotherapy in older AML patients (Tarazona et al. 2017; Sanchez-Correa et al. 2016).

Natural Killer Cells

NK cells are derived from a lymphocyte progenitor and represent a prototypical member of the ILC family. NK cells are included into group 1 of ILC family together with ILC1 (Spits et al. 2016). NK cells display cytotoxic capacity as well as regulatory functions by cytokine production. Traditionally, human NK cells are defined as lymphocytes that lack CD3 and express CD56 and/or CD16. Different NK cell subsets can be distinguished on the basis of CD56 and CD16 expression. In peripheral blood, a low percentage (≈10%) of NK cells are $CD56^{bright}CD16^{-}$ representing a more immature NK cell subset in comparison with the major $CD56^{dim}CD16^{+}$ NK cell subset (≈90%). NK cell subsets display different effector functions, thus, $CD56^{bright}$ NK cells have mainly an immunoregulatory role mediated by the secretion of cytokines, whereas $CD56^{dim}$ counterpart are cytotoxic cells (Moretta et al. 2014). An additional minor subset correspond to $CD56^{-}CD16^{+}$ NK cells, this subset was initially described in HIV-1 infected patients (Tarazona et al. 2002; Mavilio et al. 2005), hepatitis virus infection (Gonzalez et al. 2009), and to some extent in healthy individuals (Campos et al. 2014b).

NK cells monitor cell surfaces of autologous cells for an altered expression of major histocompatibility complex (MHC) class I molecules and stress markers. NK cell-mediated cytotoxicity is controlled by a repertoire of inhibitory and activating receptors expressed on their surface (Fig. 1a). MHC class I-specific receptors are the major inhibitory receptors acting as sensors of healthy cells since tumor transformation and viral infection frequently lead to diminished expression of MHC class I molecules. NK cell activation requires signaling through activating receptors whose ligands are frequently expressed on tumor and viral infected cells (Waldhauer and Steinle 2008).

MHC Class I-Specific Receptors

Killer immunoglobulin-like receptors (KIR) are type I transmembrane glycoproteins belonging to the Ig superfamily with two or three Ig-like domains. KIR include both inhibitory and activating receptors. Inhibitory KIR have long cytoplasmic domains containing immunoreceptor tyrosine-based inhibitory motifs (ITIM) that recruit protein tyrosine phosphatases required for mediating inhibitory function. In contrast, activating KIR have a short cytoplasmic tail and associate to the adaptor protein DAP-12 that contains immunoreceptor tyrosine-based activation motifs (ITAM). KIR binds human leukocyte antigen (HLA)-A, -B, and -C molecules which are expressed on almost all healthy nucleated cells and protect them from NK cell attack (Campbell and Purdy 2011; Thielens et al. 2012).

The CD94/NKG2 C-type lectin-like receptors family is composed by different NKG2 members that form disulfide-linked heterodimers with an invariant CD94 chain. Several members have been described with either inhibitory (CD94/

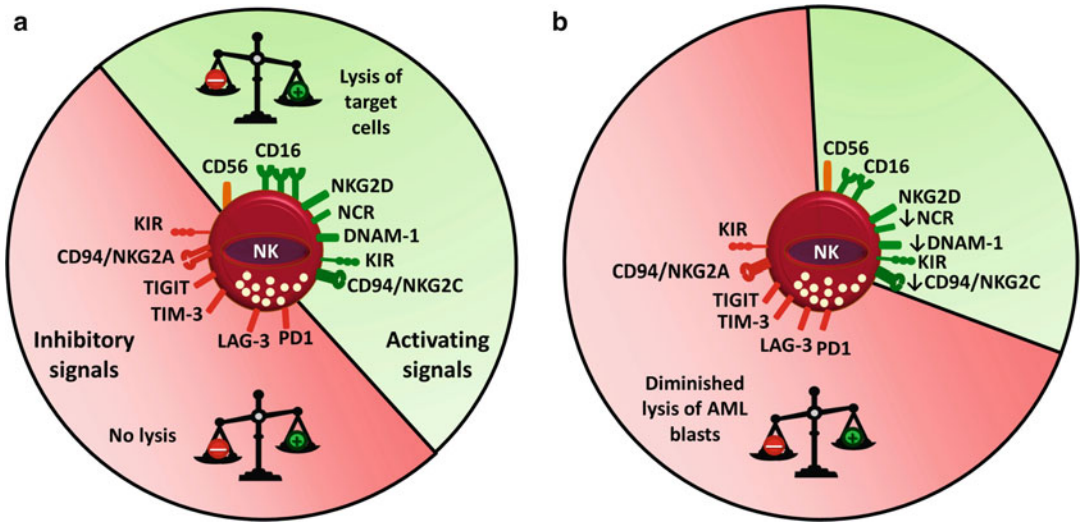

Fig. 1 Human NK cell receptors in healthy and AML patients. (**a**) NK cell activation against target cells is regulated by the balance of signals mediated by an ample set of inhibitory or activating surface receptors. NK cell receptors interact with their ligands on target cells and signal NK cells to preserve healthy cells (shift the balance to inhibition) or attack cells undergoing tumor or virus transformation (shift the balance to activation). (**b**) A reduced expression of several NK cell activating receptors has been observed in AML patients shifting the balance to inhibition and contributing to leukemic blast escape from NK cells

NKG2A, CD94/NKG2B) or activating (CD94/NKG2C, CD94/NKG2E) function. These receptors are expressed on NK cells and in a subset of T cells. CD94/NKG2 receptors recognize as ligands the nonclassical HLA class I molecule HLA-E in humans and Qa-1b in mice (Borrego et al. 2006).

Non-MHC Class I-Specific Inhibitory Receptors

Several receptors recognizing ligands other than MHC class I molecules have been described to play a relevant role in NK cell activation and consequently represent novel immune checkpoints for cancer immunotherapy. TIGIT (T-cell immunoreceptor with Ig and ITIM domains) acts as an inhibitory receptor on T and NK cells. TIGIT binds nectin and nectin-like molecules CD112, CD113, and CD155 (PVR).

The role of CD155 expression on cancer immunosurveillance has been well characterized since it binds different receptors with opposite functions (Martinet and Smyth 2015). CD155 is also a ligand for CD96 (TACTILE) a receptor expressed on human T cells, NK cells, and a subset of B cells. CD96 is also found highly expressed in AML, T-cell acute lymphoblastic leukemia (T-ALL), and myelodysplastic syndromes (Blake et al. 2016a). Human but not mouse CD96 contains within the cytoplasmic tail an YXXM motif similar to that found in activating receptors (Meyer et al. 2009). In addition, both human and mouse CD96 contains cytoplasmic ITIM-like motifs that may be involved in inhibitory signaling after receptor engagement (Martinet and Smyth 2015). It has been described that human CD96 interacts with CD155 on target cells promoting cell adhesion (Fuchs et al. 2004). In contrast, $CD96^{-/-}$ mice showed resistance to lung metastases and fibrosarcoma induction suggesting that CD96 may act as an inhibitory receptor. In this model, antibody blocking of CD96 showed a reduction of lung metastases further supporting its inhibitory function (Chan et al. 2014). In murine tumor models, anti-CD96 blockade demonstrated to be more effective when combined with anti-CTLA4 or anti-programmed death protein 1 (PD-1) (Blake et al. 2016b).

The inhibitory receptor PD-1 represents a key checkpoint in T-cell activation, and recently its role in NK cell activation has been highlighted. PD-1 mediates functional exhaustion of both T cells and NK cells. PD-1 ligand 1 (PD-L1) is expressed in lymphoid and nonlymphoid cells as well as in tumors. Thus, control of the PD-1 pathway may circumvent tumor escape not only from T cells but also from NK cells (Benson et al. 2010).

Lymphocyte activating gene 3 (Lag-3 or CD223) is an inhibitory receptor expressed on activated NK cells and T cells. Lag-3 structure resembles that of CD4 coreceptor and binds to MHC class II molecules and LSECtin, a member of the DC-SIGN family of molecules (Triebel et al. 1990; Xu et al. 2014; Anderson et al. 2016). Lag-3 associates with CD3/T-cell receptor (TcR) complex suppressing T-cell activation (Hannier et al. 1998). Lag-3 is considered a novel immune checkpoint molecule to activate anti-tumor T cells (Perez-Gracia et al. 2014). In addition, Lag-3 and PD-1 act synergistically regulating T-cell function (Okazaki et al. 2011). Further studies will be needed to understand the involvement of Lag-3 on NK cell activation.

T-cell immunoglobulin and mucin domain 3 (Tim-3) is expressed on all mature $CD56^{dim}$ NK cells and is induced by cytokines on $CD56^{bright}$ NK cells (Gleason et al. 2012; Ndhlovu et al. 2012). Tim-3 interaction with its known ligand Galectin-9 (Gal-9) has shown to mediate both inhibitory and activating signals. Thus, in healthy individuals Tim-3 engagement with its ligand Gal-9 triggers interferon (IFN)-γ secretion acting as a costimulatory receptor (Gleason et al. 2012), whereas in advanced melanoma Tim-3 blockade reversed NK cell exhaustion and improves NK cell function ex vivo (Da Silva et al. 2014). Cross-linking of Tim-3 with antibodies also suppressed NK cell-mediated cytotoxicity (Ndhlovu et al. 2012) suggesting that Tim-3 regulation of NK cell function depends on the context in which NK cell activation occurs. In addition to Gal-9, other ligands have been identified for Tim-3 including phosphatidyl serine, high mobility group protein B1 (HMGB1) and Ceacam-1 (Anderson et al. 2016). Tim-3 has been also shown to be expressed on leukemic stem cells on all types of AML by French-American-British (FAB) classification with the exception of acute promyelocytic leukemia (M3). Thus, Tim-3/Gal-9 represents an important autocrine loop promoting leukemia progression that may become a target for treating AML (Kikushige et al. 2015).

Activating Receptors

Activating NK cell receptors belong to different families including MHC class I-specific activating KIR and CD94/NKG2C. Among the activating receptors CD16, a low-affinity receptor for the Fc portion of immunoglobulin G plays an important role in ADCC. Upon recognition of antibody coated target cells, CD16 signaling activates NK cells to release their cytotoxic granules containing perforin and granzymes. Other activating receptors recognize stress-related ligands on tumor and virus-infected cells. Thus, NKG2D is a member of the NKG2 C-type lectin-like receptors. NKG2D is expressed on NK cells, $CD8^+$ and subsets of $CD4^+$ T cells, NKT cells, and γδ T cells. NKG2D forms homodimers and associates with DAP10 adaptor protein in humans, whereas in mice associates with DAP10 or DAP12. This receptor recognizes a large repertoire of ligands encoded by several genes, some of them polymorphic. In humans, NKG2D ligands are the major histocompatibility complex class I-related chain A and B (MICA and MICB) and the UL-16 binding proteins (ULBP, also known as RAET1, retinoic acid early transcript 1) with six functional proteins described so far. In general, NKG2D ligand induction is attributed to cellular stress and ligands are usually not expressed on healthy cells. The expression of one or more NKG2D ligands is observed in cancer cells and virus-infected cells. NKG2D ligand expression regulation is a complex process involving transcriptional, post-transcriptional, and post-translational mechanisms (Lanier 2015).

Natural cytotoxicity receptors (NCRs) were identified as major activating receptors eliciting cytotoxicity and cytokine production by NK cells. Three members of this family of receptors have

been described named NKp46 and NKp30 that are constitutively expressed by NK cells and NKp44 that is induced after activation. Although originally NCRs were thought to be NK cell specific receptors, different studies have demonstrated that NCRs can also be expressed on other innate lymphoid cells as well as in some T-cell subsets (Hudspeth et al. 2013). The identity of NCR ligands remains in part elusive. NCRs recognize pathogen-associated molecules as well as stress-related molecules on cell surface. Hemagglutinin (HA) protein from influenza and vaccinia virus is recognized by NKp46 and Sendai and Newcastle virus can be recognized by NKp46 and NKp44 (Mandelboim et al. 2001). NCRs also recognize intracellular bacteria and parasites (Mavoungou et al. 2007). Other NKp44 ligands include heparan sulfate and the cellular ligands mixed lineage leukemia 5 (MLL5). The proliferating cell nuclear antigen (PCNA) has been described as an inhibitory ligand for NKp44 (Horton and Mathew 2015). The human leukocyte antigen-B-associated transcript 3 (BAT3) was identified to interact with NKp30 triggering tumor lysis and cytokine release by NK cells (Pogge et al. 2007). B7-H6, a member of the B7 family of receptors, was also identified as a ligand for NKp30 (Brandt et al. 2009).

Physiologically relevant splice variants of NKp30 and NKp44 have been recognized (Siewiera et al. 2015). Whereas NKp30a and NKp30b engagement triggers NK cell activation, signaling through NKp30c isoform inhibits NK cell function. HA and pp65 a component of human cytomegalovirus (CMV) can inhibit NK cell function by binding to NKp30c (Arnon et al. 2005; Pende et al. 1999). Splice variants of NKp44 are associated with survival in AML patients (Shemesh et al. 2016). Cytokines in the local microenvironment may regulate alternative splicing of the NCRs (Siewiera et al. 2015).

DNAX accessory molecule 1 (DNAM-1), also known as CD226, was initially described as an adhesion molecule promoting cytotoxicity by $CD8^+$ T and NK cells. Further studies on DNAM-1 function demonstrated its function as an activating receptor. DNAM-1 ligands are the poliovirus receptor (CD155) and nectin-2 (CD112) that are associated with DNA damage-induced conditions such as oncogenic transformation or viral infections. CD155 expression is also observed in T cells after antigen-induced proliferation (de Andrade et al. 2014). AML blasts express DNAM-1 ligands CD112 and CD155 (Sanchez-Correa et al. 2012; Sanchez-Correa et al. 2011). It is of interest to note that CD155 binding to the receptors TIGIT and CD96 may counterbalance DNAM-1-mediated NK cell activation (Martinet and Smyth 2015).

Cancer, Aging, and Immunosenescence

Age is considered a risk factor included in almost all studies of cancer epidemiology. Cancer can be considered an age-related disease as the incidence of most cancers increases with age (White et al. 2014). It is estimated that the incidence of cancer would undergo an increasing trend in the future because of the increment of life expectancy around the world.

The age-associated deterioration of the immune system known as immunosenescence can be, at least in part, responsible of the higher incidence of several types of cancer in the elderly. Immunosenescence negatively affects both adaptive and innate immune responses reducing tumor immunosurveillance in the elderly (Fulop et al. 2013; Derhovanessian et al. 2008). On the other hand, a decline in the immune response has been described in cancer patients that mirror, at least in part, those changes observed in healthy elderly individuals (Sanchez-Correa et al. 2011, 2016; Poschke et al. 2012; Tarazona et al. 2017). This process termed "early immunosenescence" or "cancer-induced immunosenescence" can be detected as early as the onset of tumorigenesis limiting immunotherapy efficacy (Poschke et al. 2012).

Many factors contribute to immunosenescence including exposure to chronic pathogens throughout life. Latent infection by CMV constitutes a major driving force of T-cell immunosenescence. CMV can also induce changes on NK cells in young, middle-aged, and old individuals (Campos et al. 2014b, 2015). CMV infection associates

with inflammation, frailty, and mortality in the elderly (Pawelec et al. 2012) and lower responses to influenza vaccination and higher risk of influenza complications (Frasca et al. 2015). In contrast, in young individuals CMV-seropositivity associates with increased multifunctionality of $CD8^+$ T lymphocytes in response to Staphylococcal enterotoxin B (SEB) (Pera et al. 2014) and improved response to influenza vaccination (Furman et al. 2015). The determination of CMV serostatus should be considered in all studies addressed to analyze the immune system, in particular in those clinical situations in which a high percentage of patients are elderly.

NK Cells and Aging

The phenotype and function of NK cells is altered in the elderly (Campos et al. 2014b, 2015). Human NK cell immunosenescence is characterized by a redistribution of NK cell subsets showing a reduction of immature $CD56^{bright}$ NK cells and the accumulation of $CD56^{dim}$ NK cells (Gayoso et al. 2011; Solana et al. 2014).

It has been proposed a dynamic turnover model for NK cell subsets. $CD56^{bright}$ NK cells are more immature and proliferate and differentiate into $CD56^{dim}$ NK cells (Lutz et al. 2011). In the elderly, there is a decreased input of new $CD56^{bright}$ NK cells that is compensated by an increased proportion of $CD56^{dim}$ and $CD56^-CD16^+$ cells that may represent long-lived NK cells (Lutz et al. 2011; Campos et al. 2014a, b; Solana et al. 2014). The role of intrinsic factors such as cytokines (IL-15) and extrinsic factors, such as CMV, in the generation of long-lived, memory-like, NK cells has been suggested (Lopez-Verges et al. 2011, 2014). The analysis of NK cells according to age and CMV seropositivity has shown that aging affects the percentage and subsets of NK cells (Campos et al. 2014b, 2015; Solana et al. 2014).

NK cell function is also altered in the elderly; a reduced per-cell cytotoxicity is observed that is associated with a decreased expression of activating NK cell receptors (Gayoso et al. 2011; Campos et al. 2014b, 2015; Solana et al. 2014). The expression of NKp30, NKp46, and DNAM-1 activating receptors on NK cells is diminished in elderly healthy donors (Campos et al. 2014b, 2015). In contrast, the expression of NKG2D and CD244 (2B4) is preserved in the elderly (Mariani and Facchini 2003; Gayoso et al. 2009) as well as the expression of the Fc receptor CD16 and ADCC function (Solana and Mariani 2000; Lutz et al. 2005). An increased expression of CD57 and NKG2C on NK cells is associated with CMV serostatus (Campos et al. 2014b, 2015; Lopez-Botet et al. 2014). CMV seropositive young donors had a reduced expression of NKp30 compared to CMV seronegative young donors, whereas CMV seropositivity does not alter the expression of DNAM-1 and NKp46 on NK cells (Campos et al. 2014b, 2015).

NK Cell Receptors and Their Ligands in Patients with Solid Tumors

As summarized above, NK cells constitute the major component of the innate immune response involved in the recognition and elimination of cancer cells. It is generally accepted that evasion from immunosurveillance is one of the hallmarks of cancer (Hanahan and Weinberg 2011), and it has been demonstrated that tumor cells use different strategies to avoid NK cell recognition and lysis. Thus the increased expression of inhibitory receptors on NK cells or their ligands on the tumor cells has been demonstrated in patients with different solid tumors such as nasopharyngeal carcinoma (Butsch et al. 2005), neuroblastoma (Keating et al. 2015), or lung cancer (Al Omar et al. 2011). The interaction of NK cell-activating receptors with their ligands on tumor cells from different lineages is required for NK cell-mediated cytotoxicity (Casado et al. 2009; Morgado et al. 2011; Garcia-Cuesta et al. 2015; Boerman et al. 2015; Shiraishi et al. 2016). As a mechanism to escape NK cell immunosurveillance, NK cells from patients with solid tumors frequently show a decreased expression of activating receptors such as NKG2D, NCRs, or DNAM-1 (Shiraishi et al. 2016; Al Omar et al. 2011). In addition, the ligands for these NK cell-activating receptors can

be expressed by tumor cells, but they can be released from the tumor cell surface. These released isoforms can interact with the activating receptor leading to altered function. It has been found that the serum levels of the NKG2D ligand ULBP-2 inversely correlate with the survival of melanoma patients (Paschen et al. 2009). In a similar way, a soluble form of B7-H6, the NKp30 ligand, can be detected in neuroblastoma patient sera. In these patients, elevated serum levels of B7-H6 inhibited NK functions in vitro and correlated with downregulation of NK-p30 on NK cells, as well as with bad prognosis after treatment due to bone marrow metastasis and chemoresistance (Semeraro et al. 2015a, b). Taken together these results support the relevance of the interactions between NK cell-activating receptors and their ligands in cancer immunosurveillance.

NK Cells in AML Patients

NK cells from AML patients had impaired effector functions showing reduced NK cell degranulation, TNF-α, and IFN-γ production against autologous blasts and K562 cells (Stringaris et al. 2014). The analysis of NK cell-activating receptors in AML patients has demonstrated a decreased expression of several activating receptors (Fig. 1b). The expression of NKp46 and NKp30 is diminished in AML patients compared to age-matched healthy donors and may be related to patient outcome (Fauriat et al. 2007; Sanchez-Correa et al. 2011, 2012). Thus, preserved expression of NKp46 was correlated with survival of AML patients (Fauriat et al. 2007). DNAM-1 expression is also diminished in AML patients and CD112 expression on blasts inversely correlates with DNAM-1 expression on NK (Sanchez-Correa et al. 2011, 2012). It has been suggested that chronic exposure to ligands on tumor cells is responsible of the decreased expression of NCR and DNAM-1 in AML patients (Fauriat et al. 2007; Sanchez-Correa et al. 2011, 2012).

Paired receptor-ligand interactions between DNAM-1, TIGIT, and CD96 receptors sharing the same ligands are relevant in the context of tumor immunity (Martinet and Smyth 2015). In AML patients, the axis DNAM-1/TIGIT/CD96/CD155 shifts the balance to inhibition over activation due to the reduced expression of DNAM-1.

A lower expression of CD94/NKG2C and CD16 is also observed in AML patients compared to age-matched healthy donor. In contrast, the expression of the activating receptor NKG2D is conserved on NK cells from AML patients (Sanchez-Correa et al. 2011). However, a limitation for NKG2D-mediated activation of NK cells in AML patients is the lower expression of NKG2D ligands on AML blasts compared to solid tumors such as melanoma (Sanchez-Correa et al. 2011; Casado et al. 2009).

NK Cells in Elderly AML Patients

Elderly AML patients have a poor prognosis due, among others, to higher incidence of drug toxicity, overexpression of genes associated with drug resistance, higher frequency of poor risk cytogenetic abnormalities, and comorbidities. Age itself constitutes an independent prognostic factor for AML (De Kouchkovsky and Abdul-Hay 2016; Heiblig et al. 2017). Recent advances in the treatment of AML have led to significant improvements in outcomes for younger patients. However, the prognosis in the elderly AML patients is poor, and treatment options remain limited for the majority of older patients (Appelbaum et al. 2006).

The study of NK cells in AML patients according to age showed a decreased expression of NKp46 in elderly AML patients compared to healthy elderly donors suggesting that both age and AML may contribute to the diminished expression of activating receptors on NK cells (Sanchez-Correa et al. 2012). Due to the high prevalence of CMV in the elderly, CMV-related changes on NK cells can also facilitate leukemic blast escape. Thus, it has been proposed that chronic antigenic stimulation by CMV and tumors is additive leading to immune exhaustion reducing adaptive immune responses to new antigens and also diminishing immunological memory (Fulop et al. 2013). On the other hand, the

deleterious participation of CMV infection in tumor immunosurveillance is supported by the finding of CMV-induced downregulation of both MHC class I and class II molecules on infected cells limiting adaptive immune responses. In addition, CMV blocking of MICB and ULBP1/2 expression on cell surface avoids NKG2D-mediated activation of NK cells and costimulatory signals for T cells. In addition, tumor growth factor (TGF)-β1 secreted by CMV-infected cells also promotes immunosuppression in the tumor microenvironment (Michaelis et al. 2009). The question of how the effect of aging, CMV, and cancer is cumulative requires further analysis.

Because many AML patients are elderly at diagnosis, immunosenescence may impair NK cell function and allow AML blast escape from NK cell-mediated immunosurveillance restraining the exit of NK cell-based immunotherapies (Sanchez-Correa et al. 2016; Tarazona et al. 2017).

NK Cell-Based Immunotherapy in AML Patients

The discovery of NK cell spontaneous cytotoxicity, originally demonstrated in vitro against leukemia cell lines, together with the clinical benefits observed in KIR-ligand mismatched allogeneic stem cell transplantation support the pivotal role of NK cells against leukemia and consequently their exploitation in immunotherapies. Evidence for graft-versus-leukemia (GVL) effect mediated by NK cells was observed in both murine models and in clinical studies with haploidentical donor transplants where the presence of alloreactivity was correlated with higher survival rates (Ruggeri et al. 2002). KIR-ligand mismatch was demonstrated to be responsible for the GVL effect mediated by NK cells. Interestingly, NK cells do not induce graft versus host disease (GVHD) and also can decrease GVHD mediated by T cells by targeting recipient's antigen presenting cells. As a result, NK cells exert their cytotoxicity preserving healthy cells, and in contrast to T cells, tumor control can be achieved in the absence of GVHD (Rezvani and Rouce 2015).

Recent advances on the integration of NK cell activating and inhibitory signals highlight that NK cell-based immunotherapies are feasible for the treatment of cancer. NK cell-based immunotherapy includes adoptive immunotherapy with ex vivo-expanded NK cells or NK cell lines such as NK-92. A major limitation for adoptive NK cell immunotherapy is the failure of transferred NK cells to persist and expand in vivo. Thus, NK cell engineering to express chimeric antigen receptor (CAR) has shown great promise in preclinical settings. CAR-engineered NK cells are advantageous compared to CAR-engineered T cells due to their shorter life span that may diminish side effects. In addition, strategies directed to increase ADCC, modulate activating receptor expression and redirect NK cytotoxicity toward tumor cells by using recombinant antibody constructs also constitute new approaches to control cancer (Rezvani and Rouce 2015). The use of bispecific or trispecific killer engagers (BiKE and TriKE respectively) containing single-chain variable fragments directed to CD16 to trigger NK cells, anti-CD33 to bind leukemia blasts, and in the case of TriKE a modified IL-15 crosslinker have shown to induce NK cell-mediated killing of blasts and to promote survival and in vivo expansion of NK cells in a xenograft murine model of AML (Vallera et al. 2016). Finally, checkpoint blockade constitutes a novel alternative for NK cell-mediated therapies against tumors (Tarazona et al. 2017; Carotta 2016; Blake et al. 2016b).

During the last decade, a valuable number of NK cell-based clinical trials for leukemia have been developed (Table 1). However, the inclusion of elderly AML patients in clinical trials is very limited. NK cell transfer is feasible and safe and its effect can be improved by selection of optimal donors, ex vivo or in vivo stimulation of infused NK cells by cytokines, use of antibodies to induce ADCC, checkpoint blockade by antibodies directed to inhibitory receptors such as KIR, and by the use of CAR-engineered NK cells (Handgretinger et al. 2016). Monitoring NK cells in AML patients, in particular in elderly patients, is important in order to stratify patients at diagnosis and to evaluate NK cell status after standard chemotherapy and immunotherapies.

Table 1 NK cell-based clinical trials for leukemia

Category	Strategy	Start date-completion	Conditions	Phase	Age	Identifier/ references
Autologous NK cells	Autologous NK cells & Bortezomib	2008–2018	Hematological malignancies (MM, CML, CLL and SLL) and solid tumors	1	18–70	NCT00720785
Allogeneic NK cells	Haploidentical NK cells	2004	Refractory AML and solid tumors	1		(Miller et al. 2005)
	Haploidentical KIR-ligand mismatched NK cells	2005–2009	AML	1	>18	NCT00799799 (Curti et al. 2011)
	Haploidentical KIR-ligand mismatched NK cells	2006–2014	AML and MDS	1	≤70	NCT00402558 (Lee et al. 2016)
	Haploidentical NK cells & aldesleukin post HSCT	2005–2011	High risk AML	1/2	18–70	NCT00303667
	Haploidentical NK cells post HSCT	2007–2015	Hematologic malignancies	2	≤120	NCT00526292
	NK cells post HSCT	2008–2017	Hematologic malignancies	1/2	All	NCT00789776
	NK cells post HSCT	2009–2013	Advanced cancer (solid and hematologic)	1/2	15–75	NCT00823524
	Haploidentical NK cells & TcRαβ-depleted cells from the same donor	2011–2019	High risk AML and MDS	2	18–75	NCT01370213
	Haploidentical NK cells expanded by K562mb15-41BBL	2014–2018	Acute leukemia and MDS	1	6–80	NCT02123836
	Haploidentical NK cells & IL-15	2015–2019	Relapsed/refractory AML	2	>18	NCT02395822
	UCB NK cells (PNK-007) & IL-2	2016–2019	Relapsed/refractory AML	1	18–70	NCT02781467
	UCB NK cells post UCB transplant in C2C2 patients	2016–2020	Hematologic malignancies	2	18–80	NCT02727803
	non-HLA matched NK cells & ALT803	2016–2019	Hematologic malignancies and other tumors	1	>18	NCT02890758
	Haploidentical NK cells & IL-2	2015–2020	High risk Elderly AML	2	≥60	NCT02229266
	Haploidentical NK cells & ALT803	2017–2020	Relapsed/refractory AML	2	18–70	NCT03050216
	CNDO-109 (CTV-1 leukemia cell lysate)-activated haploidentical NK	2012–2016	AML in CR1	1/2	>18	NCT01520558
	Haploidentical NK cells	2010–2012	Relapsed/refractory AML	2	>2	NCT01106950 (Bachanova et al. 2014)

(*continued*)

Table 1 (continued)

Category	Strategy	Start date-completion	Conditions	Phase	Age	Identifier/ references
	Cytokine induced memory-like haploidentical NK cells	2014–2020	AML and MDS	1	>18	NCT01898793
	Cytokine induced memory-like NK cells post HSCT	2017–2022	Refractory AML	2	>18	NCT02782546
NK cell line	NK92 cells	2005–2012	Hematologic malignancies	1	>18	NCT00990717
	Neukoplast™ (NK92)	2014–2016	Relapsed/refractory AML	1	>18	NCT00900809
CAR-NK	(α-CD7-CAR-NK92)	2016–2018	Hematologic malignancies	1/2	>18	NCT02742727
	α-CD33 CAR-NK92 cells	2016–2018	Relapsed/refractory AML	1/2	3–80	NCT02944162
	α-CD19 CAR-NK92 cells	2016–2019	Hematologic malignancies	1/2	3–80	NCT02892695
Checkpoint blockade	α-KIR (IPH2101)	2007–2013	Elderly AML in CR	1	60–80	NCT01256073
	α-KIR (IPH2102)	2012–2016	Elderly AML in CR	2	60–80	NCT01687387
	α-KIR (IPH2102, lirilumab) & Rituximab	2015–2021	Relapsed/refractory or high risk leukemia (CLL, SLL)	2	>18	NCT02481297
	α-NKG2A (IPH2201, monalizumab) & ibrutinib	2015–2019	Relapsed/refractory CLL	1/2	>18	NCT02557516

AML Acute myeloid leukemia, *CLL* chronic lymphocytic leukemia, *CML* chronic myelogenous leukemia, *CR* complete remission, *MM* multiple myeloma, *MSD* myelodysplastic syndromes, *SLL* small lymphocytic lymphoma, *UCB* umbilical cord blood

NK cells from elderly AML patients in first remission were evaluated in a clinical trial (NCT00540956) to determine the evolution of NK cell receptors after chemotherapy and the kinetics of NK cell recovery of cytotoxic function. The effect of the immunomodulatory drug lenalidomide on NK cells in AML patients was also evaluated in a clinical trial (NCT02525250). In AML patients previously treated with IL-2, the relationship between NK cell cytotoxicity against leukemia cells and the outcome was analyzed (NCT00896701). To our knowledge, results from these clinical trials have not yet been published.

Adoptive transfer of allogeneic NK cells post HSCT or in nontransplant scenarios has demonstrated to be superior to whole lymphocyte infusions (Suck et al. 2016). Infused NK cells can persist and expand in vivo and can be used for the treatment of leukemia (Miller et al. 2005). In a phase I study (Dutch Trial Register NTR2818), the feasibility, safety, and toxicity of the infusion of allogeneic umbilical cord blood NK cells following an immunosuppressive preparative regimen in nontransplant eligible elderly AML patients was evaluated. NK cell transfer was safe and could induce or sustain remission in elderly AML patients.

NK cell alloreactivity was assessed after infusion of KIR-ligand mismatched NK cells. Elderly AML patients, in first complete remission, received haploidentical KIR ligand-mismatched NK cells in combination with IL-2. The results suggested that infusion of high numbers of NK cells was associated with prolonged disease free survival (Curti et al. 2011; Curti et al. 2016).

The use of NK-92 cells transduced with CAR is under study in clinical trials directed at the treatment of hematological malignancies (NCT02742727, NCT02944162, NCT02892695). The NK-92 cell line can be expanded in vitro under good manufacturing conditions highlighting its potential for immunotherapy.

Recently, two clinical trials using anti-KIR in elderly AML patients in complete remission have been performed to analyze the safety and tolerability of IPH2101 (NCT01256073) and the efficacy of IPH2102 as maintenance treatment (NCT01687387). Other inhibitory receptors such as TIGIT, Lag-3, and Tim-3 represent novel checkpoints for both T and NK cell-based immunotherapy.

Conclusions

Immunotherapy represents a promising approach to induce cancer immunity. Recent progress in our understanding of NK cell biology has allowed the development of novel NK cell-based immunotherapies for the treatment of leukemia. Adoptive transfer of autologous or allogeneic ex vivo expanded or NK cells, CAR-engineered NK-92 cells, or checkpoint blockade of inhibitory receptors combined with NK cell engagers are novel areas of research on NK cell-based immunotherapy against cancer.

Nowadays, translational research on NK cells is moving to the forefront of cancer immunotherapy. The detrimental effect of immunosenescence on the clinical success of immunotherapy should be considered. In addition, strategies directed to overcome immunosenescence in cancer patients may constitute a new avenue for future directions in leukemia treatment.

Cross-References

- ▶ Acute Myeloid Leukemia in Older Adults
- ▶ Immunosenescence and Cancer Immunotherapy at Old Age: Basics
- ▶ Chronic Myelogenous Leukemia and Myeloproliferative Disorders in Older Adults
- ▶ Hematopoietic Stem Cell Aging and Malignant Hemopathies
- ▶ Role of Cell Cycle Control, Checkpoints, and DNA Repair Mechanisms in Stem Cells and Changes with Aging and Cancerogenesis

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Hematopoietic Stem Cell Aging and Malignant Hemopathies

12

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Contents

Abstract

The probability of developing cancer, primarily malignant hemopathies, increases with age. This complex relationship between cancer and aging has been extensively studied; cellular senescence, a protective mechanism in response to DNA damage, can induce permanent growth arrest and resistance to apoptosis. Chronological age also favors the accumulation of genetic and epigenetic changes that are

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important contributing factors in the complex pathogenesis of cancer. Indeed recent studies have highlighted the role of epigenetics and, in particular, a decline in heterochromatin integrity as important factors contributing to the loss of stem cell function during HSC aging in premature aging syndromes. Furthermore, impairment of cancer prevention pathways and the clonal restriction of hematopoietic stem cells observed with age may also contribute to the increased frequency of malignant transformation. However, at present our understanding of the process of aging is far from complete, and many open questions are currently under investigation. This chapter will focus on the complex multistep interplay between aging and the higher incidence of malignant hemopathies.

Keywords

Aging · Elderly · Tumor suppressor genes · Malignant hemopathies · Hematopoietic stem cell · Epigenetics · Senescence · DNA damage repair

Introduction

Though not a disease per se, aging is a complex phenomenon that progressively leads to organ dysfunction and represents a major risk factor for chronic diseases and primarily cancers. Cellular senescence is a major contributor to this biological process.

Since adult stem cells are responsible for maintaining tissue homeostasis, an attractive hypothesis is that age-related degenerative changes may be due to an alteration in tissue stem cells, particularly the hematopoietic stem cells (HSCs), with progressive waning of our immune defenses. Concomitant genetic and epigenetic modifications are observed in all malignant hemopathies leading to activation of oncogenes or loss of tumor suppressive genes.

This chapter will thus focus on the accumulation of mutations, epigenetic changes, and age-related clonal hematopoietic cell expansion. These age-related events decrease anticancer immunity and alter the DNA damage response pathway. This complex multistep interplay ultimately favors a higher incidence of cancer in the aging population.

Senescence: A Dual Phenomenon

Cellular senescence is thought to be one of the major molecular processes in biological aging. It serves primarily as a protective mechanism to shut down damaged cells and force them into a state of irreversible growth arrest (Ben-Porath and Weinberg 2004, 2005). Various triggers can induce cellular senescence including telomere erosion, irreversible DNA damage, lysosomal stress, unresolved unfolded protein response (UPR), oncogene activation, or reactive oxygen species (Sharpless and Sherr 2015). The induction of senescence in a damaged cell protects the organism from abnormal cell growth that could lead to cancer, because it prevents the cell from reentering the cell cycle in response to mitogenic or oncogenic stimulation and uncontrolled proliferation and dissemination. Senescence is believed to be an evolutionarily selective mechanism designed to preserve the integrity of a young organism during its reproductive period.

Senescence is induced by the upregulation of several genes, which are primarily CDKN2A (p16/INK4A/ARF), TP53, and RB (retinoblastoma gene). A fourth gene, CDKN1A (p21/WAF1/CIP1) also plays a role in the induction of growth arrest but is a less reliable senescence marker because the growth arrest it induces is more transient (Sharpless and Sherr 2015; Vandenberk et al. 2011). CDKN2A is a complex gene that encodes two distinct proteins, p16INK4a and p14ARF. Their locus has a complex architecture containing two separate promoters that can generate transcripts with distinct first exons followed by common second and third exons. p16INK4a is encoded by exons 1α, 2, and 3. It functions as a cyclin-dependent kinase inhibitor of the cell cycle by inhibiting the activity of the cyclin-dependent kinase complex "cyclinD/CDK4/CDK6" thereby blocking pRB phosphorylation and the passage from G1 into S (Serrano

et al. 1993; Rocco and Sidransky 2001). The alternate reading frame product, p14ARF, is encoded by the second first exon, exon 1β, located upstream from exon 1α together with the same second exon as p16INK4a in a different reading frame (Rocco and Sidransky 2001; Haber 1997). p14ARF functions by preventing p53 degradation, thereby allowing p53-mediated apoptosis or cell cycle arrest.

P53 and related proteins, p63 and p73, are key factors in the DNA damage response (DDR). Members of this family are directly involved in the induction of cell cycle arrest, necessary for cellular repair. Alternatively, they promote cell death when there is prolonged or irreparable DNA damage. They also take part in a direct task by modulating the expression of core factors involved in DNA repair processes or direct interactions with them (Nicolai et al. 2015). TP53, a tumor suppressive gene (TSG) first described 50 years ago, belongs to the group of "gatekeeper" genes typically involved in elimination or arrest of damaged cells.

PTEN is another potential candidate involved in senescence (Ortega-Molina and Serrano 2013). An established tumor suppressor gene, PTEN is often mutated in human tumors (Cantley and Neel 1999). Transgenic mouse models have highlighted its role in the aging process as well (Ortega-Molina et al. 2012; Garcia-Cao et al. 2012). Two mouse models with systemic PTEN overexpression under normal regulatory controls have, in addition to reduced adiposity and metabolic changes, higher median and maximal lifespans that are independent of PTEN's tumor suppressor function. Downregulation of the nutrient-sensing IIS (insulin/insulin-like growth factor signaling) pathway has been shown to be an important modulator of longevity across evolution. The observation that PTEN overexpression in mice extends their life-span adds further evidence to this paradigm.

A remarkable feature of senescent cells is the increase in protein secretion, including proinflammatory cytokines and growth factors (Bavik et al. 2006). This phenotype, known as senescent-associated secretory phenotype (SASP), induces changes in the microenvironment that increase proliferation and degenerative defects of non-senescent cells, thereby favoring the development of tumors such as lymphoma or myeloma (André et al. 2015; Coppé et al. 2008; Xue et al. 2007).

This seems to be a high price to pay for senescence as a protection mechanism. In exchange for the integrity of our organism early in life, senescent cell accumulation throughout the body causes biological aging in later life. An in vitro finding that senescent cells accumulate with increased population doublings until the majority of the culture has reached replicative senescence was an important observation. This led to the hypothesis that as senescent cells accumulate in an organism coupled with their lack of regenerative capacity, there is a failure of organ homeostasis and functions and consequent tissue aging (Jeyapalan and Sedivy 2008). Senescent cells have been identified in vivo, in various tissues from different organisms including mice, primates, and humans (Herbig et al. 2006; Jeyapalan et al. 2007; Dimri et al. 1995; Satyanarayana et al. 2003; Molofsky et al. 2006). There have also been studies, mostly in the skin, providing evidence that frequency of senescent cells increases with age (Herbig et al. 2006; Jeyapalan et al. 2007; Dimri et al. 1995; Ressler et al. 2006). The detection of signs of senescence at specific sites in age-related pathologies further suggests there is a link between cellular senescence, aging, and chronic diseases (Fenton et al. 2001; Matthews et al. 2006; Minamino et al. 2002; Price et al. 2002).

What Have We Learned from Progeroid Syndromes?

Many progeroid syndromes such as ataxia telangiectasia (ATM gene (=TSG) mutation and severe depletion of ATM protein), Werner syndrome (mutation of the WRN gene leading to genetic instability) and Hutchinson-Gilford progeria syndrome, and restrictive dermopathy (mutation in the LMNA gene involved in chromatin structure) (Cheng et al. 2008; Pereira et al. 2008) cause genomic instability due to defective

DNA repair. They present as a premature aging phenotype associated with an increased incidence of cancer. In these patients, damage in DNA integrity results from poor DNA repair, telomere shortening, chromosome instability, altered intercellular communications, and senescent environmental loss of apoptosis-regulating genes.

Among TSG, the TP53 gene codes for p53 protein which is an important regulator of the cell cycle (DNA repair, growth arrest, and apoptosis) and can be described as the "guardian" of the genome. p53 is usually low in normal cells but can be upregulated by DNA damage and other types of stress. TP53, located on chromosome 17 (17p13.1), is frequently mutated in progeroid syndromes and many patients with malignant hemopathies (Whibley et al. 2009).

The trade-off between cancer and aging has been nicely illustrated in murine experiments where TP53 was manipulated to investigate its effects on the aging process and cancer development. Mice with one allele of TP53 knocked-out died mainly of cancer. If however they escaped from cancer, they had a longer life-span than their normal counterparts, demonstrating that decreased senescence limits aging. Mice transfected with a constitutively active allele of TP53 had a greatly reduced cancer incidence but had signs of premature aging. If mice were armed with an extra allele of TP53, but under normal controls (i.e., not constitutively activated), they did not display this enhanced aging phenotype but did have improved tumor clearance (Donehower 2002; Donehower et al. 1992; Garcia-Cao et al. 2002; Maier et al. 2004; Tyner et al. 2002).

Hematopoietic Stem Cell Aging

A large body of evidence indicates that many important aspects of hematopoietic aging may be driven by age-associated changes in the functional properties of hematopoietic stem cells (HSCs). Paradoxically, this multipotent stem cell population that is responsible for the lifelong maintenance of the hematopoietic system increases in both number and frequency with age (Garrick et al. 2015). However, the HSCs that accumulate with time in elderly individuals, like in aged mice, demonstrate a poorer long-term engraftment capacity, clonal restriction, as well as a myeloid-biased differentiation output (Kuranda et al. 2011; Pang et al. 2011; Jan et al. 2017).

Clonal Expansion of Hematopoietic Stem Cells

The analysis of blood-derived sequence data from 2,728 individuals in the cancer genome ATLAS revealed mutations in 2% (up to 6% if they were older than 70 years). Among these mutations, 83% were divided among 19 hematological cancer-associated genes (DNMT3A, TET2, JAK2, ASX11, TP53, etc.). These common mutations are likely to initiate clonal expansion of HSCs in the elderly and may thus be responsible for the increased rate of leukemias and lymphomas observed in this age group (Xie et al. 2014a). This was confirmed on a large series of 17,182 samples, recently published by J. Aiswal (Jaiswal et al. 2014a), where somatic mutations in 160 genes that are characteristically mutated in hematological cancers had an increased incidence of mutation in older individuals.

Role of Epigenetics in Hematopoietic Stem Cell Aging

Recent studies have indicated that one important factor contributing to age-associated changes in HSC function is alterations in the epigenetic state and chromatin structure of HSC. The term epigenetic refers to changes to gene transcription and other DNA-templated processes (including DNA damage repair and replication) which are not due to alteration of the underlying DNA sequence. Recent findings implicating epigenetic changes in the aging of human HSC as well as genome-wide epigenomic studies carried out in mouse models are outlined below.

One of the most frequently studied epigenetic marks is the methylation of cytosine residues in double-stranded DNA to produce 5-methyl cytosine (5meC). This mark is associated with

repressive chromatin structure and transcriptional silencing. Profiling of murine HSC has revealed that the DNA methylome is surprisingly stable during aging, although specific localized changes (both hypo- and hypermethylation) are observed (Beerman et al. 2013; Sun et al. 2014; Taiwo et al. 2013). These localized changes in DNA methylation appear to have little direct effect on the expression of underlying genes, many of which encode lineage determining factors which are not normally expressed in the HSC themselves. These results suggest that alterations in DNA methylation may not give rise to functional changes in the stem cell population per se but may impact upon downstream cell fate decisions during differentiation (Beerman et al. 2013). Conditional knockout experiments in mice have indicated that the enzymes that catalyze DNA methylation, and in particular the de novo DNA methyltransferases Dnmt3a and Dnmt3b, play a critical role in regulating HSC self-renewal versus differentiation decisions (Challen et al. 2011, 2014). Consistent with this, it has been shown that the expression of all three DNA methyltransferases (Dnmt1, Dnmt3a, and Dnmt3b) is decreased with age in mouse HSC (Beerman et al. 2013; Sun et al. 2014). HSCs from aged mice also exhibit decreased expression of members of the 10–11 translocation (Tet) family of 5meC deoxidases, which are involved in the process of active DNA demethylation (Sun et al. 2014). In humans, exome sequencing studies of peripheral blood have revealed that aging is also associated with the acquisition of somatic mutations in genes affecting global DNA methylation patterns (primarily DNMT3A and TET2) (Jaiswal et al. 2014b; Genovese et al. 2014; Xie et al. 2014c). These mutations appear to confer a proliferative advantage on HSC, resulting in eventual dominance of the mutant stem cells and clonally restricted hematopoiesis. As these age-associated mutations observed in healthy aged individuals mirror those that are detected in malignant conditions, it is thought that these dominant HSC clones constitute a preleukemic pool in which the accumulation of secondary mutations eventually leads to the emergence of myeloproliferative disorders and myeloid leukemias.

Aside from DNA methylation, another important form of epigenetic information is a range of different covalent modifications that can occur on histone proteins and which alter the structure and accessibility of the underlying chromatin, thereby affecting DNA-templated processes including gene transcription (Kouzarides 2007). HSC aging is associated with altered expression of a number of histone-modifying proteins and regulators of chromatin structure (Beerman et al. 2013; Sun et al. 2014; Rossi et al. 2005; Chambers et al. 2007; Djeghloul et al. 2016), and knockout mouse models for several of these activities exhibit HSC and hematological defects (Djeghloul et al. 2016; Hidalgo et al. 2012; Xie et al. 2014b; Lee et al. 2015). Consistent with these observations, epigenomic profiling of mouse HSC by ChIP-seq has revealed that aging is associated with widespread but subtle changes in the distribution of several key histone modifications (Sun et al. 2014). In particular, HSC aging is associated with an increase in both the number and especially in the breadth of peaks of enrichment of trimethylation of lysine 4 of histone H3 (H3K4me3), a mark associated with transcriptional activation. A strong correlation was observed between augmentation in H3K4me3 at gene promoters and age-associated increases in gene expression. Among the sites most affected by these changes, there was an enrichment for genes associated with HSC self-renewal and loss of differentiation capacity, suggesting that these epigenetic changes could be an important factor contributing to the accumulation of HSC and impaired differentiation which is observed with age (Sun et al. 2014). A net increase was also observed with age in the size and strength of peaks of enrichment of trimethylation of lysine 27 of histone H3 (H3K27me3), a repressive histone modification laid down by the PRC2 Polycomb complex. There was also an increase in the number of so-called bivalent chromatin domains (marked by both H3K4me3 and H3K27me3), a signature which indicates a state of transcriptional priming for subsequent rapid activation (Bernstein et al. 2006). Changes in the global levels of other active (acetylation of lysine 16 of histone H4; H4K16ac) and repressive (trimethylation of

lysine 9 of histone H3; H3K9me3) histone modifications have also been observed with age in both human and mouse HSC (Djeghloul et al. 2016; Florian et al. 2012a).

Loss of Heterochromatin

More recently, studies of human HSC aging as well as epigenetic studies in patients with premature aging syndromes have highlighted the role of heterochromatin alterations as a driver of aging (Djeghloul et al. 2016; Zhang et al. 2015). Heterochromatin domains are regions of compacted chromatin that are generally refractory to transcription. The formation of heterochromatin is critical for many aspects of nuclear biology, including the regulation of gene expression, repression of genomic repeat elements, maintenance of genome stability, as well as centromere and telomere function (Peters et al. 2001; Grewal and Jia 2007; Schoeftner and Blasco 2009; Bulut-Karslioglu et al. 2014). One of the initial steps in the formation of heterochromatin is the trimethylation of lysine 9 of histone H3 (H3K9me3), a repressive histone modification that serves to recruit the HP1 family of heterochromatin proteins as well as other chromatin-modifying factors, that together cause chromatin condensation and gene silencing. Relative to those of young individuals (35 years), human $CD34^{+}CD38^{-}$ HSCs, isolated from the elderly (>70 years), show a global decrease in the levels of H3K9me3 and decreased expression of the histone H3K9 methyltransferase SUV39H1 (Djeghloul et al. 2016). Similar changes occur with age in murine HSC, leading to reduced HP1 binding and resultant heterochromatin decondensation. That this decline in heterochromatin is likely to be functionally important in driving the changes observed in HSC during aging is supported by the observation that inhibition of SUV39H1 in HSC from young individuals reduced their B-cell output, while enforced expression of SUV39H1 enhanced the capacity of HSC from elderly individuals to generate B cells and attenuated the age-associated myeloid bias (Djeghloul et al. 2016). Decline in expression of SUV39H1 in human HSC with age is associated with increased expression of the microRNA miR-125. This miR targets the SUV39H1 transcript via a conserved 8-mer recognition site within the 3′UTR. Interestingly, miR-125 is the homologue of lin-4, one of the first microRNAs to be implicated in the control of life-span and aging in *C. elegans* (Boehm and Slack 2005). The groups of John Dick and Gerald de Haan have recently shown that increased expression of miR-125 leads to enhanced HSC self-renewal (Wojtowicz et al. 2016). In this way, the increased expression of miR-125 observed with age could lead to clonal expansion of HSC similar to that resulting from mutations in DNMT3A and TET2 in elderly individuals (Pang et al. 2017). Further, miR-125 is a known oncomir, implicated in a number of myeloid and lymphoid leukemias (Shaham et al. 2012). Together these observations suggest that the increase in miR-125 observed in HSC with age may contribute to the expansion of preleukemic stem cell clones and enhanced susceptibility of the elderly to myeloproliferative neoplasms and other hematological malignancies (Sant et al. 2010).

A more relaxed chromatin resulting from an age-associated loss of heterochromatin is predicted to lead not only to deregulation of gene expression but also to increased DNA damage and genome instability. Indeed, it has been shown that aging of human $CD34^{+}38^{-}$ HSC is associated with upregulated expression of human endogenous retroviral elements as well as satellite II repeats (Chambers et al. 2007). Upregulation of the same repeats is observed in HSC from young individuals in which decreased expression of SUV39H1 is experimentally induced by overexpression of miR-125. Similarly activation of repeat elements is observed in hematopoietic progenitors of Suv39h1-null mice. Together these results indicate that the age-associated decline in SUV39H1 expression and resultant disruption of heterochromatin observed in human and mouse HSC leads to derepression of genomic repeat elements, including endogenous retroviruses. As dysregulation of genomic repeats has been postulated as an important factor driving genomic instability and transcriptomic changes that contribute

to oncogenesis (Tufarelli et al. 2013), it is possible that the age-associated decline in the SUV39H1/heterochromatin axis is an important factor contributing to the accumulation of DNA damage observed in HSC with age and the predisposition to hematopoietic malignancy observed in elderly individuals (Beerman 2017).

Malignancies: Not Only an Accumulation of Mutations

As described for myelomas and lymphomas, genomic and epigenomic instability, which requires multiple abnormal genetic events, has a major role in the development of malignant B cells. Chronological age itself favors the accumulation of genetic alterations that contribute to tumorigenesis. Aging is associated with the release of reactive oxygen species (ROS) and their accumulation can induce oncogenic mutations, as reported by Gosselin et al. (2009). Age-related defects in cancer protection, including altered immune clearance of premalignant or malignant cells, provide another explanation for cancer occurrence.

Accumulation of DNA damage, primarily in the stem cell compartment, increases with age thereby deregulating the mechanisms that control genome integrity (Rübe et al. 2011). Successive mutations that individually do not have significant detrimental effects can accrue over time, promoting aging and through cumulative abnormal genetic events lead the cell to deviate from normal development. As described above, the protective mechanisms of cellular senescence that occur in response to DNA damage can be bypassed by some genetic changes that favor cellular evolution toward malignancy.

Even small epigenetic changes can lead to significant alterations in expression patterns (either directly through the loss of regulatory controls or indirectly by additive effects), ultimately leading to transcriptional changes, cellular degeneration, or uncontrolled proliferation of stem cells. Taken together, this DNA damage prepares the ideal ground for cancer development. In addition to genetic and epigenetic mutations, alterations to the surrounding microenvironment play a key role in cancer development. When a senescence program is activated the cells express a specific phenotype (SASP). These senescent cells produce inflammatory mediators (IL-6, IL-7, IL-8, MIP3a), angiogenic factors (VEGF), and growth factors (IGFBP, HGF, etc.), with the probable dual purpose of maintaining permanent growth arrest while attracting immune cells to eliminate these irreversibly damaged cells. Unfortunately, the active secretion of biological mediators (SASP) has harmful bystander effects on the stromal cells in the microenvironment. There is experimental evidence confirming the hypothesis that malignant cells surrounded by senescent cells have measurably more rapid growth (Capparelli et al. 2012).

In the HSC microenvironment, mesenchymal stromal cells (MSC) are major partners in cell differentiation, cell growth, and cell survival. Our studies have shown that MSC from patients with multiple myeloma (MM) overexpress the β-galactosidase marker associated with senescence and are larger and characterized by reduced proliferative capacity. We also found a reduction in the capacity of osteoblasts to differentiate and their immunomodulatory properties. Overall, these observations support the hypothesis that the HSC microenvironment does play a role in cancer development. It is also worth noting that our studies have shown that current treatment of MM (thalidomide, lenalidomide, bortezomib) is capable of partially reducing the abnormal release of factors such as VEGF, GDF-15, and DKK1 and restoring proliferative and osteoblastogenic capacity (André et al. 2013).

Lymphomagenesis and Lymphomas

During normal B-cell development in the bone marrow, recombination of VDJ Ig segments (variable region of the BCR) is mediated by the RAG-1 and RAG-2 recombinases, which provoke DNA double-stranded breaks (DSB) at a specific recombination signal sequence. These breaks stimulate the DNA damage repair (DDR) pathway and particularly nonhomologous end joining

systems (NHEJ). In mice, different studies have shown that errors in NHEJ can lead to translocations such as t(11–14) or t(11–18) that together with P53 dysfunction can underlie lymphoma development. Furthermore, activation-induced cytidine deaminase (AID) transgenic mice that do not express P53 inconsistently develop lymphoma (Muto et al. 2006). This supports a multistep process for age-related oncogenesis that includes genome mutation, epigenomic changes, and DDR deficiency. In humans, approximately 70% of healthy individuals carry the t(14–18) translocation, but they do not develop non-Hodgkin's lymphoma (NHL) (Roulland et al. 2006).

Gene expression is controlled at many levels, including epigenetic mechanisms that govern chromatin architecture and regulate transcription via cytosine methylation and histone acetylation. In NHL, somatic mutations are frequently observed in chromatin-modifying proteins such as the histone methyltransferases (EZH2 and MLL2), histone demethylases (UTX and JMJD2C), and histone acetyltransferases (CBP and P300) suggesting that epigenetic changes play an important role in the etiology of this disorder (Morin et al. 2010).

In addition to the accumulation of mutations, age is associated with a decline in immune surveillance due in part to decreases in the T- and B-cell repertoire. The homeostatic nature of the adaptive immune response suggests that as humans age replicative stress from multiple rounds of proliferation during antigen-specific responses begins to take its toll. Immune responses to DNA damaged cells and pathogens would therefore be less efficient. Wang et al. (2014) reported that chronic infection with CMV and EBV can alter the B-cell immune repertoire. In addition, although not fully understood, persistent viral infections (CMV, EBV, Herpes simplex and Zoster) lead to an increase in the CD8+ T-cell population, characterized by a higher resistance to apoptosis (Fulop et al. 2013). One hypothesis is that dysfunctional CMV-specific CD8+ T cells accumulate resulting in a restriction of the T-cell repertoire and increased susceptibility to infection and cancer. This "inflamm-aging" is discussed elsewhere in detail by T. Fulop and G. Pawelec (Wang et al. 2014). Profound immune-senescence associated with chronic CMV infection also correlates with poor outcome. In addition, EBV-associated clonal reactive B-cell hyperplasia and EBV+ DLBCL are more common in the elderly. Other bacterial or virally associated lymphomas have also been reported to be more frequent in older populations (Zucca et al. 2014).

Acute Myeloid Leukemia

Among malignant hemopathies, acute myeloid leukemia (AML) has been extensively investigated in terms of cytogenetic and molecular changes, most frequently observed in older patients. The median age of AML patients is indeed 69 years (National Cancer Institute. SEER Cancer Statistics Review (CSR) (1975–2011)), and older patients have a higher rate of poor prognostic factors such as high-risk cytogenetics. Reliable data on cytogenetic and age have been recently published (Juhl-Christensen et al. 2012). However, because of several new mutations described during the last decade, only the recent literature can be analyzed. A major comprehensive review is reported by U. Creutzig et al. who analyzed two large cohorts of pediatric (n = 1,192) and adults (n = 4,372) patients (1–100 years old), among four countries (Germany, Austria, Czech Republic, and Switzerland) (Creutzig et al. 2016). Her analysis confirms that older patients are carrying a higher proportion of unfavorable cytogenetic abnormalities, with the exception of infant below 2 years old who express 45% of 11q23 (MLL) aberrations (Creutzig et al., 2016; Mrozek et al. 2012; Bacher et al. 2005). Interestingly, these genotypes seen in infants are different from older adults; indeed, the frequency of 11q23/MLL abnormalities decrease from infancy to young adults and is rarely detected in older patients (Creutzig et al. 2016). These observations suggest a different mechanism of AML pathogenesis in the infants.

NMP1 and CEPBA mutations are correlated with favorable outcome, and the occurrence decreases above 60 years old (Creutzig et al. 2016). Chromosome 5 and 7 monosomies,

carrying a poor prognosis, increase in the oldest age group. Patients whose AML is characterized by monosomal karyotype (MK) defined as two or more autosomal monosomies or one monosomy combined with structural abnormalities have a 2 year OS of only 7 (Perrot et al. 2011).

Complex karyotypes increase continuously (up to 28%) in the oldest group and are significantly related to aging (Juhl-Christensen et al. 2012). These complex aberrations indicate multiple genetic – including epigenetic – events during lifetime, changes that contribute to the development of AML (Galm et al. 2006; Chen et al. 2010). It could be due to carcinogens but also to genetic error in cell division (Bleyer 2002). Indeed, it has been demonstrated by several groups that clonal hematopoietic stem cells (HSC) accumulate mutations by aging (Welch et al. 2012). These mutations can target DNA repair genes, telomerase gene, and complex aberrations leading to ring chromosomes (Gisselsson et al. 2004; Nicklas 1997; Obe et al. 2002). Epigenetic changes – such as methylation of P15 and RARB2 – are more frequent in older adults (Juhl-Christensen et al. 2012). The CBF abnormalities (t(8–21); t(15–17); inv16) represent less than 5% of patients above 70 years old (Creutzig et al. 2016). Altogether, unfavorable cytogenetics increases with age in AML patients, leading to worse outcome. This observation was already made in 2009 by D Grimwade and B Juliussen (Grimwade et al. 2001; Juliusson et al. 2009).

On the other hand, survival rates for specific risk groups also decrease with increasing ages; i.e., in a British study analyzing more than 600 AML patients older than 65 years, the relapse rate of patients carrying t(8–21) or inv 16 was 70% (vs 56 in younger population). These abnormalities seem thus associated with a less favorable outcome in older patients (Cancer and Leukemia. Group et al. 2006).

Similarly, NPM1+ and FLT3-ITD ^{neg} genes in older patients (65+) do not carry the same favorable prognosis as in younger population. The 2 year OS was only 19% in two trials (Ostronoff et al. 2013; Cornelissen et al. 2012). Finally, a poor outcome is observed in all specific risk groups, and the possible bias of dose-reduced chemotherapy and/or comorbidities in this older population could also play a role in the poor outcome of elderly AML patients (Keplin et al. 2014; Bron et al. 2016).

The Future

Aging of HSCs has long been thought to be an intrinsically irreversible process. Recent studies, however, indicate that the functional decline of aged HSCs can be reversed by pharmacological intervention targeted to specific age-altered signaling pathways or epigenetic modifications. Such restorative interventions hold promise for treatment of many age-related diseases, including sarcopenia, heart failure, and neurodegeneration (Djeghloul et al. 2016; Bron et al. 2016; Geiger et al. 2013; Florian et al. 2012b).

This chapter highlights the complex multistep interplay between aging, epigenetic and genetic changes, and alterations in the microenvironment which contribute to tumor development in the hematopoietic system. Further investigation of these interrelationships promises to advance our fundamental understanding of malignant hemopathies and to lead to novel and better-targeted therapeutic approaches.

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Mitochondria, Oxidative Stress, Cancer, and Aging

13

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Abstract

In human cells, the main source of reactive oxygen species (ROS) and oxidative stress are mitochondria, the organelles where oxidative phosphorylation take place. Although ROS are an inevitable by-products of respiration, they do not necessarily have detrimental effects; low doses of ROS can have beneficial effects on cells, and their production can be finely regulated in mitochondria. Increasing ROS levels and products of the oxidative stress, which occur in aging and age-related disorders, are related to progressive dysfunction of mitochondria, due to damage to mitochondrial DNA or to oxidation and damage of mitochondrial proteins, and are also present in cancer. This chapter focuses on the regulation of ROS production in mitochondria and on the mechanisms that lead to its dysregulation in aging and cancer.

Keywords

Mitochondria · mtDNA · ROS · Aging · Cancer

Introduction: The Role of Mitochondria in Oxidative Stress

Structure and Functions of Mitochondria

Mitochondria are organelles broadly conserved in almost all *Eukarya*. Energy metabolism, β-oxidation of fatty acids, mitochondrial matrix calcium homeostasis, amino acids metabolism, heme- and iron-sulfur (Fe-S) cluster biogenesis, control of cell death, steroid synthesis, and hormonal signaling are processes in which mitochondria play a fundamental role.

The structure of the mitochondria consists of two membranes, the outer and the inner (OMM and IMM, respectively), which occasionally come together to form junctional complexes or contact sites, interspersed with the intermembrane space. The IMM encloses the mitochondrial matrix and forms a large number of invaginations, named *cristae*, which increase the IMM surface area. The protein composition of the compartments is different: in the outer membrane, porins are the most represented proteins, while the inner one, largely impermeable and the main barrier between cytosol and the mitochondrial matrix, contains proteins involved in mitochondrial fusion, transport of nuclear-encoded proteins, oxidative phosphorylation (OXPHOS), iron-sulfur cluster biogenesis, protein synthesis, and transport of mitochondrial DNA-encoded proteins. The intermembrane space is characterized by the presence of a large number of proteins, which play major roles in cell physiology, in mitochondrial energetics, and in cell death (Galluzzi et al. 2012).

Consistently with the hypothesis of their bacterial origin, mitochondria, along with chloroplasts, are the only organelles with their own DNA. Mitochondrial DNA (mtDNA) is a small circular double-stranded DNA molecule of 16,569 bp, present in multiple copies in the mitochondrial matrix. The replication of mtDNA is performed many times and independently from the cell cycle. Interestingly, mtDNA encodes only a fraction of the proteins that are fundamental for mitochondrial function, while the vast majority of proteins are encoded in the nucleus and transported to mitochondria. The strands distinguish for their nucleotide composition: the heavy strand (H-strand) is guanine rich, whereas the light strand (L-strand) is cytosine rich. It contains 37 genes: 13 of these encode for proteins, which are all components of the electron transport chain (ETC), while the remaining genes encode 22 mitochondrial tRNA and 2 rRNA molecules. Mutations in mtDNA are likely to cause alterations of the encoded protein and compromise the ETC function. Thus, the frequent mtDNA mutations

observed in a variety of human cancers are thought to contribute to respiratory malfunction in cancer cells (Carew and Huang 2002).

The morphology of this organelle is not always the same and, rather, it differs in different cell types and organism. Mitochondria could appear as small, bean-shaped compartments dispersed throughout the cytosol, or they could form elongated tubules or a single, highly branched reticulum. The main reason of these differences resides in the continuous growth, fission, and fusion of the mitochondria throughout the life of a cell. Many key regulators of fusion and fission have been identified. Mitofusin 1 and 2 (MFN 1/2) and optic atrophy 1 (OPA1) are the three GTPase proteins that regulate the process of fusion (Cipolat et al. 2004). On the other hand, the GTPase proteins that regulate mitochondrial fission are FIS1 (mitochondrial fission protein 1) and DRP1 (dynamin-related protein 1). Notably, in the fusion process, mitochondrial content is unavoidably intermixed but electrical conductivity is maintained throughout the mitochondria (Hoppins 2014).

Mitochondria play a key role in energy metabolism and, particularly, in glucose metabolism. This can be splitted in three major stages: glycolysis, citric acid cycle, and ETC. While glycolysis occurs in the cytosol, the last two steps take place in the mitochondria.

The ETC is formed by a series of protein complexes responsible for the OXPHOS process. It is organized in five multisubunit enzymes embedded in the mitochondrial inner membrane, namely complex I, II, III, IV, and V. These complexes are also indicated as NADH dehydrogenase, succinate dehydrogenase, ubiquinol-cytochrome c reductase, cytochrome c oxidase, and F1F0-ATP synthase, respectively. In addition, two diffusible factors that function as electron shuttles within the mitochondrial intermembrane space take part to the system: coenzyme Q, a lipophilic quinone, and cytochrome c (cyt c), a hydrophilic heme protein localized on the external surface of the inner membrane (Galluzzi et al. 2012). Mitochondrial complexes do not exist as physically separate entities within the IMM but rather co-assemble into higher-ordered structures referred to as "supercomplexes" or, otherwise, "respirasomes" (Genova et al. 2008).

All these complexes form the ETC that transfer electrons from a donor, for example, reduced NADH accumulated during metabolic processes to an acceptor, molecular oxygen (O2), thus reducing it to water. The free energy decrease accompanying electron transfer is exploited to create an electrochemical gradient by proton translocation from the matrix to the intermembrane space. The proton gradient is then used as a source of energy to synthesize ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi) by the F1F0-ATP synthase complex or complex V. The synthesized ATP is moved to the cytoplasm in exchange with ADP by the ATP/ADP translocase.

The proton gradient is kept because of the impermeability of the IMM. However, mitochondria can increase its permeability to ions and solutes, which weigh less than 1500 Da, through a well-known process called mitochondrial permeability transition (PT). This can has a crucial role in regulating many different cellular processes, including Ca^{++} storage and programmed cell death. Permeability transition pore (PTP) is the high-conductance channel at the center of this process, formed probably by assembly of different proteins, including dimers of F1F0-ATP synthase, and regulated by several factors (for example, calcium ions, adenine nucleotides, and reactive oxygen species, ROS) (Bernardi et al. 2015). In particular, Ca^{++} is an essential permissive agent for PTP but alone is not enough for the permeability transition (Bernardi 1999).

Mitochondria as a Source of Reactive Oxygen Species

The mitochondrial metabolism is oxidative and it lead to the production of highly reactive and unstable oxygen, which in turn can oxidize different molecules and form ROS (Ray et al. 2012) and/or radical nitrogen species (RNS) (as reported in Table 1). Not only mitochondria produce ROS, as they are generated intracellularly in different compartments through multiple mechanisms, but

Table 1 Main reactive oxygen species and reactive nitrogen species relevant for aging and cancer

Name	Formula	Formation/chemical reaction	General function	References
Reactive oxygen species				
Singlet oxygen	O_2	From O_2 by xanthine oxidase	DAMAGE (DNA: G to T transversion due to 8-oxodG generation; inactivation of PTP)	Salet et al. (1997), Kudryavtseva et al. (2016)
Superoxide anion	O_2^-	One-electron reduction of oxygen by flavins, quinones, and others. From NO synthase, xanthine oxidase and NADPH oxidase	DAMAGE; SIGNALING (MAPK, ERK, Akt kinase)	Powers et al. (2010)
Hydrogen peroxide	H_2O_2	Dismutation of superoxide anion	DAMAGE; SIGNALING ($p66^{shc}$ through cyt c; Akt kinase)	Giorgio et al. (2005), Numajiri et al. (2011)
Hydroxilic radical/anion	OH/OH^-	From H_2O_2 in presence of Fe^{++}	DAMAGE (very short in vivo half-life, high reactivity)	Sies (1993)
Reactive nitrogen species				
Nitric oxide	NO	NO synthases (nNOS, iNOS, and eNOS)	DAMAGE (apoptosis and necrosis); SIGNALING (src tyrosine kinases, PI3K-Akt, MAPK)	Adams et al. (2015)
Peroxynitrite Peroxynitrose acid	$ONOO^-ONOOH$	From superoxide reacting with nitric oxide	DAMAGE; SIGNALING (cGMP, PKG in neurons and smooth muscle)	Klotz et al. (2002)
Nitrogen dioxide	NO_2	From NO and O_2	DAMAGE	Patel et al. (1999)
Dinitrogen oxide	N_2O_3	From NO and O_2	DAMAGE (nitrosation)	Patel et al. (1999)

they are the main site of ROS generation. Singlet oxygen (O_2), superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), hydroxyl radical ($OH^•$), and hydroxyl ion (OH^-) are the mitochondrial-derived ROS (mtROS). Among RNS, nitric oxide (NO), peroxynitrite and peroxynitrose acid ($ONOO^-$ and ONOOH, respectively), nitrogen dioxide (NO_2), and dinitrogen oxide (N_2O_3) are the most common. The condition of oxidative stress occurs when a disturbance in the balance between the production of ROS and antioxidant defenses arises.

An important node linking mitochondria to cell metabolism is NO (Brown 2003), as it inhibits respiration at cytochrome c oxidase, and S-nitrosothiol inhibition of mitochondrial complex I causes a reversible increase in mitochondrial H_2O_2 production (Borutaite and Brown 2006). Indeed, flavin mononucleotide (FMN) may become a major source of ROS production after complex I destabilization (Fato et al. 2009), and a reasonable hypothesis is that FMN becomes exposed to oxygen when complex I is dissociated from complex III, in keeping with the idea that dissociation of the supercomplexes causes conformational changes that enhancing reactivity of individual complexes with oxygen (Dudkina et al. 2005).

Lipid peroxidation, carbonylation of proteins, and DNA damage are the three basic ways through which oxidative stress could lead to cell injury and damage. Lipid peroxidation affects cell membranes and other lipid structures. The oxygen released after β-oxidation of lipids is reduced to water through the ETC. At the same time, lipid radicals and water can be produced after oxidation

of lipids with efficient ROS initiators, particularly hydroxyl radical and perhydroxyl radical (HO_2•). This is the initial reaction of lipid peroxidation. Afterwards, the lipid radical reacts directly with molecular oxygen and produces a lipid peroxyl radical, an unstable molecule, that can react with itself or it can combine with fatty acid to form a lipid hydroperoxide and different lipid radicals. These molecules can react with oxygen again to produce another lipid peroxyl radical, creating the chain reaction of lipid peroxidation. Lipid hydroperoxides (LOOHs), the intermediate products, are dangerous for cells, because they can disturb membrane structure. Other dangerous products are toxic and mutagenic aldehydes, malondialdehyde (MDA), and 4-hydroxynonenal/4-hydroxy-2-nonenal (HNE) (Michiels and Remacle 1991).

Protein carbonylation is a process that leads to the formation of reactive ketones or aldehydes, highly reactive with 2,4-dinitrophenylhydrazine (DNPH), with the final effect to form hydrazones (Suzuki et al. 2010). Primary and second protein carbonylation can be distinguished: in the first type of carbonylation, side chains of lysine, arginine, proline, and threonine residues undergo an oxidative reaction that produces DNPH detectable protein products (Levine 2002). The addition of aldehydes produced by lipid peroxidation, as mentioned above, to the proteins is typical in the second type of carbonylation. The result of this reaction is the formation of DNPH derivatizable protein products (Grimsrud et al. 2008). Carbonylated protein can be used easily as biomarkers of oxidative stress, since their relative early formation and the relative stability of carbonylated proteins. The most common assay reveals the stable dinitrophenyl hydrazine product, after the derivatization of the carbonyl group with DNPH (Dalle-Donne et al. 2003).

ROS and products of lipid peroxidation can also have an effect on both genomic and mtDNA. Double- and single-strand breaks, intra- and interstrand DNA crosslinks, DNA-adduct formation, and DNA base and deoxyribose modifications are the DNA damage types that can be caused by them. The DNA double-strand breaks cause severe genetic mutations leading to various disorders and tumor progression (Zhou and Elledge 2000). Repairing in time can avoid damages caused by single-stranded breaks. Otherwise, even these breaks cause serious lesions and their contribution to many human diseases becomes possible (Caldecott 2008).

MtDNA results to be directly exposed to oxidative stress and mtDNA mutations occur due to replication errors and to accumulated damage (Park and Larsson 2011). The consequence is that mtDNA damage are more than a half higher and more extensive compared to nuclear DNA. MtDNA has no histones and presents a limited repertoire of DNA repair pathways (Larsen et al. 2005). For these reasons, authors formulate a hypothesis, still being discussed in different fields of research (aging and cancer, for example (Cheng and Ristow 2013; Shokolenko et al. 2014)), that contemplate a vicious circle, described later.

It is important to note that, although mitochondrial ROS are potentially able to damage cellular macromolecules, their production is not necessarily a negative process. Indeed, it has been widely demonstrated that the release of ROS by mitochondria is not simply a collateral effect of OXPHOS, but it is a finely regulated process that is used to control many physiological cell processes, including apoptosis and cell proliferation.

For example, redox events become crucial in the regulation of the PTP (Bernardi et al. 2015). Oxidation of matrix pyridine nucleotides and dithiols, along with dithiols reagents, favor PTP opening. Moreover, using reducing agents can reverse the effect, whom can be blocked using 1-chloro-2,4-dinitrobenzene, with a possible involvement for matrix glutathione. Again, quinones regulate PT and oxidation of succinate causes an augment in ROS production and PTP opening, while rotenone exerts as inhibitor for both effects. Interestingly, F1F0-ATP synthase can be transformed in Ca^{++}-dependent channel, similar to PTP in terms of electrophysiological properties, upon oxidative stress in mammals, yeast, and *Drosophila* (Bernardi et al. 2015). Finally, it has been observed that increased ROS production, due to mitochondrial dysfunction, provokes damage to neurons in Alzheimer's

disease, after the formation of the PTP (Rao et al. 2014).

Mitochondria can actively promote the production of ROS. The most important factor known to regulate ROS production in mitochondria is the protein 66^{shc} ($p66^{shc}$). It is one of three isoforms encoded by ShcA locus with the weight of 66 kDa and is a crucial redox signaler. It is similar to other two isoforms at molecular level, $p46^{shc}$ and $p52^{shc}$, having the same Src homologues type two domain, the phosphotyrosine binding domain and a region glycine and proline rich. An interesting and additional CH region at its N-terminus constitutes the peculiarity of $p66^{shc}$. From functional point of view, $p66^{shc}$ differs from the other two isoforms. While $p42^{shc}$ and $p52^{shc}$ are activators of Ras signaling pathway, $p66^{shc}$ causes a negative effect on this pathway (involving also MAPK and Fos) (Migliaccio et al. 1997; Pacini et al. 2004).

$P66^{shc}$ exerts its main function increasing ROS levels through three mechanisms: a decrease in ROS scavenging, an augment in the activity of membrane oxidases, and a leakage in ETC. It has also been observed that hydrogen peroxide produced by $p66^{shc}$ in the mitochondria, through a mediating action on the electron transfer from reduced cyt c to molecular oxygen, leads to the PTP opening and, in turn, to the rupture of mitochondrial integrity and release of proapoptotic factors and, finally, activation of apoptotic cascade. Notably, $p66^{shc}$ knockdown animal models revealed important results. In fact, these animals display a decreased amount of ROS, suggesting a role of $p66^{shc}$ in the regulation of redox balance and oxidative stress levels. Moreover, levels of systemic and intracellular oxidative stress decrease in KO organisms (Trinei et al. 2002; Napoli et al. 2003; Francia et al. 2004). Again, $p66^{shc-/-}$ cells resist more to apoptosis induced by several factors, such as UV radiation, growth factor deprivation, and others (Migliaccio et al. 1999; Orsini et al. 2004; Pacini et al. 2004). Even a link with p53 pathway exists; indeed, $p66^{shc}$ half-life results increased when cells undergo a p53-dependent apoptotic stimulation. Therefore, it appears clear that $p66^{shc}$ assumes a central role in regulating redox levels and, in turn, programmed cell death pathways. Other roles for $p66^{shc}$ has been reported in insulin-induced gene expression, while PTEN (phosphatase and tensin homolog) and other phosphatases inhibiting insulin signaling result to be inactivated by oxidation (Lee et al. 2002b; Trinei et al. 2009).

Mitochondrial Stress Response

In the presence of excessive ROS, mitochondrial components can be severely damaged. Thus, mitochondria are provided with many defense mechanisms to counteract these detrimental effects. In particular, three different and correlated levels exist for the degradation of oxidized mitochondrial components: mitochondrial proteases, mitochondrial unfolded protein response (UPRmt), and mitophagy. Mitochondrial proteases are enzymes which share the same location (exclusively in mitochondria or both in mitochondria and cytosol). Degradome is the result of the collectivity of mitochondrial proteases and is defined as the complete set of proteases acting in mitochondria. Authors proposed to divide the human mitochondrial proteases (25 already identified) in three main categories, depending on their location, function, and structural characteristics. Three subcategories for each main category exist, based on the different catalytic site: cysteine, metallo-, and serine proteases. Notably, next to the first group, which groups classical enzymes and, thus, named intrinsic mitochondrial proteases, the second group contains the pseudo-mitochondrial proteases, and the third group encase the transient mitochondrial proteases.

Proteases of the first group, localized in mitochondria or both in cytosol and mitochondria, present two functions: protein processing from cytosol to mitochondria, removing the mitochondria import signals and, on the other hand, quality control, leading misfolded and/or damaged proteins to degradation. The Lon protease (LONP) family is the most widespread family of ATP-dependent mitochondrial proteases, which are highly conserved throughout all phylogenetic kingdoms. LONP is fully included in the downstream pathways involved in energy metabolism, like SIRT1

and PGC-1α. Although the majority of LONP is soluble within the mitochondrial matrix, it is also found in mitochondrial nucleoids with the roles in mtDNA maintenance (Lu et al. 2003). LONP shows several crucial properties, which include: binding and hydrolyzing of ATP and protein substrates (for example, misfolded and oxidatively damaged proteins for quality control or other proteins as a regulatory mechanism), chaperoning, and mtDNA binding (Pinti et al. 2015). Importantly, LONP is upregulated by oxidative stress (Pinti et al. 2010, 2011)

Pseudo-mitochondrial proteases lacks some crucial residues for catalytic activity and they intervene only in regulation on the activity of homologue proteases, or they display complete different functions, as in the case of UQCRC1 and 2 (cyt b-c1 complex subunit 1 and 2), component of the ETC. The name of the third group members come from their capacity to translocate to mitochondria only under specific conditions (autophagy and apoptosis, mainly), in order to perform additional proteolysis. Despite of this fine categorization, mitochondrial proteases, normally, do not have only one role. In fact, majority of them displays overlapping activity. However, seven main functions have been identified: processing, quality control, mitochondrial biogenesis, stress responses, mitochondrial dynamics, mitophagy, and apoptosis (Quiros et al. 2015).

Mitochondrial unfolded protein response (UPRmt) is a retrograde stress response that contemplates the activation of several transcription factors, C/EBPβ (CCAAT-enhancer-binding protein β) and CHOP (C/EBP homolog protein) as principal actors, which leads to the upregulation of chaperones, such as Hsp60, Hsp10, Hsp70 (heat shock protein 60, 10, and 70, respectively), and CLPP (caseinolytic mitochondrial matrix peptidase proteolytic subunit). Collectively, they have a fundamental prevention action to avoid accumulation of misfolded proteins in mitochondria.

Mitophagy is a highly specific form of macroautophagy that targets dysfunctional mitochondria, with a clear role in maintaining the energy homeostasis and in the adaption to nutrient stress (Liesa and Shirihai 2013). This process presents shared components with autophagy but also comprises distinct and specific traits. Mitochondrial proteases, such as LONP, PARL (presenilin associated rhomboid like), USP30 (ubiquitin specific peptidase 30), and HtrA2 (high temperature requirement protein A2), gained prominent position in interaction of known regulators of mitophagy (Quiros et al. 2015). Two types of mitophagy exist on the basis of the molecular pathways and the activating stimuli. The first contemplates a PINK1/Parkin-dependent pathway. Normally, PINK1 (PTEN-induced putative kinase 1) translocates into the mitochondrial inner membrane, it undergo a cleavage by PARL, and, finally, a degradation by proteases within the mitochondria (Jin et al. 2010). As a consequence of mitochondrial membrane depolarization, PINK1 remains at the outer membrane of mitochondria and associates with the TOM20 (translocase of outer membrane 20) complex. This leads to the recruitment of Parkin (or PARK2, Parkin RBR E3 ubiquitin protein ligase), which is phosphorylated in its ubiquitin-like domain. Thus, E3 ligase activity of Parkin is promoted and, after further polyubiquitination, the p62/SQSTM1 adaptor proteins are recruited and Parkin interacts with LC3 (microtubule associated protein 1 light chain 3 alpha) (Bjorkoy et al. 2009). Finally, this complex is degraded by the autophagic machinery. The second type is mediated by a PINK1/Parkin-independent pathway. BNIP3 (BCL2 interacting protein 3) and NIX (BCL2 interacting protein 3 like) are two OMM proteins, with a BH3 domain which interacts with BCL2 proteins, that regulate mitophagy (Bellot et al. 2009; Ding et al. 2010). The activation of this pathway is mediated by hypoxia inducible factors (HIFs), transcription factors composed by the α and β subunit, expressed when the supply of oxygen is low. (Schwarten et al. 2009). Recently, the adaptor protein FUNDC1 (FUN14 domain-containing protein 1) has been discovered as a mitophagy receptor, which is regulated by ULK1 (Unc-51 like autophagy activating kinase 1) phosphorylation (Liu et al. 2012). The mechanism is similar to that described for BNIP3 and NIX and is mediated by HIF1α (hypoxia inducible factor 1 alpha).

Mitochondria and Oxidative Stress in Aging

The Mitochondrial Free Radical Theory of Aging

During years, a number of aging theories have been proposed, and the mitochondrial free radical theory of aging (MFRTA), proposed by Harman, has been the most important one for several decades. Harman proposed that aging is the result of the accumulation of damage caused by free radicals generated as by-products during normal metabolism (Harman 1956). The observations that constitute the foundations of this theory are: (a) the decline in mitochondrial function, observed during aging, causes an increase in the mtROS production, (b) several ROS-scavenging enzymes decrease their activity as a consequence of aging processes, (c) mtDNA accumulates mutations during aging, and (d) this causes an impairment in ETC functions, leading to a further increase in ROS production and, finally, to an accumulation of oxidative damage in DNA, proteins and lipids, establishing a vicious circle. Therefore, it appears clear that mitochondria play a crucial role in the oxidative stress mechanisms that drives the aging process.

However, data from different authors raised doubts on MFRTA, particularly focused on the role of mtDNA mutations and mtROS in aging and, more, on the way through mitochondria and signaling pathways that regulate longevity are linked (Vina et al. 2013). A linear dose-response relationship exists between the increasing amounts of ROS and the oxidative stress and, therefore, the aging process. However, a beneficial role of ROS as redox signaling molecules has been demonstrated by several authors. Thus, mtROS are thought to exert a double-edge sword effect; while high levels of ROS cause cellular damage and to promote aging, low levels may improve defense mechanisms by inducing an adaptive response. This concept has been named mitochondrial hormesis (Ristow and Schmeisser 2014). Deficiencies in mitochondrial function, organelles that are fully integrated into the cell, may alter nuclear gene expression, inducing an adaptive response (Yun and Finkel 2014).

Concerning mtDNA mutations, ex vivo and in vivo observations argue against the order of events that occurs in MFRTA and points to a crucial role of mtDNA mutations in stems cells as a crucial event for the aging process. First experimental evidence was obtained by the creation of a mouse that is homozygous for a mutation that leads to the expression of a proofreading-deficient catalytic subunit of mtDNA polymerase, called mtDNA mutator mouse (Kujoth et al. 2005). It shows extensive mtDNA mutagenesis and a range of phenotypes reminiscent of naturally occurring aging (anemia, hair loss, hearing loss, etc.). It has been suggested that, in this murine model, the instability of ETC subunits can be due to the high number of mtDNA point mutations. (Edgar et al. 2009). The elevated levels of mtDNA mutagenesis affects stem cells, in terms of both quantity and quality, and interfere with the maintenance of the quiescent state, fundamental for reconstitution capacity and long-term sustenance of somatic stem cells. The premature onset of an aging phenotype in mtDNA mutator mouse could be due to the early onset of dysfunction of somatic stem cells (Ahlqvist et al. 2012). Again, it has been observed that most somatic mutations in mtDNA mutator mice occur as replication errors during development and do not result from damage accumulation during adult life (Ameur et al. 2011). How the increased mutation rate in this murine model results in early-onset dysfunction of somatic stem cells still being discussed. However, neural progenitor cells recover their self-renewal ability, after the treatment with the antioxidant N-acetyl cysteine (Ahlqvist et al. 2012). Hence, it implies that alterations in cellular redox state or ROS levels, even mild, become important for the regulation of somatic stem cell function.

Indeed, numerous studies show that mitochondrial metabolism is important in mediating longevity through nutrient-sensing pathways and dietary restriction. The effects of reduced nutrient availability (also defined CR, caloric restriction) on longevity are very complex and include many organs and different pathways. Although the exact

underlying mechanisms remains unknown, it has been observed that CR extends life span in several species, even mammals, and determine an improvement in the health status of rodents and primates (Kaeberlein et al. 2007; Colman et al. 2009). It has been proposed that the inhibition of signaling pathways regulated by mitochondria-derived ROS, as a consequence of the reduction of metabolic rate and oxidative damage, finally determines an antiaging effect (Dai et al. 2012). The nutrient-sensitive pathways TOR (target of rapamycin) and IIS (insulin/IGF-1 signaling) become fundamental in the regulation of aging in various animal models (Selman et al. 2009), through the activation of the common downstream effector ribosomal protein S6 kinase (S6K). Among the characteristics of the S6 K knockout mice, ameliorated age-related pathology, life span extension, and gene expression changes, similar to those observed under CR, are very interesting and they confirm the key role of S6 K. Interestingly, it seems that AMPK (AMP-activated protein kinase) could be the link between the three molecules mentioned above. In fact, AMPK, that regulate the activity of TORC1 (mammalian homolog TOR complex 1), increases its activity after the loss of S6 K (Selman et al. 2009). This increase has been observed, only in worms, even when IIS is altered. Such alteration causes an elevated cellular AMP/ATP ratio that activates AMPK. The consequence is an induction of a metabolic shift, with an increased respiration, transiently increased ROS production and, finally, a life span extension (Zarse et al. 2012). Therefore, it seems that the common mechanism through AMPK, shared by impaired IIS and CR, contemplate a role for ROS at physiological levels, whom act as signaling molecules to induce mitochondrial metabolism and, in the end, to trigger a health-promoting metabolism (Zarse et al. 2012). Thus, the ETC itself, along with TOR kinase and AMPK, could be crucial in mediating longevity. However, further experiments are needed, especially to determine whether changes in mtROS production or, instead, a cellular bioenergetics deficiency could clear up the role of mitochondrial dysfunction to different age-related diseases.

Additionally, a number of studies also show that SIRTUIN1 (SIRT1) and PPARγ coactivator 1 alpha (PGC-1α) have a precise role in this process: the activation of the first one during CR leads to an increase in mitochondrial biogenesis and respiration in mice and rats, further activating PGC-1α, its downstream effector (Cohen et al. 2004). Importantly, it should be noted that PGC-1α is involved in increasing mitochondrial function on demand by activating the expression of certain nuclear genes in different tissues (Lee et al., 2002) and this means that it does not intervene on the basal mitochondrial biogenesis. In summary, all that is mentioned above suggests that the improvement in mitochondrial function is responsible, at least partly, for the beneficial effects of CR on longevity.

Impairment of Mitochondrial Stress Response During Aging

As described previously, mitochondrial proteases are deeply involved in quality control and alterations at this level can lead to mitochondrial dysfunction, one of the nine hallmark of aging process. Several authors reported that mitochondrial proteases and in particular LONP, HtrA2, PARL, and CLPP, assume crucial role in aging (Cipolat et al. 2006; Maltecca et al. 2008; Gispert et al. 2013; Kang et al. 2013).

In yeast cells, lack of Pim1, the genes that encodes yeast Lon protease, results in premature aging cells, with a shorter replicative life span, increased cytosolic levels of oxidized and aggregated proteins as well as decreased proteasome activity (Erjavec et al. 2013). On the other side, the constitutive overexpression of LONP in *Podospora anserina* has several beneficial effects: a decrease in levels of carbonylated and carboxymethylated proteins, an increase in the resistance to exogenous stresses, and an extension of the lifespan (Luce and Osiewacz 2009).

In rodent models, LONP expression and activity decrease with age, causing the accumulation of oxidized and carbonylated proteins in the matrix and a decrease in the activity of mitochondrial aconitase (Bota et al. 2002). CR and, partially,

exercise training (in association with the mitochondrial biogenesis) has the effect to rescue the reduction described above in muscle cells (Lee et al. 1999). This explains why LONP can be included in the downstream pathways involved in energy metabolism (Guarente 2008).

Decreased mtDNA levels, mtRNA and protein expression, increased oxidative stress, and increased accumulation of oxidatively modified proteins are all index of an exponential decline of mitochondrial capacity, which characterizes aging phenotype (Lanza et al. 2008). Unavoidably, even mitochondrial quality control decrease with aging (Friguet et al. 2008). Relevantly, LONP, essential component of this system, presents lower levels and activity in skeletal muscle of the old mice, if compared to young mice (Bota et al. 2002). Moreover, different authors observed an increase in LONP levels but not in its activity; in aged rat hearts (Delaval et al. 2004), the possible explanation could be given by the progressive accumulation of inactive LONP, probably because of oxidative damage that hit LONP directly (Hoshino et al. 2014).

Since the presence of mitochondrial dysfunction within hallmarks of aging, it appears clear that UPRmt can play a role in aging process. Indeed, augment of activity of UPRmt permits to preserve mitochondrial functionality, and although not alone, it promotes longevity. Next to the UPRmt, it is likely that multiple pathways and different actors take part in the response to stressors. At least in worms, ATFS-1 (activating transcription factor associated with stress 1), transcription factor involved in mitochondria-to-nucleus communication during UPRmt, gained prominent role in regulation of response to oxidative stress. In fact, it regulates chaperones and glycolysis genes and, more interestingly, it acts directly on the OXPHOS gene promoters. Again, OXPHOS complex assembly and function is guaranteed with a balanced ATFS-1 accumulation, suggesting the importance of this gene in respiratory recovery process (Nargund et al. 2015). Moreover, UPRmt likely intervenes in maintaining high levels of NAD^+. Increased NAD^+ levels, which can be induced also by pharmaceuticals, improve functionality in mitochondria, and, at the end, leads to longevity. When the transcription of gene involved in the cycle returns to normality, a restore of normal levels occurs and UPRmt ends its action (Lin and Haynes 2016).

Important findings of reduced adiposity in $p66^{shc}$-KO organisms suggest that this protein can have relevant effect on the lifespan (Berniakovich et al. 2008). Obesity, cardiovascular diseases, and diabetes are typical of the aging phenotype. Moreover, the metabolic syndrome, among other characteristic traits, contemplates oxidative stress and this is a contributor to the aging process. Researchers suggest that reduced oxidative stress in $p66^{shc-/-}$ animals could reduce adiposity and, in turn, extend lifespan (Bluher et al. 2002; Berniakovich et al. 2008). On the other hand, it has also been reported a strong counterselection of $p66^{shc-/-}$ organisms, if compared to wild type, when they live in outdoor environment, with food competition and cold temperature exposition. Defects in fat accumulation, thermoregulation, and reproduction are typical of the KO animals. This suggests an evolutionary selection of $p66^{shc}$ in order to refuel energy metabolism. Hence, the beneficial or harmful role of $p66^{shc}$ seems to depend on the specific life conditions of the organism (Giorgio et al. 2012).

Besides mitochondrial proteases and UPRmt, also the third macroprocess which deeply regulate mitochondrial function, mitophagy, is crucial for aging process. In fact, it has been observed a gradual accumulation of mitochondria in several tissues of aged *Caenorabditis elegans*. They observed the same effect of aging on mitochondria in young individuals that undergo the depletion of BEC-1, homolog of the mammalian general autophagy regulator Beclin 1 (BECN1). Therefore, inhibition of autophagy leads to a defect in mitochondria degradation and a subsequent accumulation during aging. DCT-1 protein acts as its mammal homologues, BNIP3 and NIX, functioning as mitophagy receptors and interacting with LGG-1, homolog of the mammal LC3 (the autofagosome membrane-associated protein), for the removal of mitochondria (Palikaras et al. 2015).

DCT-1 plays a key role in the control of mitophagy, in order to maintain mitochondrial homeostasis and to increase the survival under stress condition, as a downstream effector of PINK1 and PDR-1 (*C. elegans* homologues for PINK1 and Parkin observed in mammals). Thus, mitophagy-deficient animals display pronounced mitochondrial dysfunction, sensitivity to various stressors and abrogation of different life span-prolonging interventions in *C. elegans*. Mitochondrial dysfunction, sensitivity to various stressors, and absence of interventions that target a prolongation in the life span are hallmarks of mitophagy-deficient animals. Notably, they present activation of SKN-1, homolog of NFE2L2 (nuclear factor, erythroid 2 like 2), that causes the accumulation of damaged mitochondria. This activation follows oxidative stress conditions and encourages the expression of important mitochondrial biogenesis genes, as its mammalian homologues.

Therefore, a fine coordination exists between mitochondrial biogenesis and mitophagy, in order to regulate the quantity and quality of mitochondrial population and allows cells to intervene on their mitochondrial content after the exposure to stress conditions or change in cellular metabolic state. DCT-1 and SKN-1 and, presumably their homologues in mammals, become nodal elements in this pathway. Particularly, SKN-1 might be a sort of central rheostat of homeostasis in mitochondria, promoting detoxification and cell survival after sensing mitochondrial damage. After the disruption of this fine and vital balance between mitochondrial biogenesis and mitophagy, functional deterioration of biological systems, promotion of cell death, and increase in mitochondrial mass occur, as observed during aging and in several pathologic conditions (Fan et al. 2008; Vafai and Mootha 2012).

Mitochondria and Oxidative Stress in Cancer

Mitochondrial dysfunction, caused by mtDNA mutations or mitochondrial enzyme defects, perturbs bioenergetics of the cells, supporting the metabolic reprogramming observed in cancer, and can trigger changes which ultimately promote cancer transformation, through the release of metabolites, calcium, or ROS.

Research from past three decades revealed the strong and complex link between oxidative stress and cancer. Complexity can be primarily explained by the several ROS produced and their properties, (chemical nature and reactivity, half-life, ability to diffuse in the cellular and intercellular compartments, among others). Furthermore, molecular targets and pathways affected by ROS are difficult to be identified. Last but not least, ROS has a dual role, with a biologically active function or a toxic effect depending on the concentration. The ratio between ROS production and detoxification performed by antioxidant systems (Hernandez-Garcia et al. 2010) is crucial in determining the beneficial or toxic effects. Scavenging antioxidant natural compounds can contribute to this detoxification effects and has been widely proposed as anticancer molecules among which quercetin revealed excellent, although the intracellular availability of glutathione is sine qua non condition for its activity. Interestingly, quercetin shows also a direct and proapoptotic effect in tumor cells and, again, it intervenes in blocking growth of several human cancer cell lines (Gibellini et al. 2011, 2015a).

Oncogenes, Mitochondria, and ROS: A Complex Interplay

Transformation, growth promotion, and malignant progression are three fundamental steps which characterize cancer pathogenesis. A huge number of genes, molecules, and pathways take part to these three steps, and ROS strongly interact with most of them, in different compartments.

Transformation characterizes for the loss of control of proliferation and deregulated apoptosis, with the formation of the tumor. Oncogenes or oncosuppressor genes are genes that undergo mutations which lead to alterations in cell cycle and apoptosis and excessive proliferation. Afterwards, tumor starts to grow and to increase its volume and cell number. Insufficient or abnormal

angiogenesis and inflammatory status typically occur at this step, with the formation of areas of hypoxia and the activation of inflammatory reparative response (IRR) as a consequence, respectively. On one side, unavoidably, this promotes ROS production, suggesting a central role for hypoxia and ROS as regulators of tumor cell adaption (survival, growth, motility, invasion, metastasis, metabolic changes, and resistance to chemotherapy). On the other side, classical and physiological IRR contemplates ROS as important players in both defensive and reparative mechanisms. In several cases, even the direct influence by ROS in nonphysiological IRR lead to the acquisition of many hallmarks of malignancy by tumor cells.

Several oncogenes and oncosuppressors have been shown to regulate mitochondrial functions and ROS production by this organelle and, not surprisingly, they have been shown to promote carcinogenesis, at least in part, through metabolic reprogramming and alterations of mitochondrial functions.

Among oncosuppressors, p53 protein is a principal actor, since its several functions in maintaining genomic integrity (Vousden and Lu 2002). Wild-type p53 regulates transcription and activation of numerous target genes, directing cells to cell cycle arrest, senescence, or apoptosis (Liu and Chen 2006). The precise and specific cellular outcomes of p53 activation are determined by the capability to differently activate its effectors among which proteins and noncoding RNA. A complex interplay exists between ROS and p53. Treating human cells with hydrogen peroxide and performing microarray analysis, authors found that, among the highly H_2O_2 responsive genes, one-third of them are targets of p53 (Desaint et al. 2004); moreover, p53-dependent DNA repair is favored by nuclear oxidative stress (Ueno et al. 1999). ROS intervene in triggering p53 activation (figuring as upstream signal) and, at the same time, in mediating apoptosis (as a downstream signal). Moreover, p53 can modulate cellular ROS status with a direct control on the expression of pro- and antioxidant genes or, less directly, intervening in cellular metabolic pathways.

Different covalent posttranslational modifications (ubiquitylation, phosphorylation, etc.) act on the stability and activity of p53. Particularly, ROS play a role in phosphorylation through kinases, such as p38α MAPK (mitogen activated protein kinase) (Bragado et al. 2007), ATM (ataxia-telangiectasia mutated protein) (Kurz and Lees-Miller 2004), and ERK (extracelluar signal-regulated kinases) (Persons et al. 2000), although these pathways are shared with genotoxic stresses, such as UV light (Bode and Dong 2004; Kurz and Lees-Miller 2004; Moiseeva et al. 2006). Instead, ubiquitylation represents the major turnover pathway for p53: cysteine residues of p53 can suffer oxidative modifications, due to ROS, and conformation changes could occur, affecting the stability of p53, favoring ubiquitylation and, finally, proteasome degradation.

DNA-binding activity of p53 is abolished after the treatment with oxidizing reagents, but this activity can be replenished by using antioxidants (Sun et al. 2003; Velu et al. 2007). Moreover, thioredoxin (TRX) and other redox proteins influence and modify p53 activity (Ueno et al. 1999; Seo et al. 2002; Hanson et al. 2005; Seemann and Hainaut 2005), although their effectors still partially unknown.

Important research shows a decrease in p53 binding to GADD45 (growth arrest and DNA damage-inducible 45) when p53 is oxidized in a specific cysteine residue, but authors do not observe any decrease in p21 binding (Buzek et al. 2002). Notably, GADD45 proteins take part to the regulation of numerous cellular functions, including DNA repair, cell cycle control, and senescence, besides to present proapoptotic activities (Tamura et al. 2012). P21 (or Cip1/Waf1) is an inhibitor of Cdk 1 and Cdk2 (cyclin-dependent kinase 1 and 2). It causes the arrest of the G1-S transition and G2-M transition after DNA damage, enabling the repair processes. Furthermore, it induces replication and stress-induced premature senescence. Binding to caspase 3 and to ASK1 and JNK (apoptosis signal-regulating kinase 1 and c-Jun N-terminal kinase, respectively, two apoptosis kinase), it display also antiapoptotic activity (Cmielova and Rezacova 2011). This confirms the relationship

between ROS and p53, suggesting that redox modification represents a possible mechanism for target gene selection.

$P66^{shc}$ in cancer displays numerous functions, correlated to the metabolism of cancer cells. This protein cause the damp of growth factor signaling, leading to a suppressive effect on tumor metabolism. Mammalian TOR (mTOR) and S6K program a shift in metabolism, with increased glycolysis and favoring anabolic metabolism, when $p66^{shc}$ is silenced (Soliman et al. 2014; Lebiedzinska-Arciszewska et al. 2015). This shift causes a decrease in mitochondrial ROS production and drives the metabolism in a biosynthetic direction. Indeed, $p66^{shc}$ inhibits mTOR, cell growth, and glucose metabolism (Soliman et al. 2014) and, moreover, it acts as a sensor of glucose, amino acids, and insulin, regulating mTOR/S6K pathway. Therefore, $p66^{shc}$ guarantees a specific link between ROS, mTOR/S6K and nutrients and, particularly, it seems that it can translate nutrient availability into mitochondrial ROS production. $P66^{shc}$, and p53, display altered expression, associated with augmented cell proliferation and metastatic potential, in cancer cells and in cancer stem cells (Veeramani et al. 2008). Thus, a leading role for $p66^{shc}$ for autophagy and programmed cell death on the basis of the bioenergetic profile represents a concrete hypothesis. Finally, it has taken into account that $p66^{shc}$ favors also the acquisition of resistance properties by these cells, with roles in carcinogenesis and self-renewal (Sansone et al. 2007; Beltrami et al. 2013).

Notably, upon oxidative stress, serine residues of $p66^{shc}$ are phosphorylated, inducing conformational changes, which lead to the binding with prolyl isomerase 1 (Pin1) (Galimov 2010). As a consequence, $p66^{shc}$ moves in the intermembrane mitochondrial space, where determines cyt c oxidation, that, in turn, provokes H_2O_2 levels increase and impairment in mitochondrial calcium buffering, favoring mitophagy (Giorgio et al. 2005). On the other side, the absence in the cytosol of $p66^{shc}$ interrupts its normal activity, leading to a raise in lipid and protein injury and in autophagosome assembly.

PTEN, main regulatory member of the signaling cascade that promotes cell survival through activation of PI3K/Akt (phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B) pathway, intervenes, upon normal condition, decreasing Akt transduction. This leads to an augment in apoptosis and a reduction in cell survival, proliferation, and migration (Griesser et al. 2009). When ROS production results increased, in particular H_2O_2, PTEN undergoes a reversible inactivation, making it ineffective on Akt transduction, promoting cell survival (Numajiri et al. 2011). Moreover, ROS induce direct and adaptive modifications on Akt, increasing the nuclear export of FoxO1 (Forkhead box protein 1) and, in the end, leads to the synthesis of TRX reductase, important antioxidant enzyme. Thus, a counterattack to ROS increase and enhancement in Atg (autophagy related proteins) activity are guaranteed.

The importance of FoxO family is not limited to that mentioned above. In fact, FoxO3 promotes the activation of BECN1, Atg12, Atg4, and LC3, promoting, at last, autophagy. Furthermore, BNIP3 increases its activity, as an effect of FoxO3 action, leading to augment in autophagosome complex activity and in mitophagy (Mammucari et al. 2007). Finally, FoxO3 provokes an increase in PI3K activity, which in turn determines increase in Akt activity. Therefore, the nuclear export of Foxo1 is favored and this promotes autophagy in mammals cells (Zhou et al. 2012).

It has been observed that ROS intervene also in regulating Atg family activity. Particularly, Atg4 suffers a decrease in its activity, after the augment of H_2O_2 levels. Consequently, it does not remove arginine residue on Atg8 and this impedes the binding and the activation of Atg8 by Atg7. The first one stills free and it conjugates to autophagosome (Scherz-Shouval et al. 2007).

Another crucial regulator of mitochondrial functions and ROS is SIRT3 (SIRTUIN 3). It is a nuclear-encoded, mitochondrial deacetylase that regulates the function of several mitochondrial proteins involved in oxidative phosphorylation, fatty acid oxidation, the urea cycle, and the antioxidant response system (Xiong et al. 2016).

SIRT3 acts as an oncosuppressor in several types of cancer, including breast, colorectal, hepatic, lung, and gastric cancers. Accordingly, its loss promotes carcinogenesis, through the increase intracellular ROS levels and HIF1α stabilization which in turn promotes the switch to an aerobic glycolytic metabolism, the so-called Warburg effect (Finley et al. 2011). In most tumors, HIFs, HIF1α in particular, display high activity even if pseudohypoxia, instead of hypoxia, occurs. This particular condition contemplates HIF stabilization upon normoxia. HIFs and their downstream effectors are targets of several antitumor agents. To cite a few, PX-478 acts decreasing HIFs levels both in vitro and in vivo, while bevacizumab targets VEGF (vascular epithelial growth factor), a downstream effector of HIFs (Tennant et al. 2010).

At last, it is important to underline the link between ROS and HIFs in autophagy and mitophagy signaling processes. Whether normoxia conditions are guaranteed, PHD (prolyl hydroxylase containing-domain) enzyme hydroxylates HIF1α subunits, causing the ubiquitination of the latter one by pVHL (E3 ubiquitin ligase von Hippen-Lindau protein). This mechanism goes out when hypoxia occurs. Nonhydroxylated HIF1α subunits does not undergo ubiquitination and they can operate favoring transcription of VEGF, COX4-2 (cyt c oxygenase 2), and others. Importantly, presence of HIF1α leads to the stabilization and regulation of BNIP3, which binds BCL2 and, in turn, leaves BECN1 free. This protein triggers mitophagy and a reduction in number of mitochondria occurs (Zhang et al. 2008). ROS intervene at pVHL level, avoiding HIF1α ubiquitination and stabilizing it. However, it has taken into account that this model fits only in mild hypoxia conditions.

Mitochondrial Proteases, Oxidative Stress, and Cancer

As mentioned above, different mitochondrial proteases assume prominent roles in the regulation of mitophagy. Particularly, LONP seems to be fundamental in cancer. Indeed, several tumor cell lines present higher expression levels of LONP, such as colorectal (Gibellini et al. 2014b) or mammary epithelial cancer cells, either at RNA and protein levels. Increasing expression leads, at mitochondrial level, to changes in organelle architecture and functionality, which deeply increase the resistance to stress conditions typical of tumor microenvironment. To name one example, upon hypoxic condition, upregulation of LONP by HIF1α occurs, determining the degradation of cyt c oxidase 4-1 subunit and favoring the assembly of COX4-2, cited previously, that gives better chances for the adaption of cancer cells to the hypoxic environment (Aksam et al. 2007). Moreover, switch from respiration to glycolysis, proliferation, and transformation cells are favored when LONP is ectopic overexpressed. In the same nude mice model, even migration and metastasis formation result increased (Quiros et al. 2014). Again, NDUFS8 (NADH:ubiquinone oxidoreductase core subunit S8) of complex I undergoes an upregulation in its expression, after LONP overexpression in different tumor cell lines (293T, OEC, to cite a few), probably determining an impairment in complex I assembly and, finally, leading to an increase in ROS production. Authors proposed that cell proliferation is promoted by ROS production, through MAPK (p38, ERK1/2, and JNK) and Ras-ERK signaling, with the important evidence that LONP overexpression drives oncogenic transformation. This overexpression drives also another type of transformation, the epithelial-mesenchimal transition, or EMT. Particularly, E-cadherin, N-cadherin, Vimentin, and Snail result to be increased in their expression as a consequence of LONP overexpression, which even enhance cell migration through MMP-2 matrix metallopeptidase 2). Interestingly, N-acetyl cysteine, antioxidant molecule, inhibits EMT, suggesting a probable cause-effect relationship between ROS generation and LONP-induced EMT (Cheng et al. 2013).

LONP confirms to be linked to numerous pathways, since even SIRT3 causes deacetylation of LONP in colorectal cancer cells, as a posttranslational mechanism (Gibellini et al. 2014a). The importance of SIRT3, as a regulator of mitochondria integrity and function in cancer, is sustained

by a lot of works from many authors (Gibellini et al. 2014a). Probably, this is due also to the ability of SIRT3 to regulate LONP activity and, in turn, to regulate the switch from respiration to glycolysis, to regulate citric acid cycle proteins, or to regulate the degradation of damaged proteins as a consequence of oxidative stress. This explains, at last, the high resistance of tumor cells to stressors typical of the tumor environment.

Notably, it has been clearly demonstrated that LONP can be fundamental for the cell survival upon conditions of excessive stress load, since administration of two triterpenoids, CDDO and CDDO-Me, which inhibits LONP expression, leads to depolarization, increased mtROS, alterations in mitochondrial morphology and mitochondrial dynamics proteins, increased levels of protein carbonyls in mitochondria, and intrinsic apoptosis (Gibellini et al. 2015b).

Unfolded and misfolded proteins represent common trait in tumor environment. A recent study revealed high correlation between LONP expression and Hsp60, Hsp10, Hsp70, and CLPP expression (Wu et al. 2014b), principal components of the UPRmt machinery. Moreover and importantly, LONP is included in the category of proteases activated by CHOP, along with heat shock proteins. LONP cannot be included in the UPRmt machinery, but it shows relevant proteolytic activity in the mitochondrial stress response (Gibellini et al. 2016). In addition, downregulation of LONP causes increased starvation-induced autophagy (Gibellini et al. 2014b) and accumulation of PINK1, as already cited as essential regulator of mitophagy (Jin and Youle 2013). PINK1 degradation is promoted by LONP, in the mitochondrial matrix of *Drosophila*, avoiding healthy mitochondria undergo mitophagy (Thomas et al. 2014).

The essential function of chaperones is to de novo fold protein or to refold misfolded proteins (Voos 2013). LONP shows also important chaperon-like functions. As observed in yeast and humans, LONP takes part in the assembly of mitochondrial membrane complexes (Quiros et al. 2014). Although precise targets of LONP still unknown, recent study investigated on LONP binding partners NDUFS8, Hsp60, both cited above, and mtHsp70 (mitochondrial heat shock protein 70) (Kao et al. 2015).

Mitophagy, Oxidative Stress, and Cancer

Dysregulation of mitophagy is now considered as an etiological factor in tumorigenesis (Chourasia et al. 2015b). Particularly, inhibition of this process is fundamental for tumorigenesis, whereas functional mitophagy likely is requested for tumor progression. Naturally, ROS figure as principal actors in regulating autophagy and mitophagy, through oxidative modification in proteins directly involved in the autophagy machinery or in signaling pathways that enhance autophagy and mitophagy.

The Parkin gene, located at chromosome 6, represents a fragile site, highly susceptible to genetic mutations. In fact, many tumors, which include lung, melanoma, gliomas, and colon cancers, presents this kind of mutations (Veeriah et al. 2010; Lee et al. 2016). Besides, Parkin knockout animals and cell lines show increased tumorigenesis (Matsuda et al. 2015). This suggests a possible tumor suppressive role for Parkin gene (Dehennaut et al. 2013). Parkin knockout mice are prone to spontaneous hepatic tumors, while various cell models show increased tumorigenesis.

Hypoxia, and a consequent activation of HIF1α, is a hallmark of the microenvironment of solid tumors. This is a clear a helpful condition for cancer stem cells and potentiates cancer progression and metastasis (Semenza 2016). Whether mitophagy inhibition occurs in tumorigenesis because of Parkin mutations, vice versa, during cancer progression and metastasis, mitophagy displays an increase through BNIP3. Excessive mitochondrial damage derived from tumorigenesis could lead to a decrease in fitness of cancer cells and the apparent contradiction would be explained. Using other words, increase in mitophagy observed in tumor progression could represent a sort of adaptive response acted by tumors, in order to increase survival.

The role for BNIP3 in both tumorigenesis and tumor progression still, almost apparently, controversial and not clearly elucidated. A list of studies investigates on its protumorigenic role, highlighting, for example, reduced cell migration and vascular mimicry with a remodeling of the cytoskeletal actin, after BNIP3 knockdown in melanoma cell line (Maes et al. 2014). On the contrary, recent findings displayed antitumorigenic properties for BNIP3 and its possible role as a tumor suppressor gene (Chourasia and Macleod 2015). To name one example, BNIP3 loss, and consequent mitophagy defects, results in increased metastasis in a mammary tumor rodent model (Chourasia et al. 2015a). It has taken into account that BNIP3 can undergo alternative splicing of exon 3, determining the formation of a truncated splice variant that presents prosurvival and, as a consequence, protumorigenetic properties (Gang et al. 2015). This finding can be useful to elucidate the dichotomial role observed for BNIP3.

Concerning FUNDC1, its role in hypoxia-induced mitophagy has been well established (Wu et al. 2014a), but further studies are needed in order to establish whether FUNDC1 has also a key role in cancer mitophagy.

KRAS is commonly mutated in several type of cancer, such as lung, colorectal, and pancreatic (Chan et al. 2003; Karachaliou et al. 2013; Quiros et al. 2014). Mutations present in the form of a single nucleotide substitution, finally leading to the hyperactivation of this proto-oncogene (Flemming 2013). Consequently, it activates the proliferative pathway, involving PI3K, and it upregulates GLUT1 (solute carrier family 2 member 1), moving the metabolism to an aerobic glycolysis profile (Kerr et al. 2016), alias Warburg effect (Lunt and Vander Heiden 2011; Quiros et al. 2014). Consistently with these issues, autophagy determines the augment of malignancy of tumors with oncogenic transformation of KRAS (Kim et al. 2011). Interestingly, shift from adenoma and carcinoma to oncocytoma, a more benign and rarer form, has been observed in mouse model that presents KRAS G12D mutation, after loss of Atg7. Oncocytoma displays an increase in number of dysfunctional mitochondria. It seems that mitophagy has a different role in KRAS-mutated tumors, since it appears to increase malignancy, instead of inhibits it, as seen previously in other models of cancer.

Conclusions

Aging and carcinogenesis are multistep processes whose hallmarks have been progressively defined in the last 40 years. Among other features, both processes are characterized by alterations of metabolism, in which mitochondrial dysfunctions play a direct, central role.

DNA mutations or arrangements, genomic instability, impairment of protein functions and proteostasis, altered metabolic and signaling pathways are features present both in aging and in neoplastic transformation. ROS, normally produced by mitochondria, may cause all these phenomena and determine a progressive deregulation of cell functions, which in turn could induce further mitochondrial dysfunctions and increase in ROS production.

Thus, a deeper comprehension of the fine regulation of ROS production in physiological aging, or in pathological conditions related with aging, such as chronic inflammatory diseases or neurodegenerative diseases could also help to better comprehend the dysregulation of metabolic processes observed in cancer, and to pave the way for the identification of new therapeutic targets for cancer.

Cross-References

- ▶ Biomarkers of Aging (With a Clinical Potential in Oncology)
- ▶ Calpain-Calpastatin System in Lymphoid Neoplasm of the Aged
- ▶ Cellular Senescence and Tumor Promotion
- ▶ Chronic Mechanistic Target of Rapamycin Inhibition: Preventing Cancer to Delay Aging or Vice Versa?
- ▶ Colorectal Cancer in Older Adults: Surgical Issues

- Colorectal Cancer in Older Adults: Systemic Treatments
- Digestive Organ Aging and Cancer
- Early-Stage Breast Cancer in Older Adults
- Lung Cancer in Older Adults: Local Treatment
- Multidisciplinary Management of Liver, Pancreatic, and Gastric Malignancies in Older Adults
- Pharmacology of Aging and Cancer
- Principles of Cancer Targeted Therapy in Older Adults
- Principles of Chemotherapy in Older Adults
- Respiratory Organ Aging and Cancer
- Role of Cell Cycle Control, Checkpoints, and DNA Repair Mechanisms in Stem Cells and Changes with Aging and Cancerogenesis
- Systemic Treatment of Metastatic Breast Cancer in Older Adults

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Part III

(Patho)physiology of Aging and Cancer

William Dale

Normal and Abnormal Aging (General Perspective for the Oncologist)

14

George E. Taffet

Contents

Abstract

Normal aging, from maturity to senescence, is accompanied by a large number of physiologic, organ, biochemical, and molecular changes. In the unchallenged state, at homeostasis, age-related decrements in function from these changes are few in part because reserves are used to maintain homeostasis. When challenged, whether by diseases, environment, medications, etc., those age-related changes become apparent. These changes lead to increased vulnerability with aging, called "homeostenosis." Rather than the reserves disappearing with age, the reserves are invoked in the older person just to maintain homeostasis. Therefore, less are available to respond to disease or medication or other challenge. Broadly this pattern is seen in the cardiovascular system, the hematological system, and the renal system, and elsewhere. When there are essentially no reserves available for challenges, when any challenge overwhelms them, that is frailty. Additionally, aging can modify the impact, presentation, and natural history of any illness. This is because the substrate, the aging person, more than the disease pathophysiology, has been modified. In any given person, the system where the reserves are the least may be the most likely to fail with any challenge. For example, in older patients with dementia, delirium may be the presenting symptom for a urinary tract infection, gastrointestinal bleed, or myocardial infarction; the weakest link fails first. Understanding homeostenosis helps one to understand the apparent vulnerability of the elderly that are in our care.

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Homeostenosis · Frailty · Physiologic reserves · Vulnerability

Introduction

While aging produces changes at the physiologic, organ, biochemical, and molecular levels, the general increase in vulnerability that may accompany aging and drives the increases in adverse responses to therapy, increases in complications after procedures, and increases in mortality after challenges, is the theme of this chapter. The diminution in the physiologic reserves or functional capacity over time is considered a characteristic hallmark of aging. Some of the changes are specifically relevant to oncologists and are discussed in detail elsewhere (see ▶ Chaps. 57, "Exercise and the Older Cancer Survivor," ▶ 60, "Decision Making and Safety Issues in Older Cancer Patients," ▶ 54, "Principles of Cancer Targeted Therapy in Older Adults," ▶ 56, "Digestive Symptoms Control and Nutrition Issues in Older Cancer Patients," ▶ 59, "Integrating Geriatric Oncology into Clinical Pathways and Guidelines," ▶ 62, "The Older Cancer Patient: Religious and Spiritual Dimensions," ▶ 52, "Principles of Radiation Therapy in Older Adults," ▶ 61, "Improving Communications with Older Cancer Patients," and ▶ 51, "Principles of Cancer Surgery in Older Adults"). Aging leads to increased mortality for many cancers, and increased frequency and severity of adverse effects in response to many chemotherapeutic agents and other interventions.

But aging also leads to slower growth of some tumors, famously for laboratory scientists, the B16 melanoma line. This line, possibly dependent upon host immune responses for robust growth, produces lower growth and longer survival in old mice compared to young ones (Ershler et al. 1984). Similarly poor angiogenesis has been implicated (Pili et al. 1994). That is the age-related decrease in the ability to develop new blood vessel limits tumor growth (Pili et al. 1994). So age-associated changes in both humoral and local host factors might contribute to the behavior of a transplanted tumor into an old host compared to a young one (Anisimov 2006). Geriatricians frequently see breast cancers and lung cancers that seem to follow a protracted or indolent course (Kaesberg and Ershler 1989). So not all aging phenomenon are directly harmful.

Homeostenosis

The overall goal of this chapter is to discuss the increased vulnerability with aging, called "homeostenosis." For this chapter, aging is post-developmental, ranging from maturity to senescence. Homeostenosis has direct implications on therapeutic choices for older people and toxicities they experience (Sawhney et al. 2005; Sehl et al. 2005). The concept of homeostenosis in aging is not new. The famous physiologist Walter Cannon described it in the quote below (Cowdry and Allen 1939). Figure 1 graphically displays one model of homeostenosis. In the unchallenged state, at homeostasis, age-related decrements in function are few. Things like vital signs, cardiac output, and activities of daily living are unchanged by age. When challenged, whether by diseases, environments, medications, etc., the impact, presentation, and natural history of diseases are modified with age. This is because the substrate, the aging person, more than the disease pathophysiology, has been modified.

> Homeostasis is not affected to any marked degree (with aging) . . . When subjected to stress, . . . (older people) are revealed as being more and more narrowly limited in their ability to preserve uniformity of the internal environment.
>
> Walter Cannon, in Cowdry and Allen (1939).

In the figure, challenges are displacements (arrows) off the baseline, away from homeostasis, and larger challenges are larger arrows, and they require greater physiologic reserves to bring the person back to homeostasis. The "precipice" is any clinical sign or symptom, including death, such as ill enough to have a cardiac arrest or for hospital admission. The precipice can be

nonspecific, presentations such as confusion or incontinence, etc. Overall, the loss of physiologic reserves with aging brings the individual closer to the precipice. The area where a person is able to bring themselves back to homeostasis decreases with aging. This has the appearance of a stenotic valve, thus homeostenosis. Furthermore, frailty is the extreme condition, where challenges of small magnitude lead to loss of homeostasis, and frailty and the inability to maintain homeostasis increases the risk of death (Kane et al. 2012).

This paradigm fits most practitioners' experiences, but direct evidence can be seen by examining the physiologic scores as deviation from normal which are components of the "APACHE" severity of illness scales used in many ICUs. The APA, the acute physiologic assessment, gives an increasing number of points for increased deviation from normal values for 12 variables (Knaus et al. 1985; Zimmerman et al. 1998). The variables include heart rate, blood pressure, oxygenation, blood pH, electrolytes, hematocrit, white count, and creatinine (Knaus et al. 1985). At homeostasis, a normal person, independent of age, will have an APA score close to or equal to zero. Younger patients (mean age, 59 years) who experienced a cardiac arrest had significantly higher (by 20%) APA scores than the older group (mean age, 75) (Beer et al. 1994). The precipice, here having a cardiac arrest, is closer to homeostasis for the older person than for the younger one. In practice, the creators of the APACHE severity of illness scales recognized this and the scales give "bonus points" for age (Zimmerman et al. 2006). Therefore, the total scores between the younger and older groups that arrested were not different (Beer et al. 1994).

The physiologic reserves have not "disappeared," with age as suggested in Fig. 1, but they are unavailable to the older person to maintain homeostasis. A primary contributor to the lack of physiologic reserves is that older persons are actively employing some of those reserves just to maintain homeostasis in the unstressed state. In the elderly, as in youth, maintaining homeostasis is a dynamic, active process. The reserves appear depleted not because they have disappeared with age, but because they in are already in use as shown in Fig. 2. For illustration, examples from the cardiovascular system – heart rate, cardiac hypertrophy, metabolic pathways, and diastolic function – will be shown below, because the data provide an ample molecular, biochemical, and physiologic foundation to show how reserves are invoked at rest to maintain homeostasis.

Homeostenosis in the Aging Cardiovascular System

Resting heart rate does not change with age. In contrast, maximum heart rate attained with exercise or pharmacological manipulation decreases progressively. Healthy, highly screened individuals in the Baltimore Longitudinal Study give a

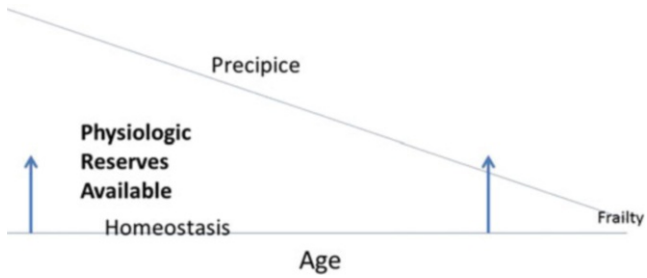

Fig. 1 Standard schematic of homeostenosis. With age, the older person's capacity to bring themselves back to homeostasis after a challenge decreases. Challenges to homeostasis are arrows off the baseline. Larger challenges require greater reserves. Aging brings the precipice closer to individual because of the loss of physiologic reserves. The precipice can be death or ill enough to have a cardiac arrest or for hospital admission or the appearance of common and protean symptoms, such as confusion, weight loss, falls, or incontinence

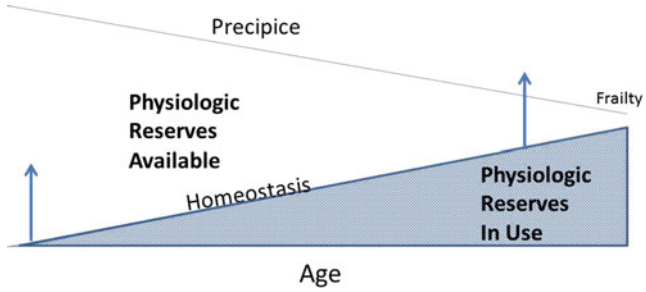

Fig. 2 Revised homeostenosis. Maintaining homeostasis is a dynamic process and older persons are actively employing reserves to accomplish this. The available reserves look like they have disappeared because they are already in use by the old heart (or other organ or system) to compensate for primary age-related or other changes. Nevertheless, there are few reserves available for subsequent challenges

regression equation of $208-(0.95 \times \text{age})$ for maximum heart rate attained with exercise (Fleg et al. 1995). Some suggest that women have lower maximum heart rates in youth than men and show a less steep decline with age than this equation predicts. The decrease in maximum heart rate is due to a number of factors. First, primary aging decreases in the intrinsic heart rate (the heart rate in the absence of sympathetic and parasympathetic stimulation) from 120–130/min to less than 80 (Craft and Schwartz 1995; Christou and Seals 2008). As there is no difference in resting heart rate with age, the extent of parasympathetic tone, slowing heart rate, is decreased at rest (Craft and Schwartz 1995). Removal of vagal, parasympathetic tone is the first mechanism invoked to increase heart rate with exercise. This is less effective for the elderly because vagal tone is already diminished at rest. The observed attenuated heart rate response of healthy elders to administration of atropine is consistent with the decreased vagal tone (Craft and Schwartz 1995). The attenuated response to lysis of parasympathetic tone is added to an age-related decrease in sympathetic, beta-adrenergic heart rate response that results in the overall decreased maximal heart rate in exercise (Craft and Schwartz 1995; Christou and Seals 2008). Thus reserves used by the young to attain high maximum heart rate with exercise are already partially invoked to maintain adequate resting heart rate in the elderly (Fig. 2).

Similarly, reserves used in youth to maintain homeostasis in response to increased systemic pressure are reduced in the old in part because they are already in use. When younger adult male rats (9 months) have blood pressure increased experimentally by constricting the aorta, there is a 40% hypertrophy of the left ventricle, increasing wall thickness. This same increase in afterload results in only trivial increase in left ventricular mass in older rats (18 months of age) (Isoyama et al. 1987). As would be expected, older rats already have hypertrophy, thicker left ventricular walls, and higher mass (Isoyama et al. 1987). Older people, even in the absence of hypertension or other disease also have left ventricular hypertrophy with age (Cheng et al. 2010; Hung et al. 2017).

With exercise and the accompanying increased heart rate, young persons increasingly use left atrial systole to increase left ventricular filling (Channer and Jones 1989). The hypertrophy described above decreases early diastolic filling. In the elderly, the compensation is used at rest to maintain ventricular filling, contribution of atrial systole to diastolic filling increases from 10% to 15% at age 20 to almost 50% at age 80 (Kuo et al. 1987; Kitzman et al. 1991).

The hypertrophy includes myocyte and non-myocyte components. Evidence of myocyte hypertrophy in aging, by examining myocyte size, is seen in reports of 25% in increased myocyte length and 50% or more increases in myocyte width (Strait and Lakatta 2012). Ventricular myocytes from older persons and animals are larger; the myocyte hypertrophy is in response to uncertain stresses.

The molecular response to increased afterload is also attenuated in these old hearts, little

induction c-jun and c-fos, immediate early response genes and skeletal actin, which precedes cardiac actin (Takahashi et al. 1992). Atrial natriuretic peptide (ANP), a marker for myocyte hypertrophy, was increased significantly after banding in the young heart but was already very high in the old heart at rest and was not increased further in response to afterload (Isoyama et al. 1987; Takahashi et al. 1992). The increased left ventricular mass, wall thickness, and molecular markers all provide evidence that the old heart has already invoked the hypertrophic response and it is no longer available for subsequent challenges.

Other changes with aging in the cardiovascular system and elsewhere follow the paradigm described above. Older persons are frailer, more likely to cross a given "precipice" after a stress, not only because they have lost some reserves because of aging, but because they are already utilizing reserves to compensate for those lost just to maintain homeostasis. The older person is more likely to drown when thrown a brick not because they are unable to swim, but because they are already treading water. For all these examples, the apparent loss of physiologic reserves in aging reflects the use of compensatory reserves available for challenges in youth just to maintain homeostasis in the elderly and the magnitude of that use of compensatory reserve is called allostatic load.

Allostatic Load and Aging

Is there any evidence that the state of using compensatory reserves, the extent of the allostatic load, is in itself bad? MacArthur Study of Aging data and a long series of papers from Seeman and McEwen support the concept that the presence of invoked compensation in healthy elders is associated with worse outcomes (Seeman et al. 1997). Of community dwelling people, aged 70–79, only 7% had no evidence of compensation and the lack of compensation was associated with highest level of function over the next few years. Seeman's measures of this activation, allostatic load, were not perfect, but broadly reflected the activity of sympathetic nervous system, immune system, or hypothalamic–pituitary–adrenal axis. Those with high allostatic load had decreased physical and cognitive function at 2-year follow-up (Seeman et al. 1997). If over the next 2 years, the allostatic load decreased, the cognitive and physical function was better than for those where the load increased or did not change (Karlamangla et al. 2006). This suggests efforts to disengage reserves may decrease vulnerability.

Invoking compensatory mechanisms has the additional effect of constraining the complexity of many variables. Heart rate variability decreases with aging, and this constriction of heart rate may be due to decreased parasympathetic tone and possible activation of the sympathetic nervous system while at rest (Lipsitz and Goldberger 1992). A similar constriction is seen in blood pressure variability. The decrease in variability may correspond with the ongoing activation of compensatory reserves.

It then is possible that low levels of nonharmful challenge may be beneficial. Masoro and colleagues believe that one mechanism by which caloric restriction lengthens life is through the low-intensity, nonharmful stress produced by the decreased availability of calories (Masoro 2006). This concept, hormesis, suggests that persistent, harmless stresses, such as caloric restriction or radiation, may be good for us; larger stresses may be harmful (Masoro 2006; Demirovic and Rattan 2013). The beneficial effects of methionine or tryptophan restriction may also be via this mechanism (Masoro 2006).

Homeostenosis and Altered Presentation of Disease in the Elderly

The precipice shown in the figures also helps explain the altered, nonspecific, presentations of disease that characterizes the elderly. Delirium or altered mental status is a very common presentation of a wide variety of illnesses in the elderly, from urinary tract infection to gastrointestinal bleeding. In some individuals, where the "anti-confusion reserves" are exhausted, delirium may be their presentation for almost all their illnesses

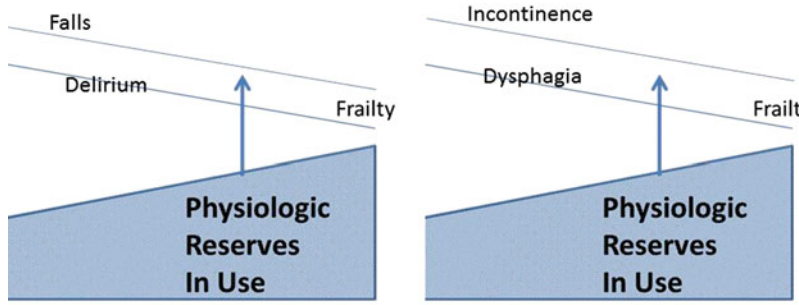

Fig. 3 Altered presentation of illness. Altered presentations may be another manifestation of homeostenosis. With age, different precipices may approach homeostasis at differing rates and different reserves may be invoked differentially so that small challenges cross different precipices. In this case, the same challenge results in new onset of incontinence for one individual and confusion in another

(Fig. 3). In that individual, homeostasis and the delirium precipice lie very close to each other, any challenge crosses the precipice. Another individual may present with incontinence as their catch-all presentation. The extent that any precipice approaches homeostasis may determine whether that threshold is crossed by a given challenge. This phenomenon may be relatively common in frail older people because the systemic responses to these differing illnesses may be similar, involving cytokines, catecholamines, etc. It means that one needs to have a broad differential for the nonspecific presentations in the elderly patient.

The increased frequency of falls in response to challenge fits this model perfectly. Decreases in recognition of thirst, baroreceptor sensitivity, arterial compliance, cardiac compliance (and greater dependence on cardiac filling to maintain cardiac output), renal sodium conservation, plasma volume, vasopressin response to standing, and renin, angiotensin, aldosterone levels all contribute to increase the propensity to fall with postural change in the older person in the absence of illness. That is the precipice representing falling gets closer to homeostasis with age. With illness, dehydration or other perturbation occurs and falls ensue. Many of the problems with medications in the elderly, once attributed to altered pharmacodynamics, may be explained by this apparent depletion of physiologic reserves. Falls are the nonspecific presentation of a wide number of underlying processes.

The lines representing the precipices are unlikely to be straight in reality, because none of the processes are necessarily linear. For example, the rate of loss in muscle mass increases with increasing age and the loss of lower extremity strength also follows this same pattern.

The concept of homeostenosis also allows understanding of, therapeutic nihilism, the idea that treating older people has no yield. Indeed, the opportunity for treatment focused only at a disease to benefit a patient is limited by the length of the arrow displacing them from homeostasis. We verbalize this as “a little COPD exacerbation” in the older person. The lesser opportunity for “cure” creates a greater impetus for prevention or active treatment. Additionally, treatment directed at the depleted or activated reserves can be considered.

Summary

Physiologic reserves appear to be lost with age leading to an intolerance of challenges to homeostasis. Some of those reserves have not disappeared but are invoked to maintain homeostasis. Nonspecific presentations of illness in elderly may reflect their individual homeostenosis. Frailty is, in part, the extreme where the older person is continuously expending reserves to compensate for existing chronic disease and primary age changes. Providing ways to improve the resilience of the elderly may lead to rich rewards. Interventions that increase longevity, but do not prevent homeostenosis, may lead to longer years of disability and dependence.

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Respiratory Organ Aging and Cancer

15

Leah J. Witt and Carolyn J. Presley

Contents

Abstract

Lung aging begins in the third decade, initiating a gradual decline in maximal pulmonary function that continues throughout the remainder of life. Lung aging may mimic obstructive and restrictive lung diseases. Lung parenchyma loses elasticity via alveolar wall and mesenchymal degradation and distortion, similar to emphysema. Muscles of respiration become sarcopenic and weaken, while the

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thorax contorts due to osteoporotic vertebral fractures, all of which manifest as a restrictive lung function pattern. Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) and their pathogenesis may be related to accelerated cellular aging. Chronic lung disease impacts cardiopulmonary fitness, which can lead to decreased physical exertion and resultant frailty.

Lung cancer incidence also increases with age and is increased in older adults with COPD and IPF. Lung cancer is the leading cancer-related cause of death in the world. Most lung cancer in the USA is attributable to smoking. Globally, indoor air pollution is also a significant risk factor. Approximately 85% of lung cancer is non-small cell lung cancer (NSCLC), and adenocarcinoma is the predominant histologic type. Depending on stage at diagnosis, treatment options can include surgical resection, medical therapy (e.g., chemotherapy, driver mutation-targeted agents, and immunotherapy), and radiation therapy (photon or proton). Best care practices mandate that multidisciplinary teams formulate treatment plans to optimize care. Comprehensive geriatric assessments are useful decision-making tools and may improve survival while limiting treatment toxicity. Surgical resection impacts postoperative lung function, so preoperative evaluations must include pulmonary function testing with additional cardiopulmonary testing as indicated. Early palliative care interventions should be a cornerstone of medical management in advanced lung cancer.

Keywords

Lung aging · Dyspnea · COPD · IPF · Lung cancer

Introduction

Lung function peaks in the third decade of life, and then begins to slowly decline, precipitated by degradation of lung parenchyma, weakening of respiratory muscles, and distortion of the thorax. The natural history of chronic lung disease may mimic chronic obstructive pulmonary disease, due to air trapping (increased residual volume) and decreased forced expiratory volume in one second (FEV_1). However, respiratory muscles weakness and restriction of the thoracic cavity may counteract some of these obstructive changes on pulmonary function testing.

Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are prototypical chronic lung diseases of aging. Not only does prevalence and incidence of both diseases rise with age, but the pathogenesis of each overlaps with hallmarks of aging, such as shortened telomeres, defective DNA repair, genomic instability, cellular senescence, stem cell exhaustion, and mitochondrial dysfunction. Emerging evidence suggests that individuals with chronic lung disease experience physiologic aging that outpaces chronologic aging, therefore they are disproportionately burdened with geriatric syndromes such as frailty.

The prevalence of lung cancer is increased with COPD and IPF. Lung cancer is the deadliest of all cancers in the USA and causes substantial morbidity and mortality for aging populations. Given the increasing prevalence of lung cancer with age, understanding lung aging is an important element of caring for these patients. This chapter will discuss lung aging, chronic lung disease, lung cancer screening, and the nuances of caring for geriatric patients with lung cancer.

Recent guidelines recommend initiating low-dose computed tomography (LDCT) lung cancer screening in select at-risk populations with smoking exposures. These new guidelines are altering clinical practice particularly for geriatric patient populations, as screening targets patients between ages 55 and 80 years, and Medicare now pays for annual screening in select populations. Primary care physicians must decide how to incorporate lung cancer screening into their care of geriatric patients and use shared-decision making to determine when to stop screening.

When lung cancer is suspected, a multidisciplinary team including primary care

providers, geriatricians, pulmonologists, oncologists, and thoracic surgeons helps to shape the management plan for geriatric patients. Geriatric populations are heterogeneously resilient to the risks of cancer treatment; some high-risk subgroups are burdened with decreased physical function, disability, multimorbidity, and/or geriatric syndromes (including falls, incontinence, and polypharmacy). It is essential that providers appropriately risk-stratify patients to make the complex decisions required in care planning, so to avoid overtreatment of high-risk groups and undertreatment of resilient groups.

Lung Aging

Lung aging begins in the third decade of life, far earlier than what could be described as a "geriatric" age. Understanding lung aging, therefore, mandates an understanding of the embryologic underpinnings of the respiratory system (Bush 2016). Lung development first begins at week 3 of embryologic development, when the lung bud develops from the foregut (Burri 2006). By week 4, the lung bud has divided into two bronchial buds. Primitive alveolar sacs develop at approximately 16 weeks and proliferate. At 24 weeks, more alveoli have developed and the epithelium is thin enough for respiration, at which time the type 2 pneumocytes begin to produce surfactant. The lungs continue to develop throughout postnatal life, by increasing the size and number of respiratory bronchioles and alveoli until approximately age 8. Lung aging, the gradual decline of maximal lung function, begins just 20 years later (Janssens et al. 1999; Janssens 2005; Meiners et al. 2015).

Aging incites structural and functional changes throughout the respiratory system, including the thorax, muscles of respiration, bronchioles, and alveoli. The elasticity of lung parenchyma deteriorates, impeding bronchiole patency, alveolar integrity, and the alveolar/capillary interface. Muscles of respiration, including the diaphragm, intercostal muscles, and other accessory muscles, gradually lose muscle mass with age (called sarcopenia) and may functionally weaken (Cruz-Jentoft et al. 2010). The thorax, including the spinal column and rib cage, contorts due to osteoporotic vertebral body fractures and resultant kyphosis, hampering the lungs' expansion (Leech et al. 1990).

There are several objective assessments of respiratory organ aging. Such tools include lung volume measurements (by body box plethysmography or single breath helium dilution) **(**Fig. 1a**)**, airflow measurements (by spirometry), gas exchange capability (via diffusing capacity of the lung for carbon monoxide (DLCO)), respiratory muscle strength (by maximal inspiratory and expiratory pressure), exercise testing (6-min walk testing, shuttle walk testing, and cardiopulmonary exercise testing), and oxygenation measures (by arterial blood gas or pulse oximetry) (Table 1). Lung volumes are measured in liters, and these values are reported along with "predicted" values based on height, age, and gender (Quanjer et al. 1993).

Age-related changes in airway and alveolar structure impede air egress, which decreases forced expiratory reserve volume in one second (FEV_1) particularly as compared to the total forced expiratory reserve volume (FVC), consistent with airflow obstruction **(**Fig. 2a–c**)** (Schmidt et al. 1973). These changes mimic chronic obstructive pulmonary disease (COPD). Alveolar distortion impairs gas exchange which decreases the DLCO. Pathologically, enlargement of the alveolar structure with age may appear similar to emphysema, though typically without the same degree of alveolar wall destruction (Janssens et al. 1999).

Lung volume changes with age vary between individuals. Airflow obstruction causes air trapping and an increased residual volume (RV), which is the volume of air remaining in the lungs after maximal exhalation **(**Fig. 1b**)**. Total lung capacity (TLC) may stay constant or shrink due to chest wall restriction from thorax distortion or respiratory muscle weakness (Enright et al. 1994). Therefore, the outcome of pulmonary function testing will vary depending on an individual's burden of aging-related lung function changes.

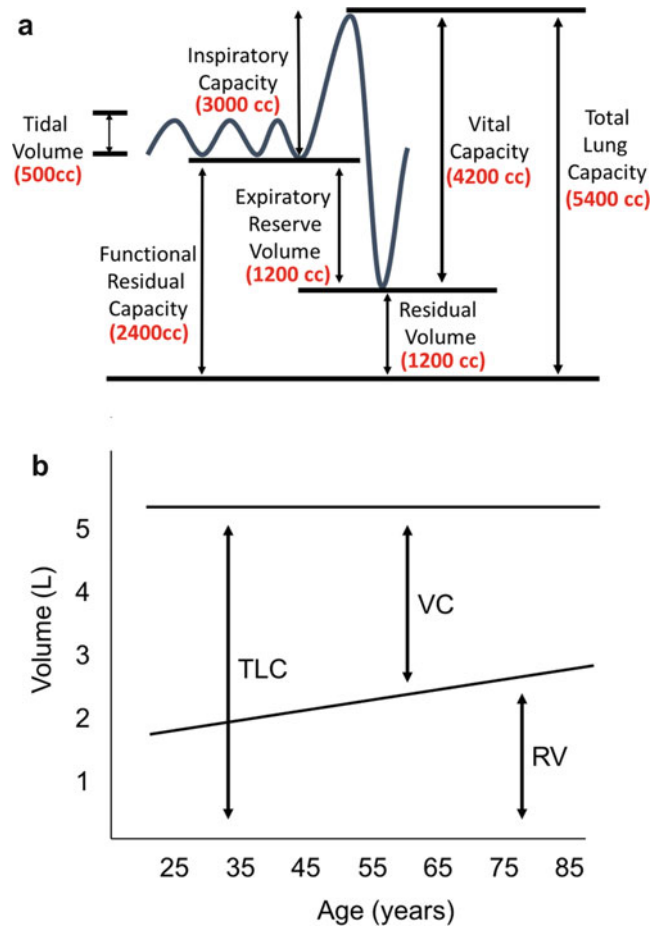

Fig. 1 (**a**) Lung volume measurements and sample volumes. (**b**) Changes seen in spirometry with aging. (Adapted from Janssens 2005)

Table 1 Lung function assessments

Lung volume measurements	TLC, FRC, RV
Spirometry	FEV_1, FVC
Gas exchange	DLCO
Oxygenation	paO_2, SpO_2
Ventilation	pCO_2
Respiratory muscle strength	MIP, MEP
Exercise testing	
Low technology	6-min walk, shuttle walk, stair climb
High technology	Cardiopulmonary exercise testing (VO_2)

TLC total lung capacity, *FRC* functional residual capacity, *RV* residual volume, *FEV_1* forced expiratory volume in 1 second, *FVC* forced expiratory volume, *DLCO* diffusing capacity of the lung for carbon monoxide, *paO_2* partial pressure of oxygen, *SpO_2* pulse oximetry, *pCO_2* partial pressure of carbon dioxide, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure, *VO_2* maximal oxygen consumption

Chronic Lung Diseases and Aging

Chronic lung diseases such as COPD, IPF, combined pulmonary fibrosis and emphysema (CPFE), asthma, and the newly described asthma-COPD overlap syndrome (ACOS) can impact quality of life and mortality of geriatric patients. General primary or specialty pulmonary

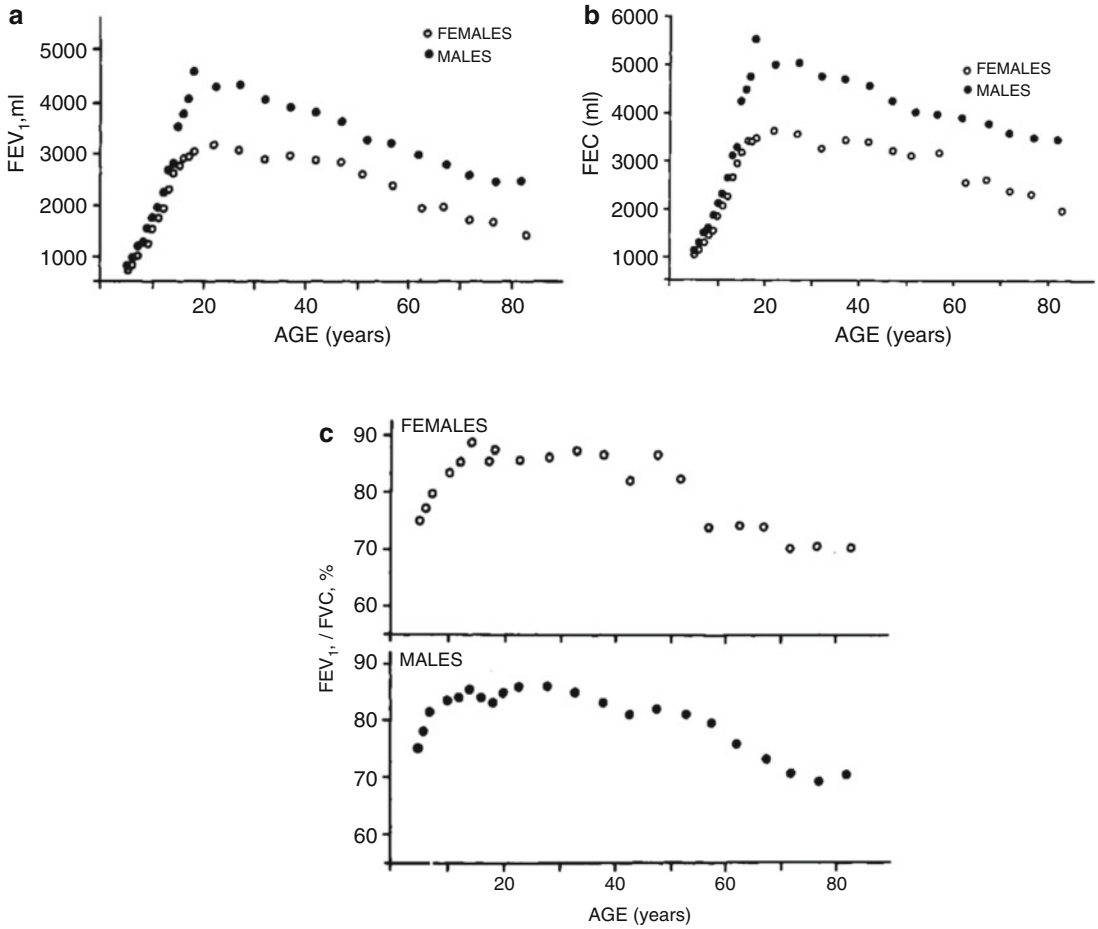

Fig. 2 (**a**) Mean forced expiratory volume in 1 second capacity (FEV_1) values by age 5–94 years. (**b**) Mean forced vital capacity (FVC) values by age 5–94 years. (**c**) Mean FEV_1/FVC values compared by age 5–94 years. (Adapted from Schmidt et al. (1973). Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. The American Review of Respiratory Disease is an official journal of the American Thoracic Society)

care for patients with chronic lung disease should include an assessment of pulmonary function (as described above), physical function (as measured by low-technology exercise testing and oxygenation), appropriate maintenance and rescue inhaler prescriptions, supplemental oxygen when indicated, and meticulous preventive care (including influenza and pneumococcal vaccination). Pulmonologists are increasingly recognizing the impact of aging on caring for patients with chronic lung disease and incorporating geriatric assessments into their care (Singer et al. 2016; Castriotta et al. 2010; Fried et al. 2012a).

Dyspnea or shortness of breath is a common complaint in geriatric populations and a frequent reason for referral to pulmonary subspecialists. Dyspnea can occur for a multitude of reasons, including cardiopulmonary impairment (e.g., congestive heart failure), neuromuscular diseases (e.g., amyotropic lateral sclerosis), and psychological distress (e.g., anxiety). Dyspnea complaints should receive a comprehensive evaluation, as detailed in the 2012 American Thoracic Society consensus statement, which includes a thorough history and physical examination to narrow the broad differential diagnosis and

Table 2 Clinical dyspnea scales

mMRC (Mahler and Wells 1988)	Modified Borg dyspnea scale (Borg 1982)
0 – No breathlessness except with strenuous exercise 1 – Breathlessness when walking up a slight hill or hurrying on level ground 2 – Walks slower than people of same age or must stop occasionally due to breathlessness on level ground 3 – Stops for breathlessness after walking 100 yards or a few minutes on level ground 4 – Too breathless to leave the house or breathless when dressing/undressing	*How much difficulty is your breathing causing you right now?* 0 – Not at all 0.5 – Very, very slight 1 – Very slight 2 – Slight 3 – Moderate 4 – Somewhat severe 5 – Severe 7 – Very severe 9 – Very, very severe 10 – Maximal

mMRC: modified Medical Research Council

determine further testing (Parshall et al. 2012). In a study of home-dwelling elderly individuals (aged 70 and older), the prevalence of dyspnea by the modified Medical Research Council scale (mMRC) (Table 2) was 32.3% (95% CI 30.3–34.3%) (Ho et al. 2001).

Dyspnea also appears to be related to mortality. In a cohort study of elderly family practice patients, dyspnea at baseline evaluation was significantly associated with death at 8-year follow-up (Huijnen et al. 2006). Some experts suggest that dyspnea be considered a geriatric syndrome. In an analysis of the 4413 community dwelling people in the Cardiovascular Health Study, moderate to severe dyspnea (Miner et al. 2016) was associated, expectedly, with cardiopulmonary impairments such as low FEV_1 or left ventricular function. Surprisingly, dyspnea was also associated with anxiety/depressive symptoms, inability to perform a chair stand, and grip weakness.

COPD is the third leading cause of death in the USA and fourth in the world (NCHS 2016; WHO 2016). Most patients with COPD have a history of personal or second-hand smoking (GOLD 2017). In countries with significant air pollution, such as from indoor solid-fuel use, COPD causes an even higher burden of mortality. For example, in China, COPD is the second leading cause of death due to high rates of smoking and indoor air pollution (Lin et al. 2008).

COPD is characterized by progressive airflow obstruction, defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as an FEV_1/FVC ratio $< 70\%$ (actual) and a forced expiratory volume (FEV_1) $< 80\%$ (predicted) (GOLD 2017). Traditionally, COPD staging depended solely on FEV_1 impairment, but now dyspnea symptoms and exacerbation history are included in staging. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Index can assist in predicting 4-year survival (Celli et al. 2004). Patients may have the chronic bronchitis (mucous production and increased airway resistance) and/or emphysema (impaired gas exchange and increased air trapping) subtypes of COPD.

COPD mimics the natural history of normal lung aging (Macnee 2016; Mercado et al. 2015). An emerging debate is challenging the traditional paradigm of COPD pathogenesis as solely attributable to accelerated lung aging and suggests that a subset of patients may be predisposed to develop COPD due to abnormal lung development but normal lung aging. In 1977, Fletcher and Peto presented what would become the conventional model of COPD pathogenesis. Their epidemiological description of "British disease," so-called due to the high prevalence of COPD in Britain, suggested that gradual age-related lung function decline can be accelerated by smoking in some individuals (Fletcher and Peto 1977).

A 2015 study by Lange and colleagues contested the traditional model as the only path to COPD pathogenesis. In their review of spirometry and outcomes from three large cohort studies, the Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort, the authors showed that some patients

who develop obstructive lung disease may have failed to achieve normal lung function before experiencing normal age-related lung function decline (Lange et al. 2015). Risk factors in childhood and early adolescence, such as parental smoking (particularly intrauterine exposure by the mother), a family history of asthma, and/or a personal history childhood asthma, or respiratory infections, may predispose an individual to obstructive lung disease (Bush 2016).

Clearly, there is heterogeneity within the COPD patient population, and as a result, the rate at which FEV_1 declines in COPD is highly variable between patients. Data from a 2011 study by Vestbo et al., that followed 2163 patients over a 3-year period, found a mean (± standard error) rate of decline of 33 (±2) ml per year (Vestbo et al. 2011). Notably, patient subgroups experienced different rates of decline, with higher rates in current smokers compared to nonsmokers (21 ± 4 ml), those with emphysema compared to those without emphysema (13 ± 4), and those with bronchodilator reversibility compared to those without reversibility (17 ± 4 ml). These findings demonstrate that the clinical course of COPD is variable and difficult to predict.

Caution must be exercised before conferring COPD diagnoses on elderly individuals. Remember that normal lung aging mimics COPD **(**Figs. 2a–c**)**, yet patients may not be symptomatic and medical therapy for COPD has not been studied to "treat" normal lung aging. In a study of 208 asymptomatic never-smoker individuals over age 70 who underwent spirometry, 35% were found to qualify for stage 1 COPD by the GOLD criteria (Hardie et al. 2002). Further evidence from 2025 individuals aged 65–100 years old found airflow limitation in 28.2 per 1000 person-years when using the GOLD criteria (Luoto et al. 2015). The number of patients classified as having airflow limitation decreased to 11.7 per 1000 person-years when an age-dependent predicted lower limit of normal (LLN) value was used instead. Increasingly, experts suggest modifying diagnostic criteria to be based on standard deviations from the median (called spirometric z scores) (Vaz Fragoso et al. 2015) or LLN criteria for older patients.

Idiopathic pulmonary fibrosis (IPF), an interstitial lung disease of unknown etiology, is far less prevalent than COPD though similar aging-related changes are implicated in its pathogenesis. The incidence and prevalence of IPF increases significantly with age, male gender, and history of tobacco use (Raghu et al. 2006). Two-thirds of patients with IPF are over 60 years old at time of presentation, with a mean age at diagnosis of 66 years (Fig. 3).

In IPF, aberrant wound healing and resultant pathogenic fibrosis causes progressive lung destruction. Pulmonary function testing reveals small lung volumes and a restrictive lung disease pattern. There is typically a normal or high FEV_1/FVC ratio due to increased elastic recoil in the lungs. There is no cure for IPF, though two new recently approved medications, pirfenidone and nintedanib, slow the progression of IPF (King Jr et al. 2014, Richeldi et al. 2014). End-stage IPF may be treated with lung transplant. Median survival following diagnosis is 2.5–3.5 years and approximately 40,000 people die per year of IPF just in the USA (Blackwell et al. 2013; Ley et al. 2011), though this data was reported prior to use of antifibrotic agents.

Combined pulmonary fibrosis and emphysema (CPFE) is an increasingly recognized disease state that combines pathogenic features of COPD and IPF. Pulmonary function testing may approach normal due the balanced deficits of lung restriction and obstruction (Jankowich and Rounds 2012). Therefore, the diagnosis is often made radiographically or on pathology. Median survival is slightly higher than IPF, ranging from 2.1 to 8.5 years.

Asthma in the elderly often mimics COPD and is under recognized and undertreated (Skloot et al. 2016). Patients 65 years and older have the highest rates of asthma deaths and second highest rate of asthma hospitalizations as compared to other age groups. Further, the natural history of lung aging, such as decreased elastic recoil, can further exacerbate asthma symptoms making the disease more challenging to treat. The asthma-COPD overlap syndrome (ACOS), like CPFE, identifies a unique subset of older patients with an overlapping asthma and COPD phenotype.

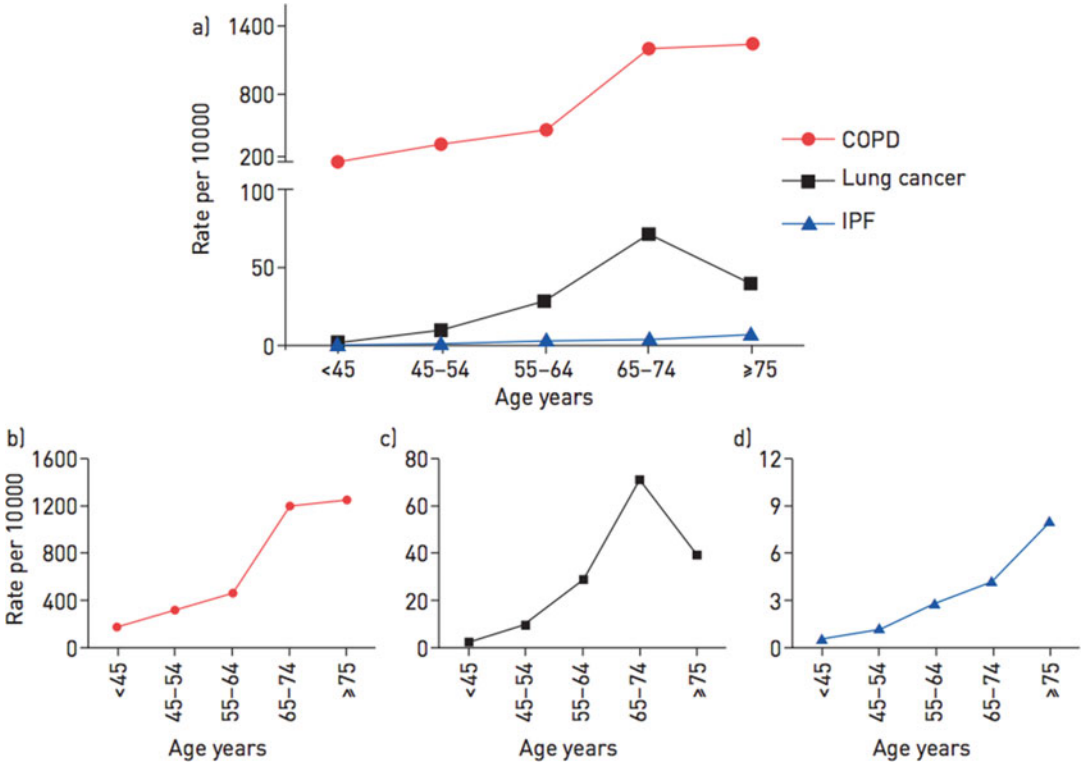

Fig. 3 The all-gender incidence rates of chronic obstructive pulmonary disease (COPD), lung cancer, and idiopathic pulmonary fibrosis (IPF) according to age in the USA. (Reproduced with permission from the European Respiratory Society ©. European Respiratory Journal. 2015;45(3):807–827. https://doi.org/10.1183/09031936.00186914)

(Postma and Rabe 2015). One study estimated the prevalence of ACOS in individuals with COPD at 17.4%, and noted increased dyspnea, wheezing, respiratory-related quality of life by the St. George' Respiratory Questionnaire (SGRQ) and reduced physical activity, as compared to nonoverlap COPD patients (Miravitlles et al. 2013).

Primary care for patients with chronic lung disease can be complex (Fried et al. 2012b). These patients often have multiple comorbidities such as arthritis, osteoporosis, congestive heart failure, and depression (Schnell et al. 2012). One study noted a prevalence of four or more comorbid conditions in over half of patients with moderate to very severe COPD (Vanfleteren et al. 2013). Comorbid conditions such as gastroesophageal reflux and cardiac dysfunction can exacerbate asthma and COPD (Hanania et al. 2011; Le Jemtel et al. 2007). The guideline-based management of multiple comorbid conditions, when taken together, may offer contradictory advice or be financially or logistically impractical to undertake (Boyd et al. 2005).

Chronic Lung Diseases and Frailty

Patients with COPD are more likely to be frail. Frailty is a phenomenon of impaired physiologic reserve and resilience, first described by the Cardiovascular Health Study in 2001, through the creation of the Fried Frailty Phenotype (FFP) (Fried et al. 2001). The FFP is an aggregated score of five assessments: grip strength, walk speed, weight loss, exhaustion, and physical activity level. Fried's original study revealed that a frailty phenotype was significantly associated

with COPD even when adjusted for age. Lahousse et al. confirmed these findings through a study of community-dwelling individuals, finding that those with COPD by spirometry were more likely to be frail by FFP (10.2%) as compared to those without COPD (3.4%) ($p = 0.001$) (Lahousse et al. 2016). Frail patients with COPD had a mortality rate three times that of nonfrail patients with and without COPD. The authors noted that frailty predicted mortality better than FEV_1 or other comorbidities.

Not surprisingly, frailty is highly prevalent in patients seen in outpatient pulmonary clinics. In 2016, Mittal and colleagues described a frailty prevalence of 18% and prefrailty prevalence of 64% in pulmonary outpatients (Mittal et al. 2016). Fried frailty phenotype assessments can be arduous to complete, so the authors used easily collected ambulatory data such as 100 feet gait speed, as frailty surrogates. They defined slow gait speeds as less than 60 m/min, finding that this was 95% sensitive and 34% specific to predict frailty. Gait speed may be an adequate frailty screening tool in an outpatient pulmonary clinic and could suggest referral to a geriatric clinic.

Spirometric impairment, even without diagnosed lung disease, impacts mortality. Vaz Fragoso and colleagues discovered that, among participants aged 65–80 years in the Cardiovascular Health Study, mortality was highest in those with both frailty and respiratory impairment (adjusted hazard ratio, 3.91, 95% CI, 2.93–5.22) as compared to those with and without frailty and/or respiratory impairment alone (Fragoso et al. 2012).

Sarcopenia, the phenomenon of muscle loss with age, has been described in individuals with COPD. Jones et al. applied the European Working Group on Sarcopenia in Older People (EWGSOP) criteria to 622 outpatients with COPD and found a 14.5% (95% CI 11.8–17.4%) prevalence of sarcopenia, which was associated with age and COPD severity (Jones et al. 2015). In an evaluation of the exercise capacity and muscle strength of 41 patients with COPD, Gosselink et al. found that lung function and peripheral muscle strength were significantly related to exercise capacity in these patients (Gosselink et al. 1996). Pulmonary rehabilitation, a pillar of chronic lung disease management, improves sarcopenia (Jones et al. 2015).

End-stage lung disease can be treated with single or double lung transplant in appropriate candidates, and transplant centers are examining the role of geriatric assessments in further evaluating transplant candidates. While the current lung allocation score incorporates some candidate characteristics (e.g., 6-min walk distance and functional status) accumulating evidence about global functional impairment in patients with severe lung disease suggests the utility of frailty and sarcopenia assessment tools for transplant candidates (Egan et al. 2006). A 2015 study of listed lung transplant candidates showed a high burden of frailty by FFP (28%) and Short Physical Performance Battery (SPPB) (10%) (Singer et al. 2015). Frailty was significantly associated with lung transplant delisting, disability, and death.

Lung Cancer and Aging

Lung Cancer Epidemiology and Risk Factors

Lung cancer is the leading cause of cancer-related deaths for both men and women in the USA. Until recently, lung cancer screening was not standard of care, and most patients presented with late stage disease. As a result, the 5-year survival of all stages of lung cancer from 2006 to 2012 was 17.7% (Howlader et al. 2016). The median age of lung cancer patients at time of diagnosis is 70 years old, and lung cancer is most frequently diagnosed between 65 and 74 years. Men, particularly African American men, face the highest burden of lung cancer diagnoses and death. In the USA, the incidence of lung cancer began to decline in the late 1980s for men, though it did not decline for women until the 2000s (ACS 2016). Lung cancer costs in the last year of life are the highest compared to other types of cancer (Mariotto et al. 2011).

Non-small cell lung cancer (NSCLC) comprises about 85% of all lung cancers (ACS 2016). Adenocarcinoma is the most frequently

identified histologic type of NSCLC and accounts for approximately 40% of all lung cancers. The frequency of adenocarcinoma declines with age, while the frequency of squamous cell carcinoma increases (ACS 2016). In the USA, 80% of lung cancer deaths are attributed to smoking (ACS 2016). Other lung cancer risk factors include second-hand smoke exposure, smoke from indoor burning of coal and wood for cooking and heating, air pollution, radiation therapy (e.g., for Hodgkin lymphoma or breast cancer), and environmental/occupational carcinogens (e.g., radon) (Darby et al. 2005; Pope III et al. 2002; Fontham et al. 1994; Travis et al. 2002).

The pathogenesis of chronic lung diseases such as COPD and IPF have cellular "hallmarks of aging" that overlap with those found in malignant lung cancer cells. Similar pathogenic features include shortened telomeres (Morla et al. 2006), defective DNA repair (Caramori et al. 2011), genomic instability, cellular senescence/stem cell exhaustion (Chilosi et al. 2013), metabolic alterations such as mitochondrial dysfunction (Mora et al. 2017), and epigenetic changes (López-Otín et al. 2013; Mercado et al. 2015; Pardo and Selman 2016; Macnee 2016; Vancheri et al. 2010) (Fig. 4).

Lung cancer is more prevalent in those with COPD and IPF compared to patients without chronic lung disease. In a 2009 study of patients with lung cancer, COPD prevalence by all GOLD stages was significantly higher than age/sex/smoking exposure matched-controls (50% compared to 8%) (Young et al. 2009). COPD appeared to confer a sixfold greater risk of developing lung cancer compared to participants without COPD. Emphysema on computed tomography (CT) scan is an independent risk factor for lung cancer. In a 2007 study of 1166 individuals undergoing lung cancer screening with low radiation-dose CT, the incidence of lung cancer was 25.0 per 1000 person-years in those with emphysema vs. 7.5 per 1000 person-years in those without emphysema (De Torres et al. 2007) (Fig. 5).

Patients with IPF also have higher rates of lung cancer. In a retrospective study of patients with CPFE, IPF, and emphysema, patients with CPFE were found to have the highest risk of lung cancer (adjusted hazard ratio of 4.62, 95% CI 1.58–13.55) as compared the emphysema group (Kwak et al. 2014). The IPF group also had an increased risk of lung cancer as compared to the emphysema group (adjusted HR 4.15, 95% CI 1.03–16.78).

Lung Cancer Screening

Until recently, there was no standardized lung cancer screening practice supported by strong evidence. In 2011, the National Lung Screening Trial Research Team published a randomized, prospective study of 53,454 participants who received either three annual screenings with low-dose computed tomography (LDCT) or single-view posteroanterior chest radiography, from 2003 to 2004 (Team 2011). At the end of the study, the LDCT group had fewer deaths related to lung cancer (247 deaths per 100,000 person-years) versus the chest radiography group (309 deaths per 100,000 person-years). All-cause mortality in the LDCT group was significantly reduced by 6.7% (95% CI 1.2–13.6; $p = 0.02$) as compared to the chest radiography group. A follow-up analysis of the data suggested that LDCT screening could prevent approximately 12,000 lung cancer deaths per year in the USA (Ma et al. 2013).

This data must be interpreted with an understanding of the greatest drawback of increased lung cancer screening: falsely positive tests leading to increased invasive diagnostic procedures and anxiety about test results. The 2011 screening study found a high false positive rate in both the LDCT group (96.4%) and the chest radiography group (94.5%). Further analyses of the same study population have demonstrated higher false positive rates in participants 65 years or older (Medicare-eligible) as compared to those less than 65 (Pinsky et al. 2014). More false-positive screening exams resulted in more invasive procedures to pursue diagnosis. Importantly, participants who underwent invasive procedures experienced a relatively low complication rate in both age groups, that was not significantly different (9.8% in <65 group and 8.5% in ≥ 65 group). However, the older participants had a higher prevalence of cancer and higher positive predictive

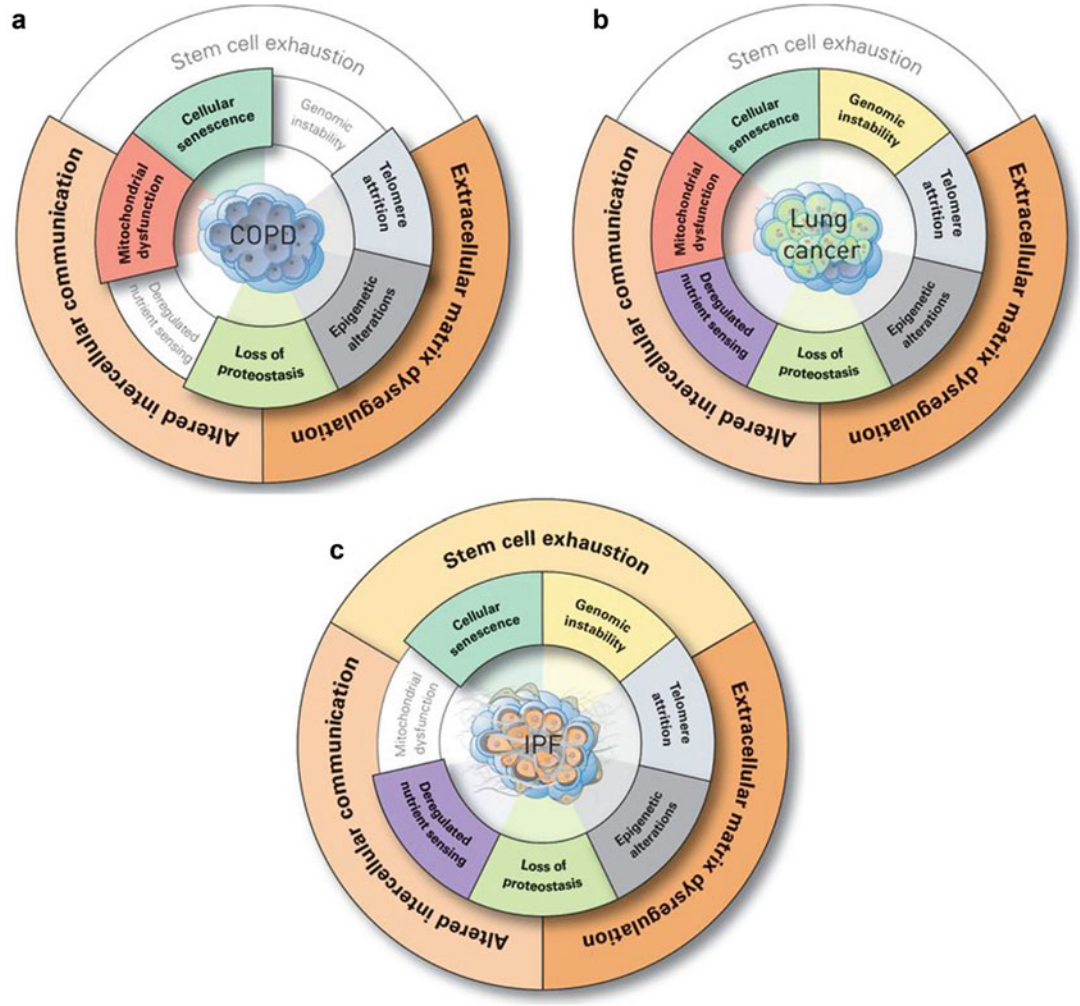

Fig. 4 The predominant hallmarks of aging in (**a**) chronic obstructive lung disease, (**b**) lung cancer, and (**c**) idiopathic pulmonary fibrosis. (Reproduced with permission from the European Respiratory Society ©. European Respiratory Journal. 2015;45(3):807–827. https://doi.org/10.1183/09031936.00186914)

value (4.9% vs. 3.0%) as compared to the group under age 65.

The findings from the National Lung Screening Trial Research Team study led the United States Preventive Task Force (USPSTF) to give a grade B recommendation for annual lung cancer screening by LDCT. This recommendation applies to adults aged 55–80 years with a 30 pack-year smoking history and current smoking behavior, or smoking cessation within the last 15 years. They suggest that screening should continue until a patient has not smoked for 15 years (Moyer 2014).

The intent of the screening practice is to identify early-stage resectable lung cancer. Therefore, annual screening should cease if a patient's life expectancy is limited by comorbidities or the patient is unwilling to have curative lung surgery or radiation treatment. In 2015, the Centers for Medicare and Medicaid Services began covering LDCT lung cancer screening as a preventive service benefit (Medicare and Services 2015).

The American College of Radiology (ACR) has suggested a standard method for evaluating LDCT, called the ACR Lung CT Screening Reporting and Data System (Lung-RADS)

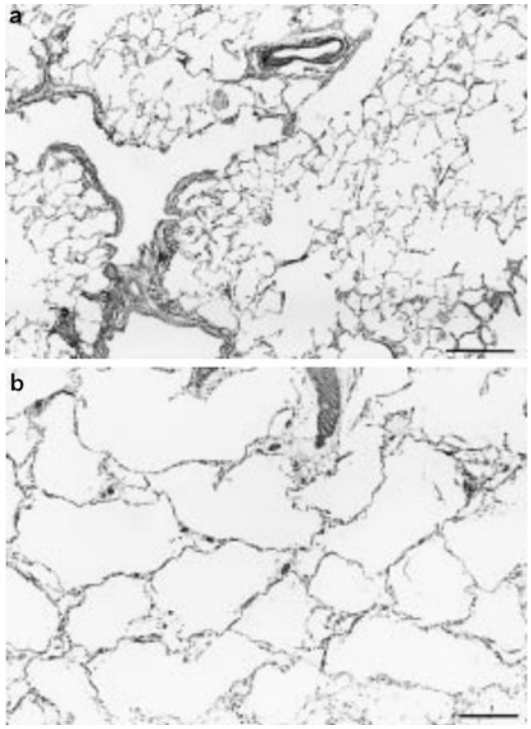

Fig. 5 (**a**) Lung parenchyma from a 29-year-old individual with no history of smoking; (**b**) lung parenchyma from a 100-year-old nonsmoking individual. The alveolar spaces are markedly enlarged as compared to the younger individual in panel a. (Hematoxylin and eosin stain; internal scale bar = 280 mm (**a**); 250 mm (**b**)). (Reproduced with permission from the European Respiratory Society ©. European Respiratory Journal. 1999;13(1):197–205)

(Mckee et al. 2016). Suggested categorization for screening LDCTs along with management recommendations is summarized in Table 3. The ACR's guidelines were retrospectively applied to the National Lung Screening Trial group's method of approaching nodules and demonstrated a decreased false positive rate (12.8% vs. 26.6%) but a lower sensitivity (78.6% vs. 93.8%)(Pinsky et al. 2015).

Some lung cancers are found incidentally on radiographic imaging obtained for other reasons. The Fleischner Society has published guidelines for managing incidentally discovered pulmonary nodules in nonimmunocompromised patients over 35 years (Macmahon et al. 2017). These recommendations stratify risk by nodule type (solid versus subsolid) and further by size (by average diameter) and pretest probability for lung cancer (Table 4).

The guidelines for management of incidental pulmonary nodules should not be used to interpret lung cancer screening LDCT studies, primarily because the pretest probability for lung cancer is higher in the preselected lung cancer screening group. A predictive calculator tool may assist in estimating a nodule's probability of malignancy (Mcwilliams et al. 2013). Increased risk is ascribed to individuals with older age, female sex, a personal history of emphysema, and a family history of lung cancer. Nodule characteristics that impart additional risk are larger size, spiculation, semisolid components, and upper lobe location.

Lung Cancer Diagnosis

Outside of screening or incidental findings, physicians may infrequently suspect lung cancer based on clinical signs or symptoms. However, patients do not typically develop symptoms suggestive of lung cancer until late in the disease course. Symptoms can include cough, chest pain, hemoptysis, clubbing, weight loss, and fever (Spiro et al. 2007). When lung cancer is suspected based on clinical symptoms, one should proceed to chest radiography or contrast-enhanced CT scanning.

If lung cancer is suspected by imaging, the patient may have either a biopsy to obtain tissue for pathologic evaluation and staging, or if radiographic characteristics strongly suggest an early stage cancer (stage IA), proceed directly to surgical resection for diagnosis and curative management. The most commonly used staging system is the TNM (tumor/node/metastasis) classification produced by the American Joint Committee on Cancer (AJCC), recently updated to an 8th edition in 2017 (Tables 5 and 6) (AJCC 2017).

There are two steps of staging lung cancer. First, patients are clinically staged prior to invasive procedures, to determine the best next step. Clinical staging should begin with contrast-enhanced CT imaging of the chest and upper abdomen and brain imaging (Silvestri et al. 2013).

Table 3 LDCT grading and management

Category	Description	Findings	Recommendation
0	Incomplete	Cannot evaluate (poor study, need prior imaging)	Additional images needed (or compare to prior)
1	Negative	No nodules or nodule(s) with benign calcifications	Annual LDCT
2	Benign appearance/ behavior	*Solid nodule(s)*: < 6 mm or new <4 mm *Part-solid nodule(s)*: <6 mm total on baseline screen *Non-solid nodule(s)*: < 20 mm or ≥ 20 mm and unchanged Category 3 or 4 without change for ≥3 months	
3	Probably benign	*Solid nodule(s)*: ≥6–8 mm at baseline or new 4 mm to <6 mm *Part-solid nodule(s)*: ≥6 mm total, solid component <6 mm or new <6 mm total *Non-solid nodule(s)(ground glass)*: ≥20 mm baseline or new	6 month LDCT
4A	Suspicious	*Solid nodule(s)*: ≥8 – < 15 mm baseline or growing <8 mm or new 6 – <8 mm *Part-solid nodule(s)*: ≥ 6 mm with solid component ≥6–8 mm or new/growing <4 mm solid component *Endobronchial nodule*	3 month LDCT, may use PET/CT if ≥8 mm solid component
4B		*Solid nodule(s)*: ≥ 15 mm or new/growing and ≥8 mm *Part-solid nodule(s)*: Solid component ≥8 mm or new/growing solid component ≥4 mm	Chest CT with or without contrast, PET/CT and/or tissue sampling
S	Significant – other	Add on to 0–4 coding	No specific recommendation
C	Prior lung cancer	Add on to 0–4 coding	

Adapted from https://www.acr.org/Quality-Safety/Resources/LungRADS. For multiple nodules, manage based on largest nodule. For follow-up screening findings, refer to the LUNG-RADS guidelines
LDCT low-dose computed tomography, *PET* positron emission tomography, *CT* computed tomography

Table 4 Fleischner criteria for incidental lung nodules

Low risk	
<4 mm	No follow-up
4–≤6 mm	Repeat in 1 year
6–≤8 mm	Repeat 6–12 months
≥8 mm	Repeat at 3, 9, and 24 months Consider PET/biopsy
High risk	
<4 mm	Repeat in 1 year
4–<6 mm	Repeat in 6–12 months
6–≤8 mm	CT at 3–6 months
≥8 mm	CT at 3,9, and 24 months

Adapted from MacMahon et al. (2017)

The evidence for use of whole body positron emission tomography (PET) or PET/CT scans to stage is mixed, and staging decisions should not be made based on PET/CT scan alone. Staging consensus guidelines suggest synthesizing radiographic data to guide tissue biopsy planning (Travis et al. 2011; Murgu 2015). A PET/CT scan may help guide clinicians to biopsy lymph nodes (via endoscopy or mediastinoscopy) or to proceed directly to surgery for resection and surgical/pathologic staging (Schmidt-Hansen et al. 2014).

Table 5 AJCC TNM staging, seventh edition and eighth edition[a] comparison

7th edition	8th edition	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	IA→**IA1**	IIA→**IIB**	IIIA	IIIB
T1 > 1–2 cm	T1b	IA→**IA2**			
T1 > 2–3 cm	T1c	IA→**IA3**			
T2 > 3–4 cm	T2a	IB			
T2 > 4–5 cm	T2b	IB→IIA			
T2 > 5–7 cm	**T3**	IIA→**IIB**	IIB→**IIIA**	IIIA→**IIIB**	IIIB→**IIIC**
T3 structures	**T3**	IIB	IIIA		
T3 > 7 cm	**T4**	IIB→IIIA			
T3 diaphragm	**T4**				
T4	T4	IIIA		IIIB	IIIB→**IIIC**
M1a	M1a	IV→IVA			
M1b (single)	M1b				
M1c (multiple)	M1c	IV→IVB			

Adapted from Goldstraw et al. (2007, 2016)

AJCC American Joint Committee on Cancer, *TNM* tumor, node, metastasis
[a]The 8th edition will not come into clinical practice until January 2018

Table 6 AJCC 8th edition regional lymph node (N) and distant metastasis (M) definitions

Nx	Cannot assess regional lymph nodes
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or hilar lymph nodes and intrapulmonary nodes, including direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal or hilar lymph nodes, or ipsilateral or contralateral scalene or supraclavicular lymph nodes
M0	No distant metastasis
M1a	Metastasis in a contralateral lobe, pleural or pericardial nodule(s), pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

Adapted from Goldstraw et al. (2016)
AJCC American Joint Committee on Cancer

The second step of lung cancer staging is pathologic staging, either surgical with mediastinal lymph node dissection or nonsurgical lymph node sampling. If Stage IB, II, or III is suspected, the preferred diagnostic and staging modality is endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), particularly for centrally located lesions or paratracheal lymph node biopsies. The EBUS-TBNA procedure allows for safe, moderately invasive tissue diagnosis, typically under general anesthesia, with on-site cytologic evaluation (Yasufuku et al. 2005). A 2014 study of 451 patients showed that the risk of complication rates among patients $\geq$70 years was similar to patients <70 years (5.1% vs. 8.7%, respectively, $p = 0.13$), in spite of worse performance status in the older patients ($p < 0.001$) (Evison et al. 2014).

If cancer is diagnosed during the EBUS-TBNA procedure, the disease is further staged during the same procedure by obtaining tissue from contralateral lymph nodes that could "up-stage" the

disease and alter treatment plans. If biopsies from the EBUS-TBNA procedure are negative or inconclusive, and clinical suspicion of regionally advanced disease is high, the patient proceeds to mediastinoscopy or thoracoscopy for regional nodal assessment (Rivera et al. 2013). When lesions are peripheral, the yield by bronchoscopy decreases, and alternative diagnostic methods such as CT-guided transthoracic needle aspiration or video-assisted thoracic surgery (VATS) may be useful. If stage IV lung cancer is suspected based on distant metastases, a more readily available metastatic tissue sample may be obtained, such as from pleural fluid or a superficial lymph node. No matter the diagnostic modality, adequate tissue must be obtained for histologic type and molecular analysis.

Non-Small Cell Lung Cancer

Making Treatment Decisions

Lung cancer treatment planning requires a multidisciplinary approach that integrates expert recommendations from medical oncologists, medical and radiation oncologists, pathologists, thoracic surgeons, pulmonologists, primary care doctors, and geriatricians (Spira and Ettinger 2004). Lung cancer stage along with comorbidities, lung function, and physiologic status informs treatment recommendations that can include surgical resection, single agent chemotherapy, doublet chemotherapy, immunotherapy, targeted driver mutation therapies, radiation, and/or palliative care. Oncologic treatment planning for elderly patients with NSCLC is nuanced, as providers must synthesize guideline-based recommendations with patient preferences and assessments of global function (Gajra and Jatoi 2014).

Traditionally, risk-stratification prior to oncologic treatment interrogated patient fitness for treatment using the Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) score, a 0–5 scale of health symptoms and disability, or the Karnofsky method, a 0–100 scale with more discrimination in disability description (Table 7) (Karnofsky et al. 1948; Oken et al. 1982). The Comprehensive Geriatric Assessment (CGA) has, over the over the last several decades, gained popularity as a more comprehensive risk-stratifying tool for elderly patients with cancer (Extermann and Hurria 2007).

The components of a CGA can vary based on the practice of the administering provider, but typically include a thorough assessment of activities of daily living (ADLs), instrumental activities of daily living (IADLs), comorbidities, functional-based assessments (e.g., 6-min walk test and grip strength), mental health, cognition, nutritional status, social support, and medications/polypharmacy (Table 7). In particular, the CGA adds additional risk information to traditional performance status measures, which often miss IADL disability. For example, a 2005 study of 566 elderly patients with advanced NSCLC found that pretreatment assessments of quality of life and IADLs were associated with improved prognosis (Maione et al. 2005). Assessments of ADLs and comorbidities, the central elements of the Karnofsky and ECOG/WHO scores, did not correlate with prognosis.

These studies support the notion that chronologic age alone should not determine treatment planning. Instead, treatment decisions should be made based on physiologic age, using CGAs such as the Elderly Selection on Geriatric Index Assessment (ESOGIA) (Corre et al. 2016). Treatment-related toxicity can be predicted using the Cancer and Aging Research Group tool (CARG) (Hurria et al. 2011) or Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) (Extermann et al. 2012) tools (Table 7).

Early-Stage NSCLC (Stages I and II)

Early stage lung cancer increases in prevalence with age. In 2005, a large retrospective analysis of 14,555 patients with early-stage NSCLC in the Surveillance, Epidemiology, and End Results (SEER) database revealed that the prevalence of stage I NSCLC increased from 79% in patients less than age 65 compared to 87% in patients older than age 75 (Mery et al. 2005). Five-year relative survival for localized lung cancer is 55% (ACS

Table 7 Pretreatment risk assessments

Traditional performance status measures	
ECOG/WHO (Oken et al. 1982)	Karnofsky[a] (Karnofsky et al. 1948)
0 – Asymptomatic 1 – Symptomatic but completely ambulatory 2 – Symptomatic, <50% in bed during the day 3 – Symptomatic, >50% in bed but not bedbound 4 – Bedbound 5 – Death	100 – Normal; no complaints; no evidence of disease 70 – Cares for self; unable to carry on normal activity or do work 50 – Requires considerable assistance and frequent medical care 20 – Very sick: hospital admission necessary; active supportive treatment necessary 0 – Dead
Chemotherapy toxicity tools	
CARG (Hurria et al. 2011)	CRASH (Extermann et al. 2012)
Age/gender/height/weight Cancer type Number and dosage of chemotherapy agents Falls IADL: Medication management ADL: Walking block Subjective assessment Labs: Hemoglobin/creatinine	Chemotherapy risk *Nonhematologic toxicity*: ECOG PS, MMSE, mininutritional assessment *Hematologic toxicity*: IADL, LDH, diastolic BP
Comprehensive geriatric assessments	
Proposed screening tools (Balducci and Extermann 2000)	ESOGIA CGA (Corre et al. 2016)
Mental status Emotional Status ADL/IADL Home Environment Social Support Comorbidity Nutrition Polypharmacy	PS (ECOG) ADL (0-6) IADL (0-4) MMSE Geriatric Syndrome[b] Charlson comorbidity Index GDS5 (0-5)

CARG scoring: http://www.mycarg.org/Chemo_Toxicity_Calculator
CRASH scoring: https://www.moffitt.org/eforms/crashscoreform
ECOG Eastern Cooperative Oncology Group, *WHO* World Health Organization, *CARG* Cancer & Aging Research Group, *CRASH* Chemotherapy Risk Assessment Scale for High-Age Patients, *ADL* activities of daily living, *IADL* instrumental activities of daily living, *MMSE* Mini-Mental State Examination, *BP* blood pressure, *LDH* lactate dehydrogenase, *GDS5* Geriatric Depression Scale 5, *PS* performance status, *ESOGIA* elderly selection on geriatric index assessment, *CGA* comprehensive geriatric assessment
[a]Abbreviated
[b]Confirmed dementia, repeated falls, or urinary or fecal incontinence

2016), but true pathologic stage I NSCLC may have five-year survival of approximately 80% (Cerfolio and Bryant 2009). However, lung cancer is infrequently diagnosed at a localized stage (16%) (ACS 2016), which is the basis for more aggressive lung cancer screening.

Surgery is the first-line treatment for early-stage lung cancer (stages I and II) (Table 8). If a patient has a potentially resectable lung cancer, multidisciplinary teams perform presurgical risk assessments, to identify patients at high-risk for surgical complications. While age has historically been used as a crude risk-stratification method, recent surgical guidelines by American (Brunelli et al. 2013) and European (Brunelli et al. 2009) societies recommend against using age cut-offs to make surgical decisions. In fact, approximately one-third of lung-resection candidates are over 70 years old. Instead, if a patient has potentially surgically resectable cancer, the patient should be further risk-stratified with appropriate preoperative testing including lung function assessments (Table 1) and evaluation of other comorbidities (Table 7).

Table 8 Suggested non-small cell lung cancer treatment by clinical stage[a]

Stage I and IIA (Local): Lungs only, without lymph node extension
Surgical resection with mediastinal lymph node dissection (if clinical stage IA, may proceed directly to resection for diagnosis, staging, and curative intent surgery)
+/− adjuvant chemotherapy
SABR +/− chemotherapy if inoperable
Stage IIB–IIIA (N0–1) (Regional): Lung and nearby lymph nodes
Preoperative mediastinal staging to determine eligibility for surgical resection
Adjuvant chemotherapy
SABR +/− chemotherapy if inoperable
Stage IIIA(N2)–IIIB (Locally advanced): Extension to central ipsilateral lymph nodes **or** to central contralateral lymph nodes/above clavicle
Role of surgery and neoadjuvant chemotherapy controversial, consider resection if noninvasive tumor and N2 disease eradicated with induction chemotherapy
N3: Definitive chemotherapy and radiation
Stage IV (Metastatic): Extension to both lungs, pleural space, or extrapulmonary site
Early palliative care
Targeted therapies if indicated (ALK, EGFR, ROS1, PD-L1)
Chemotherapy
Immune checkpoint inhibitors
Radiation targeting metastases
Stereotactic radiosurgery for limited brain metastases

Adapted from AJCC seventh edition staging (Goldstraw et al. 2007) and NCCN Clinical Practice Guidelines in Oncology (Version 5.2017): https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Consult guidelines for addition, nuanced detail

SABR sterotactic ablative therapy

[a]Recommend consultation with multidisciplinary team including medical oncologist, thoracic surgeon, radiologist, pathologist, and geriatrician. Treatment plan may be altered by discrepancy between pathologic stage and clinical stage or patient risk-assessment/treatment tolerability

Surgical resection of lung cancer will impact lung function, so presurgical evaluations must include an objective assessment of pulmonary function to calculate predicted postoperative (ppo) FEV_1 and DLCO, which is based on the number of functional segments to be removed (Brunelli et al. 2013). Regardless of lung disease, all patients should have a DLCO assessment in addition to spirometry, because ppoDLCO is strongly correlated with pulmonary complications, even in patients without COPD (Ferguson et al. 2009). Further, testing of a patient's exercise tolerance is pursued if questions remain about a patient's ability to tolerate the surgery, including low technology exercise testing such as 6-min walk testing, shuttle walk or stair climbing, and high technology exercise testing such as cardiopulmonary exercise testing (Table 9).

Interrogating preoperative lung function and calculating ppo lung function is essential to a careful assessment of projected surgical morbidity and mortality. Ferguson et al. demonstrated that, in 854 patients who underwent major lung resection, ppoFEV1 and ppoDLCO were significantly associated with mortality (HR 1.06, 95% CI 1.01–1.12, $p = 0.03$; HR 1.06, 95% CI 1.01–1.12, $p = 0.02$, respectively) (Ferguson et al. 2014). Additionally, the morbidity and mortality (including noncancer mortality) associated with a low ppoDLCO increases with age (Eguchi et al. 2016).

Frailty is an independent risk factor for postoperative complications, length of hospital stay, and discharge to skilled or assisted living facilities in older patients (Makary et al. 2010). Frailty in patients referred for lung cancer surgical resection is under recognized. A 2017 study by Beckert et al. found, in a prospective cohort study of 125 patients referred to an academic thoracic surgical clinic for thoracic surgical procedures, that

Table 9 Presurgical cardiopulmonary assessments

PPO lung function	Further testing	Risk assessment
$FEV_1 > 60\%$ and DLCO >60%	Not indicated	**Low risk**
FEV_1 or DLCO 30–60% predicted	"Low technology" exercise test (e.g., stair climbing or shuttle walk)	**Low risk** if stair climbing altitude >22 m or shuttle walk distance >400 m
FEV_1 and/or DLCO <30% predicted	"High technology" exercise test (e.g., cardiopulmonary exercise test)	**Low risk** if VO2 peak >20 ml/kg/min (or 75% predicted) **High risk** if VO2 peak <10 ml/kg/min (or 35% predicted)

Adapted from Brunelli et al. (2013)
PPO postoperative lung function, *FEV_1* forced expiratory volume in 1 second, *DLCO* diffusing capacity of the lung for carbon monoxide, *VO2* peak oxygen consumption

12% were frail and 57% were prefrail based on an adapted Fried's phenotypic frailty assessment (Beckert et al. 2017).

Various presurgical assessments of physical robustness have been explored in an effort to achieve greater precision in presurgical risk stratification. Tsiouris et al. created an 11-item modified frailty index (mFI) adapted from the Canadian Study of Health and Aging Frailty Index, a 70-item scale that predicts survival using preoperative data from the National Surgical Quality Improvement Program (NSQIP) (Tsiouris et al. 2013). Items in this index included functional status and co-morbidities (e.g., diabetes, COPD, and cardiovascular disease). The authors found that morbidity and mortality increased as mFI increased in patients who had undergone an open lobectomy. This study suggests that an objective approach to assessing preoperative frailty may improve upon single-organ assessments.

Sublobar resection may not improve long-term survival when compared to lobectomy; however, this has not been demonstrated prospectively. In 2014, Shirvani et al. retrospectively analyzed patients with early-stage NSCLC undergoing curative surgical therapy (mean age 75 years, $n = 9093$) in the SEER database. Most (79.3%) patients underwent lobectomy, while 16.5% underwent sublobar resection and 4.2% underwent stereotactic ablative radiotherapy (SABR) (Shirvani et al. 2014). Unadjusted 90-day mortality was highest for patients who underwent lobectomy (4.0%) as compared to the other two groups (sublobar resection, 3.7%, $p = 0.79$; SABR, 1.3%, $p = 0.008$). However, 3-year unadjusted mortality was lowest for patients who underwent lobectomy (25.0%) as compared to the other two groups (sublobar resection, 35.3%, $p < 0.001$; SABR, 45.1%, $p < 0.001$). Propensity score matching between sublobar resection and lobectomy groups demonstrated worse survival for the sublobar resection groups.

When comorbidities or patient preferences contraindicate surgical resection of an early stage tumor, other options include observation/best supportive therapy or SABR (Table 8). Median survival without surgical resection in patients with early stage disease is poor, with one estimate suggesting survival of 14.2 ± 2.37 months (Mcgarry et al. 2002). In Shirvani et al.'s study, a propensity score-matched analysis of SABR and lobectomy groups, showed a similar overall survival, suggesting that SABR is indicated in patients who cannot tolerate surgical risk (Shirvani et al. 2014). Further, a pooled analysis of two small randomized trials comparing SABR to surgical resection suggests that the two treatments may be equally effective, and that SABR may be preferred in individuals with multiple comorbidities (Chang et al. 2015). In 55 patients with T1 or T2 tumors, stereotactic body radiation therapy without resection had a 3-year local control rate of 90.6% (95% CI, 76.0–96.5%) and a local-regional control rate of 87.2% (95% CI, 71.0–94.7%). The median survival was 48.1 months, with a 55.8% survival rate at 3 years (Timmerman et al. 2010).

Adjuvant therapy with postoperative cisplatin-based doublet chemotherapy for stage

IIA to IIIA is standard of care (Pisters et al. 2007). A 2004 study of 1867 patients treated with cisplatin-based adjuvant chemotherapy following surgical resection showed 44.5% survival at 5 years as compared to 40.4% in the observation group ($p < 0.03$) (Group 2004). Cuffe et al. examined the Ontario Cancer Registry to assess the benefit of adjuvant chemotherapy on older age groups (<70, 70–74, 75–79, and ≥80) (Cuffe et al. 2012). This analysis found benefit of adjuvant chemotherapy in all age groups except for those ≥80 years. The main concerns with using cisplatin-based doublet therapy in older adults are the adverse side effects of renal and ototoxicity, requiring intravenous hydration pre- and postinfusion. It is also highly emetogenic, requiring adequate antiemetic support. Risk stratification taking organ function, social support, transportation, and medication management into account prior to selection of cisplatin is mandatory to prevent severe toxicity. Carboplatin is often substituted for cisplatin for high-risk older adults.

Locally Advanced NSCLC (Stage III)

Concurrent chemoradiation is indicated for curative-intent treatment of locally advanced NSCLC: stage IIIA medically inoperable or stage IIIB (Bezjak et al. 2015). However, for more frail, high-risk older adults, sequential chemotherapy followed by radiation is also an option. The 5-year relative survival rate for regionally advanced lung cancer is 28% and for distant metastatic lung cancer is 4% (ACS 2016). Surgical resection and neoadjuvant chemotherapy are controversial in patients with stage III, N2 cancers. In some centers, patients with adequate performance status and acceptable surgical risk proceed to surgery if the tumor is noninvasive and the N2 disease is completely resectable. Other centers recommend presurgical eradication of N2 disease with induction chemotherapy before proceeding to surgery (Van Meerbeeck et al. 2007; Albain et al. 2009).

There is limited strong, prospective evidence to guide surveillance of patients who have undergone curative intent therapy. Current guidelines suggest that patients who have undergone surgical resection of NSCLC have a follow-up chest CT every 6 months for 2 years, then yearly (Colt et al. 2013). When surveillance becomes yearly for the curative-intent cohort, it mimics the screening suggested for eligible patients in the new lung cancer screening guidelines (Table 3). Just as is suggested in the screening cohort, providers should reevaluate patient wishes to continue surveillance when comorbidities or functional status alter patient preferences to undergo further cancer work-up or therapy, if disease recurrence is identified on imaging.

Metastatic NSCLC (Stage IV)

Most lung cancer is diagnosed at an advanced, metastatic state of disease. Currently, the treatment for advanced NSCLC is expanding rapidly and includes targeted treatments and immunotherapy in addition to traditional chemotherapy, the original mainstay of treatment for advanced disease. All metastatic lung cancer biopsy specimens should undergo molecular marker testing for the EGFR mutation, anaplastic lymphoma kinase (ALK) rearrangement, or ROS1 translocation (Lindeman et al. 2013), to determine if driver mutation-targeted therapies can be used. In a small study of 32 patients (median age 80 with NSLC and the EGFR mutation) treated with the EGFR tyrosine kinase inhibitor erlotinib, this drug was well-tolerated and had similar efficacy (56.3% response rate) as compared to a prior study of a mixed-age cohort (58.1% response rate) (Rosell et al. 2012; Inoue et al. 2015). The most frequent adverse event was skin-related toxicity. A separate study of erlotinib versus placebo in 731 patients compared outcomes based on age (<70 years or ≥70 years). The older age group had similar survival as compared to the younger group but experienced more severe (grade 3/4) toxicity. For ALK positive tumors, ALK tyrosine kinase inhibitors (e.g., crizotinib or ceritinib) are superior to standard chemotherapy (Solomon et al. 2014; Shaw et al. 2014). Tumors with the

ROS1 rearrangement should be treated with crizotinib (Bergethon et al. 2012).

Immunotherapy utilizing checkpoint inhibitors such as programmed death-1 (PD-1) inhibitors is beginning to emerge as an important pillar of treatment in NSCLC. PD-1 inhibitors have a survival benefit as compared to first-line platinum-based doublet chemotherapy or second-line chemotherapy after treatment failure with doublet therapy. Two pivotal studies in 2015 demonstrated increased overall survival in patients treated with the PD-1 inhibitor nivolumab, as compared to docetaxel, in previously treated, advanced squamous-cell NSCLC regardless of PD-L1 expression (Brahmer et al. 2015) and previously treated, advanced nonsquamous NSCLC (Borghaei et al. 2015). Reck et al., in 2016, then demonstrated superiority of the PD-1 inhibitor pembrolizumab as compared to platinum-based chemotherapy, in untreated NSCLC (both squamous and non-squamous), in which at least half of the tumor cells were PD-L1 positive but ALK and EGFR negative (Reck et al. 2016). Progression-free survival was 10.3 months in the pembrolizumab group as compared to 6.0 months in the chemotherapy group. Importantly, overall survival was significantly longer in the group treated with pembrolizumab (HR 0.6, 95% CI 0.41–0.89, $p = 0.005$). Six-month survival was 80.2% for those treated with pembrolizumab compared to 72.4% in the chemotherapy group. Additionally, there were fewer treatment-related adverse events in the pembrolizumab group. Though promising, these results have yet to be replicated in large population-based studies. As clinical trials include younger, healthier adults, evidence of improved overall survival and decreased toxicity among frail older adults is needed.

Cytotoxic platinum-based chemotherapy is the first-line treatment for the majority of advanced NSCLC without a molecular mutation with a targeted therapy (Table 8). Standard chemotherapy consists of two agent (doublet) therapy with a platinum agent (e.g., cisplatin or carboplatin) plus a second agent (e.g., docetaxel, paclitaxel, gemcitabine, etoposide, irinotecan, or vinorelbine) (Masters et al. 2015). Several studies have shown efficacy of chemotherapy treatment in elderly patients with lung cancer. A 2011 multicenter study of 451 patients aged 70–89 years with locally advanced or metastatic NSCLC and good performance status (WHO performance status 0–2) found that platinum-based doublet chemotherapy improved survival (10.6 months) compared to monotherapy (6.2 months) with vinorelbine or gemcitabine (Quoix et al. 2011). The patients who underwent doublet chemotherapy experienced significantly more side effects, particularly cytopenias and neuropathy.

Histologic subtyping of NSCLC helps determine the preferred first-line cytotoxic chemotherapy agents. A study by Scagliotti and colleagues in 2008 found a significant survival benefit for patients with squamous cell carcinoma treated with cisplatin/gemcitabine (10.8 months) versus cisplatin/pemetrexed (9.4 months) (Scagliotti et al. 2008). In patients with adenocarcinoma, treatment with cisplatin/pemetrexed is preferred (12.6 months compared to 10.9 months). High-grade cytopenias were significantly higher with cisplatin/pemetrexed treatment.

Bevacizumab, an antibody that inhibits vascular epithelial growth factor A (VEGF-A), improves survival in patients with metastatic non-squamous NSCLC, in combination with platinum-based doublet therapy (Sandler et al. 2006). Data supporting its efficacy in elderly patients has been inconclusive, and increased adverse events (including death) appear to be significantly higher (Ramalingam et al. 2008). Therefore, the increased risk in older populations may outweigh potential benefits. Bevacizumab is not used in squamous cell lung cancer due to the increased risk of serious hemorrhagic events.

Even when patients cannot have surgical resection either due to advanced disease, risk stratification by performance status and CGA remains important, as chemoradiation therapies carry risk of serious toxicities. Elderly patients are a potentially vulnerable patient population to experience treatment-related toxicities, and oncologists have struggled with both overtreatment and undertreatment when caring for individuals with NSCLC (Presley et al. 2016). A 2010 retrospective study of the SEER Medicare database

revealed that many elderly patients with advanced NSCLC do not receive chemotherapy in spite of survival benefits in those who do (Davidoff et al. 2010).

The first evidence that undertreatment impairs patient quality of life came in 1999, when the Vinorelbine Italian Study Group presented data that, in patients over age 70 with stage IV or IIIB NSCLC ineligible for radiotherapy with good performance status, treatment with six 21-day cycles of vinorelbine (a vinca alkaloid) significantly improved survival (Group 1999).Cognitive function was better in the vinorelbine group, and they reported less pain and dyspnea. They did report worse constipation, nausea/vomiting, hair loss, and peripheral neuropathy.

Elderly patients are an at-risk group with potentially more comorbidities and functional impairments that can impact chemoradiation tolerance. Hurria et al. found that 53% of older adults experienced at least one grade 3–5 toxicity during the course of treatment across cancer types and stages (Hurria et al. 2011). A 2015 retrospective study of the SEER registry demonstrated a significant burden of toxicity on elderly patients (70 years or older) with advanced NSCLC undergoing therapy (Kale et al. 2017). Patients with stage IIIB had a nearly sixfold increase in toxicities with chemoradiation compared to those who received no treatment. The most common toxicity was esophagitis. Stage IV patients had a nearly fourfold increase in toxicities with chemotherapy, most commonly neutropenia. This study was limited by the lack of analysis by chemotherapy agent or doublet versus singlet therapy.

Rarely, chemotherapy agents and radiation therapy can cause toxicity to the lungs directly, which can include pneumonitis or acute respiratory distress syndrome (Read et al. 2002; Parashar et al. 2011). Pulmonologists crowd source and catalog treatment-related lung toxicity at www.pneumotox.com (Camus et al. 2013). Checkpoint inhibitor-related pneumonitis is an uncommon but highly morbid complication of use that is rising in prevalence with increased use of these agents. Pneumonitis is estimated to occur in 5% of patients, with onset ranging from 9 days to 19.2 months following treatment (Naidoo et al. 2017).

Improvements in risk stratification, to limit toxicities while maximizing therapy benefit, are ongoing. A 2016 study by Corre et al. assigned patients with advanced NSCLC (median age 77 years, n = 494) to chemotherapy regimens based either on performance status or CGA (Corre et al. 2016). In the standard arm, patients were assigned based on performance status; if PS $\leq$ 2 and age $\leq$ 75, patients received carboplatin-based doublet chemotherapy, and if PS =2 or age > 75 they received docetaxel. In the CGA group, "fit" patients received carboplatin-based doublet, "vulnerable" patients received docetaxel, and "frail" patients received best supportive care. In summary, patients assigned to treatment based on CGA experienced significantly less treatment toxicity, with similar overall survival and treatment failure free survival.

Joint decision-making with patients is important. Discussions should include careful counseling about expected toxicities including the likelihood of functional or cognitive impairment. Projected toxicities may influence a patient's advanced care planning more than risk of death (Fried et al. 2002). Treatment-related toxicities in older patients receiving chemotherapy can be predicted using the CRASH (Extermann et al. 2012) or CARG (Hurria et al. 2011) calculators (Table 7). Risk calculators for both targeted treatments and immune checkpoint inhibitors are needed.

Finally, palliative care should be a cornerstone of caring for patients with metastatic (stage IV) lung cancer (Table 8). In addition to improving symptom control, palliative care can also increase survival. A revolutionary study by Temel and colleagues in 2010 demonstrated that, in patients with metastatic NSCLC, an early palliative care intervention led to increased median survival compared to standard care (11.6 vs. 8.9 months p = 0.02 (Temel et al. 2010). On average, patients who received early palliative care had received less aggressive care than the standard treatment group (33% vs. 54%, p = 0.05) and noted better quality of life and less depression and anxiety. The

palliative care intervention consisted of guideline-based visits with a dedicated palliative care team, including board-certified palliative care advanced practice nurses and physicians, who met with the patient at least monthly and attended particularly to "physical and psychosocial symptoms."

Lung cancer-related symptoms are wide-ranging and can be debilitating. A frequent lung cancer symptom is dyspnea due to cancer-related etiologies that include pneumonia, pulmonary emboli, metastatic pleural effusions, or superior vena cava syndrome. Care teams can track dyspnea symptoms using clinical dyspnea scales (Table 2). Other symptoms include sequelae of metastases (e.g., bone pain and neurologic impairment), depression, anxiety, insomnia, and fatigue (Simoff et al. 2013). Rarely, airway-esophageal fistulas and paraneoplastic syndromes can occur. Palliative care teams experienced in treating these symptoms are invaluable partners in patient care.

Other Lung Malignancies

Small Cell Lung Cancer

Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy comprising about 15% of all lung cancers (ACS 2016). Unlike NSCLC, the malignant cells are characterized by rapid growth and initial sensitivity to chemotherapy and radiation that later becomes resistant to treatment (Rudin et al. 2015). It is strongly associated with a history of smoking. Classic staging for SCLC uses the Veterans Administration system of limited or extensive stage disease, though the AJCC TNM staging system is recommended due to improved prognostic discriminatory power (Micke et al. 2002; Jett et al. 2013). In limited stage disease, the cancer is localized to the ipsilateral hemithorax and regional lymph nodes. Extensive disease includes any spread beyond, such as distant metastases. Staging should be performed radiographically (head MRI/CT and PET) as well as invasively (EBUS or mediastinoscopy) if patients are being considered for curative intent surgical resection.

In stage I disease, which is uncommon, adjuvant chemotherapy should be administered following surgical resection. In limited stage disease, early chemotherapy with radiotherapy is recommended. The foundation of treatment is combination chemotherapy, typically including a platinum agent (e.g., carboplatin or cisplatin) (Rudin et al. 2015). Whether a patient has limited or extensive stage disease, prophylactic cranial irradiation is indicated. However for older adults, cranial irradiation can cause acute, subacute, and long-term impairments to cognition, a particularly pertinent side effect for elderly populations (Robbins et al. 2012).

A 2011 retrospective study of chemotherapy tolerability in the Netherlands looked at 368 patients with limited stage SCLC and 577 with extensive stage SCLC, all 75 years old or older (Janssen-Heijnen et al. 2010). Many patients (48%) did not receive chemotherapy for a wide range of reasons, including poor performance status or patient preference. Up to 75% of all patients undergoing chemotherapy developed a serious toxicity and two-thirds could not complete treatment. Survival is extremely limited without chemotherapy treatment, so even patients with impaired performance status are typically treated (Pelayo Alvarez et al. 2009).

Other Neuroendocrine Tumors, Mesothelioma, and Pulmonary Metastases

Less common malignancies of the respiratory system include malignant mesothelioma and other lung neuroendrocrine tumors such as carcinoid (bronchial neuroendocrine) tumors and large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinoma, like small cell lung cancer, has a poor prognosis and 5-year survival across all stages is approximately 35.3% (Fasano et al. 2015). Treatment can include surgical resection in early stage disease, with adjuvant chemotherapy.

Bronchial neuroendocrine (carcinoid) tumors are indolent tumors that have increased in incidence since the 1980s. Age 60 or greater strongly

predicts mortality (Perez et al. 2007). Localized disease is typically managed with surgical resection and data on adjuvant chemotherapy is mixed. Metastatic disease is treated with first with a somatostatin analog, with everolimus as second-line therapy. Cytotoxic chemotherapy if everolimus fails to control disease. A complication of carcinoid tumors is carcinoid syndrome, which can be treated with somatostatin analogs (e.g., octreotide) (Pavel et al. 2011).

Mesothelioma is an asbestos-associated malignancy, that presents insidiously (Van Zandwijk et al. 2013). The average age of diagnosis is over age 60, implying a disproportionate burden of disease on elderly patients. The average overall survival is 7 months. Malignant mesothelioma is typically treated with two-agent platinum-based chemotherapy. Surgical debulking can palliate symptoms. Radiotherapy is a cornerstone of palliative treatment, both to control symptoms and prevent relapse following surgery. Pleurodesis can be useful to manage recurrent malignant effusions.

The lung and pleural space is a frequent site of metastatic disease from non-lung primary cancers, including breast, colon, ovarian, bladder, and melanoma (Nguyen et al. 2009). In addition to chemotherapy or radiation to treat these metastatic lesions (Rusthoven et al. 2009), further palliative management may be indicated. Interventional pulmonologists can assist with palliative management using stent placement or laser therapy to treat endobronchial lesions or bronchial compression from surrounding tumor (Cavaliere et al. 1996). Pleurodesis or long-term indwelling pleural catheters may be used to manage malignant pleural effusions (Van Meter et al. 2011).

Conclusion

Maximal pulmonary function declines with aging, beginning in the third decade of life (Table 10). The natural history of lung aging involves progressive decline in lung elasticity leading to increased lung volumes and an obstructive spirometric pattern. Respiratory muscle weakness and changes to the architecture of the thorax can concomitantly cause a restrictive pulmonary function pattern. When evaluating pulmonary function testing in the geriatric patient, one must consider the natural history of lung changes so as to avoid overdiagnosis of lung disease.

Chronic obstructive pulmonary disease has been described as a disease of accelerated aging, though recent evidence indicates that a subset of affected patients has abnormal lung development with normal lung aging. Both COPD and IPF share pathogenic cellular features in common with lung cancer, including telomere attrition, defective DNA repair, genomic instability, cellular senescence, stem cell exhaustion, and mitochondrial dysfunction.

Lung cancer is the deadliest malignancy in the USA, and its prevalence increases with age. Non-small cell lung cancer is the most common of lung cancer and adenocarcinoma is the most common histologic type. Depending on the stage at diagnosis, treatment options for NSCLC can include surgical resection, single agent chemotherapy, doublet chemotherapy, immunotherapy, targeted driver mutation therapies, and/or radiation.

For early-stage NSCLC that amenable to surgical resection, patients must have presurgical pulmonary function testing with calculation of predicted postoperative lung function. Depending

Table 10 Key points

Lung aging begins in the third decade of life
COPD, IPF, and lung cancer share pathogenic cellular features, including telomere
Attrition, defective DNA repair, genomic instability, and cellular senescence
Lung cancer is the deadliest of all malignancies
Screening for lung cancer is recommended for high-risk patients (age 55–80 with $\geq$30 pack-year smoking history)
Comprehensive geriatric assessments prior to treatment limit toxicities and may improve survival
Early palliative care should be initiated for all patients with stage IV lung cancer

on the FEV_1 and/or DLCO, patients may require "low technology" (e.g., stair climbing or shuttle walk) or "high technology" (e.g., cardiopulmonary exercise testing) to determine their cardiopulmonary fitness for surgery. Frailty is under recognized, and frail patients have more surgical complications. Adjuvant chemotherapy can improve outcomes.

First-line treatment for advanced NSCLC is driver mutation-targeted therapy if eligible, against ALK, EGFR, ROS1, and/or PDL-1. Most patients do not have these mutations, so doublet platinum-based therapy is their first line treatment. Single-agent or no chemotherapy is reserved for patients with poor performance status or high-risk as determined by a Comprehensive Geriatric Assessment. In metastatic NSCLC, palliative care must be a cornerstone of best supportive care. Given the profound burden of lung cancer on geriatric patients, pretreatment global functioning should be evaluated for risk-stratification and to guide treatment decisions. Traditional risk-stratification relied on assessing performance status with either Karnofsky or ECOG/WHO tools. Variations of the Comprehensive Geriatric Assessment are gaining ground as methods for risk-stratifying patients prior to cancer treatment. Risk stratification based on CGA can lead to decreased treatment toxicity with similar or improved survival.

Avoiding undertreatment in fit elderly patients and overtreatment in vulnerable subgroups remains the shared goal of clinical partnerships between primary care providers, geriatricians, medical oncologists, thoracic surgeons, and pulmonologists. As evidence accumulates about how best to assess pretreatment global fitness, physicians must adopt a shared-decision making strategy, incorporating patient preferences into treatment decisions.

Cross-References

- ▶ Lung Cancer in Older Adults: Local Treatment
- ▶ Lung Cancer in Older Adults: Systemic Treatment

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Digestive Organ Aging and Cancer

16

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Abstract

Digestive cancer is extremely frequent and is the third cause of cancer in both sexes. Prevalence is mainly in older adults with more than half of the incidence above 75 years, and diagnosis in the elderly is done at more advanced stages.

Management is complex with intensive treatments combining all available anticancer modalities of treatment depending on stage: major surgery, radiotherapy, chemotherapy, radio-chemotherapy, targeted therapy, etc. Comprehensive geriatric assessment is an essential step in this population to assess the feasibility of available treatments and the possible supportive care. So geriatric status (frail or robust) influences the final treatment decision.

If specific recommendations of management have been elaborated for older adults in colorectal cancers, efforts need to be made to produce management guidelines for other digestive cancers.

Keywords

Digestive cancers · Aged · Geriatric oncology · Management · Treatment · Geriatric evaluation

Introduction

Digestive cancers represent a high burden of morbidity and mortality worldwide. Colorectal cancer (CRC) is the third most commonly diagnosed cancer, with 1.36 million of cases after lung and breast cancers. Liver cancer (745,000 deaths per year) and stomach cancer (723,000 deaths per year) are the second and the third, respectively, causes of death by cancer after lung cancers worldwide (Ferlay et al. 2015).

Most digestive cancers occur in an elderly population. For example, in Europe, 70% of CRCs occur in patients aged above 65 years old and 46% in patients aged above 75 years old (Institut de veille sanitaire 2018). This high prevalence is similar in other digestive cancers: 23.8% for esophageal cancers, 46.1% for gastric cancers, 27.6% for liver cancers, and 37.1% for pancreatic cancer (Institut de veille sanitaire 2018).

One critical issue facing medical science concerns the aging population. This often vulnerable group poses significant challenges with regard to address its healthcare needs.

Indeed, these patients have more often comorbid conditions and are more often diagnosed at a later stage of cancer than in younger patients

(Vercelli et al. 2000). As a result, management strategy should be adapted to the incidence of adverse treatment reactions such as morbidity and mortality (Colorectal Cancer Collaborative Group 2000).

Impact of Age on the Management Strategy of Digestive Cancers

The core principles of oncology in treatment and management of digestive cancers are similar in an older population. Given the lack of data in elderly patients, specific therapeutic strategies are difficult to establish. This population is often underrepresented in clinical trials due to their comorbidities, disability, and physiological changes (Aparicio et al. 2016a).

Because the elderly population is often more heterogeneous, chronological age is not a relevant marker for measuring healthy aging. The patient's physiological age should be ideally evaluated through a comprehensive geriatric assessment (CGA) (Caillet et al. 2014; Extermann et al. 2005) as recommended by the International Society of Geriatric Oncology (SIOG).

Comprehensive geriatric assessment evaluates functional status, mobility, comorbidities, polypharmacy, nutritional status, cognitive function, emotional status, and social support based on validated geriatric scales. The purpose of this evaluation is to identify healthy patients from vulnerable patients to adapt cancer treatment. Evaluating the benefit-risk ratio in treating older patients allows a more tailored approach between a recommended treatment and the best supportive care.

Moreover, contraindication for surgery is evaluated as well as the risk of adverse outcomes of chemotherapy. Therapeutic decision-making in an older population should take into account the nature and the extension of the tumor as well as an integrative geriatric approach where quality of life is preferred to survival. Thus, patient preference in treatment decision is essential (Fig. 1).

Digestive Surgery and Age

Surgery remains the most important part of the treatment in digestive cancer. Indeed, it is the only curative treatment and should be proposed when it is feasible. Moreover, in a palliative situation, surgery can avoid or treat intestinal obstruction and improve patient's quality of life. Older patients are often undertreated compared to younger patients (Colorectal Cancer Collaborative Group 2000).

- There is currently no geriatric screening tool which can identify if the old patient is treatable; each tool screens patients at high risk of complications (Duron et al. 2011).
- Necessity of a CGA, which can assess the patients' comorbidities, functional status, presence of cognitive dysfunction, and frailty, which are consistently associated with adverse treatment outcomes in relation to both toxicity and mortality (Sungurtekin et al. 2004).
- A geriatric assessment leads to modify treatment decision making in up to 20–50% of elderly patients (Lee et al. 2016).
- If CGA is not feasible due to lack of a geriatrician or lack of time, a rapid screening evaluation should be considered. The G8 screening tool (especially designed for a geriatric oncology population) has a good sensitivity (90%) but a poor specificity (23%) (Kristjansson et al. 2010; PACE participants et al. 2008).

Fig. 1 Principles of geriatric evaluation underlined by the SIOG (Nascimbeni et al. 2009)

Thus, surgery feasibility needs to be measured by a geriatric evaluation, to take into account underlying risk factors of perioperative morbidity and mortality and to anticipate potential complications.

Impact of Geriatric Evaluation in Digestive Cancer Surgery

If age remains the main risk factor of perioperative mortality after colorectal surgery, this operative risk has decreased these last 20 years (Nascimbeni et al. 2009). In major digestive surgery, the risk of postoperative mortality increases with age. This risk is multiplied by 2.21 (95% CI: 1.36–3.59; $p = 0.001$) in patients aged above 65 years old and especially in patients above 85 years old (Duron et al. 2011). Many studies have demonstrated major risk factors of poor surgical outcomes associated with age. Indeed, risk factors of poor surgical outcomes are better known and must be taken into account:

- Nutrition

  Nutrition in elderly digestive cancers is a major prognostic factor. The prevalence of malnutrition is estimated about 40% in the elderly hospitalized patients and increases the risk of poor surgical outcomes from 1.92 to 9.85 depending on the assessment nutrition tool. There is an increase of prolonged hospital stays, morbidity, and mortality for patients undergoing elective gastrointestinal surgery (Sungurtekin et al. 2004).
- Functional Status

  In a study including 270 patients ≥70 years (mean age 76.7 years), patients who impaired at least 2 domains of CGA had an odds ratio at 2.1 to develop postoperative complications (Lee et al. 2016). In these domains, disability is a crucial predictor of a poor postoperative outcome. Cancer patients defined as being functionally dependent according to the validated instrumental activity of daily living were found to have a two- to threefold increased risk of postoperative morbidity compared with those defined as independent (Kristjansson et al. 2010; PACE participants et al. 2008).
- Sarcopenia

  Sarcopenia is independently predictive of postoperative infections (OR = 4.6; 95% CI: 1.5–13.9) and geriatric rehabilitation stay (OR = 3.1; 95% CI: 1.04–9.4) and significantly associated with a prolonged length of hospital stay (15.7 ± 9.8 days vs. 11.8 ± 6.4 days for non-sarcopenic patients) in older CRC patients (Lieffers et al. 2012). A systematic review showed that sarcopenia and sarcopenic obesity impact outcomes of surgery in all digestive cancers (Mei et al. 2016).
- Physical Frailty

  Physical frailty defined by Fried criteria (weight loss, gait speed, grip strength, physical activity, and physical exhaustion) increases the risk of major complications following surgery of colorectal cancer [odds ratio (OR) 4.1 (1.4–11.6)] (Tan et al. 2012).
- Dementia

  In a large cohort of 207,693 patients aged above 60 who underwent major surgery, Hu et al. showed that patients with dementia had a significantly higher overall postoperative complication rate compared with controls (adjusted OR = 1.79; 95% CI: 1.72–1.86) (Hu et al. 2012).
- Comorbidities

  Certain comorbid conditions like 6-month weight loss ≥20%, smoking >20 cigarettes/day, an underweight condition, and cardiac arrhythmias showed a better predictive value on survival in colorectal cancer compared with other comorbidities in the Charlson index (Marventano et al. 2014; Janssen-Heijnen et al. 2007; Lemmens et al. 2005). However, an overall high Charlson index is predictive of perioperative complications.

Impact of Surgical Treatment on Elderly Patients

- Surgical treatment modalities as well as certain geriatric conditions may impact patient's perioperative outcomes:
- Laparoscopic surgery versus laparotomy

  A meta-analysis including 7 studies and 845 patients show that laparoscopy reduces intraoperative blood loss, time to first

ambulation visit, time to first oral intake, postoperative hospital stay, overall postoperative complication rate (odds ratio (OR) 0.39; 95% CI: 0.28–0.55; $P < 0.01$), surgical complications (OR 0.47; 95% CI: 0.32–0.69; $P < 0.01$), medical complications (OR 0.35; 95% CI: 0.22–0.56), and pulmonary infections (OR 0.49; 95% CI 0.26–0.93; $P = 0.03$) (Wang et al. 2016).

- Emergency treatment versus elective surgery

  Emergency surgery is associated with a rate of mortality of 16% in patients aged above >65 years old, and mortality increases up to 30% in patients aged above ≥80 years old (Modini et al. 2012).

Fast-Track Surgery and Prehabilitation in Digestive Surgery for Aged Patients

Since the 1990s, the multimodal rehabilitation (MMR) or fast-track (FT) surgery has shown multiple benefits on postoperative outcomes compared to usual care in older patients. The aim of this specific care is to combine patient education before surgery, stress reduction by the use of new anesthetics, analgesic and pharmacologic techniques, minimally invasive surgery, and a revision of fundamental postoperative care principles (use of tubes, drains, catheters, monitoring devices, early oral nutrition, mobilization, etc.) in order to define an active perioperative multimodal rehabilitation program (Wanden-Berghe 2016). A systematic review on fast-track care and nutritional rehabilitation, in CRC surgery in adults (16–94 years), shows that FT groups had an early bowel recovery ($p < 0.01$), less infections, less mortality, and shorter hospitalization stays compared to patients in usual care, thus showing the same benefits as in younger patients (Bagnall et al. 2014).

The nutrition management with immunonutrition (enteral nutrition with supplemental arginine) administered before and after surgery has shown a decrease in postoperative infections in colorectal surgery (Wanden-Berghe 2016).

If fast-track surgery improves surgical outcomes, recent articles show that prehabilitation surgery fails to show a benefit in elderly colorectal cancer patients (Montroni et al. 2018).

Chemotherapy and Age

Advance in age increases chemotherapy toxicity by decreasing physiologic reserves (decrease liver function, kidney function, and bone marrow function) or interaction with comorbidities and geriatric syndromes.

Extermann et al. and Hurria et al. showed that more than 50% of patients aged above 70 years old with first line of chemotherapy (especially for colorectal cancer) experienced at least one grade 3–4 toxicity. Most of the risk factors for chemotoxicity in this study were geriatric factors such as functional status, cognitive function, and nutrition. Another major risk factor is the chemotherapy intensity measured by MAX2 index (Extermann et al. 2012). Moreover, geriatric assessment reveals undiagnosed geriatric problems in more than 50% of elderly patients with cancer and thus can modify chemotherapy regimens in 21–53% of patients (Versteeg et al. 2014).

Colon Cancer

Treatment options for colorectal cancer in elderly patients are guided by clinical practice guidelines (Papamichael et al. 2015).

Surgery

See Fig. 2 and Table 1.

Local Cancer (Stages I and II)

The principles of surgical excision consist of a minimum of 5–10 cm of normal bowel that should be resected on either side of the primary colon tumor as well as lymph node dissection and mesocolon resection. Proximal and distal margins of resection must be adequate they imply at least a 1 cm margin. Celioscopic resection is advised and analysis of minimum of 12 lymph nodes is required. For very early stage, endoscopic resection in situ or intramucosal and submucosal is sufficient.

Stage II colon cancer is characterized by a low risk of recurrence, and chemotherapy improved 5-year survival rate from only 2% to 3%.

1. **Identify frail to fit patients by a comprehensive geriatric evaluation** (Van Cutsem et al. 2014).
2. **In frail patients,** a **prehabilitation program or fast-track management should be considered.**
3. **Anticipate bowel obstruction to reduce emergency to a minimum** and, in the case of obstructive disease, alternative procedures such as the construction of a diverting stoma or stenting, if cure is not the aim, must be considered.
4. **Anticipate and use with careful consideration the siting of the stoma.**
5. **Avoid the combination of an emergency procedure with a major resection or multimodality treatment.**
6. **Inform patients (especially high-risk patients) and their families** about the risks of possible functional impairment and oncological outcome before consenting to a treatment plan.
7. **Offer an alternative option for high-risk patients** ranging from no tumor-controlling treatment at all, to palliative treatment.

Fig. 2 The SIOG recommendations for personalized surgical management for elderly colorectal cancer patients (Cassidy et al. 2010)

Table 1 Principles of colon cancer treatment in the elderly

Stage of cancer	Treatment recommendations	Specificities for elderly patients
Stage I: T1–T2 N0 M0	**Radical surgery:** complete resection with at least a 5 cm margin, mesocolon resection, and lymph node dissection with an analysis of at least 12 lymph nodes	An increased risk of complications with age An increased risk of morbidity and mortality perioperative
Stage II: T3–T4 N0 M0	**Surgery +/− adjuvant chemotherapy**	**No evidence of benefits for using adjuvant chemotherapy** especially in the elderly Adjuvant chemotherapy is however often proposed for pMMR patients
Stage III: T1–T4 N1–N2 M0	**Surgery and adjuvant chemotherapy by intravenous 5-fluorouracil (LV5FU) or oral 5FU (capecitabine)**	Adjuvant chemotherapy decreased by 29% the risk of death at 5 years, even in elderly patients (Sargent et al. 2001) No evidence of benefits (disease-free survival, overall survival) compared with toxicity for use of **oxaliplatin or irinotecan and FU/LV** (Banerjee and Cunningham 2010)
Stage IV: metastasis	**Liver metastasis resection**	**Improve survival in elderly patients** (Papamichael et al. 2015)
	Palliative chemotherapy by 5FU combine with bevacizumab	**Adding bevacizumab** with 5FU improved PFS in patients >70 years old with HR = 0.53, 95% CI: 0.41–0.69, $p < 0.0001$ (Cassidy et al. 2010)
	Palliative treatments	**Hemostatic radiotherapy** **Left colic prosthesis** **Derivation colostomy**

However, adjuvant chemotherapy by FU/LV or capecitabine can be proposed in stage II CRC with high recurrence risk factors (T4, perforation, lymphovascular or perineural invasion, poorly differentiated histology), without any proof of potential benefits in an elderly population (Quasar Collaborative Group et al. 2007).

Locally Advanced Stage (Stage III)

Principles of treatment advise to combine surgery and adjuvant chemotherapy.

Indication of Liver Metastasis Resection

Around 20–34% of patients with CRC are diagnosed with synchronous liver metastasis. Liver resection still remains the only chance for long-term survival in patients with CRC liver metastasis. However, two studies found that these patients experienced more postoperative complications than younger ones, but the survival rate at 5 years was between 31.5% and 34.1%. So liver resection for CRC metastases in elderly patients can achieve a reasonable survival rate (Papamichael et al. 2015).

Adjuvant Chemotherapy

The benefit of adjuvant chemotherapy for stage III (node positive) CRC by intravenous 5-fluorouracil modulated with leucovorin (FU/LV) is well established, representing approximately a 30% reduction in the risk of recurrence and a 22–32% reduction in the risk of death even in elderly patients (Sargent et al. 2001). Chemotherapy tolerance is similar in a younger population. However adjuvant chemotherapy is proposed in 30–44% of patients aged above 75 years old, and this proportion decreases in patients aged above 85 years old (Kim 2015).

Capecitabine (an oral fluoropyrimidine) has proved to be as effective as FU/LV in adjuvant treatment in a subgroup analysis of patients aged above 70 years old, with no differences in toxicity by age, although it was more toxic than FU/LV (Twelves et al. 2005; Scheithauer et al. 2003). Patients aged above 80 years old experienced a higher incidence of grade 3 or 4 toxicity, especially diarrhea (31% vs. 13%) and hand-foot syndrome (Cassidy et al. 2002).

Adding oxaliplatin or irinotecan to FU/LV did not improve disease-free survival or overall survival (DFS, HR = 0.94; 95% CI: 0.78–1.13; OS, HR = 1.04; 95% CI: 0.85–1.27), it increases toxicities in patients aged above 75 years old with more neutropenia (OR = 17.3, 95% CI: 9.8–30.42) and nausea or vomiting (OR = 2.14, 95% CI: 1.73–2.65) (Banerjee and Cunningham 2010).

Palliative Chemotherapy

The goal of palliative chemotherapy in the elderly like in younger patients is to improve the overall survival and to limit progression compared to an observational care plan with acceptable toxicities. Studies show the same benefit of monochemotherapy based on FU/LV (Folprecht et al. 2004) compared to polychemotherapy (irinotecan (Folprecht et al. 2008) or oxaliplatin addition) (Goldberg et al. 2006) in patients over 70 years old on progression-free survival and overall survival, but older patients are more often undertreated (Doat et al. 2014). A prior impaired baseline geriatric evaluation (MMSE $\leq$27/30, and impaired ADL) is predictive of treatment failure in older patients, adverse outcomes, and poor survival (Seymour et al. 2011; Aparicio et al. 2016b). Fluoropyrimidine monotherapy appears to be the best option in first-line chemotherapy; an association should be discussed by a multidisciplinary team including geriatric physicians. (Fig. 3).

Targeted Therapy

Several targeted therapies have demonstrated activity in the treatment of metastatic CRC. Regarding antiangiogenic pathway inhibition, most of the data for elderly patients were obtained with bevacizumab. Cassidy et al. (2010) demonstrate the benefit of bevacizumab on free survival rate (6.4 months vs. 9.2 months, $p < 0.0001$) and overall survival (14.1 months vs. 17.4 months;

- Fit older patients can benefit from systemic cytotoxic combination therapy.
- Age alone should not be an exclusion criterion for the use of newer targeted agents in the treatment of patients with metastatic colorectal cancer.
- Those fit older patients selected for inclusion in clinical trials appear to derive a similar benefit to younger patients in terms of RR and PFS from the use of bevacizumab or cetuximab plus full-dose combination chemotherapy. However, the data are lacking as to whether this leads to significant patient-relevant gains such as improved survival with an acceptable quality of life.
- For those older patients for whom such therapy would be inappropriate, less intensive regimens, such as reduced-dose oxaliplatin plus 5-FU or lower dose capecitabine plus bevacizumab, may be use.

Fig. 3 Recommendations for use of chemotherapy in elderly patients SIOG (Nascimbeni et al. 2009)

$p = 0.005$) for adults and older adults subgroup (>70 years old) which leads to recommend this treatment in current practice guidelines (Van Cutsem et al. 2014). However this benefit decreases with age (Cunningham et al. 2013). This treatment was well tolerated with a similar quality of life for elderly patients after treatment, but they experienced more frequently severe thromboembolic events (1.5% vs. 4%) (Price et al. 2012; Kozloff et al. 2009).

EGFR receptor inhibition by monoclonal antibodies is a key point for a variety of processes involved in cancer cell growth, proliferation, angiogenesis, and invasion in patients with metastatic CRC lacking mutations in the RAS genes (wild-type RAS) (Scaltriti and Baselga 2006). Concerning EGF receptor inhibitors, there are very few available data in elderly patients. A Canadian study didn't show any difference between cetuximab compared to best supportive care on 572 pretreated patients with metastatic colorectal cancers (40% over 65 years old) on survival or toxicities (Asmis et al. 2011)

Rectal Cancer

The diagnosis of rectal cancer is made at an age median of 70 years and represents one third of colorectal cancers (Papamichael et al. 2015). Combination of treatment modalities is complex, and older patients are often undertreated as showed by the Netherlands Cancer Registry Study. Only 40% of fit patients with locally advanced rectal cancer received adjuvant chemoradiation (Nederlandse Kankerregistratie). However, the 5-year overall survival increased recently to reach 57% for elderly. A recent conference guideline recommends to improve elderly rectal cancer management by selecting patients with geriatric screening tools. Patients with G8 ≥15/17, Mini-Cog Score ≥4, time up and go test ≤20 s, and no fall history are considered as fit and can be treated like younger patients. However, patients with an abnormal tests need a thorough geriatric assessment to adapt care (Montroni et al. 2018).

Treatment Management Recommendations

The advances in surgical management have reduced mortality in elderly patients (>70 years old) from 7% to less than 3% in the last 10 years (Table 2). Poor prognostic factors are well known: geriatric status, American Society of Anesthesiology (ASA) score, emergency surgery, low rectal cancer, and advanced tumor stage (Alves et al. 2005; Barrier et al. 2003; Finlayson et al. 2012). Age was only linked with advanced stages and emergency procedures.

The main recommendations for elderly rectal cancer patient management aim to improve these risk factors:

Table 2 Management of rectal cancer for older patients

Stage of rectal cancer	Treatment recommendations	Specificities for elderly patients
T1 N0 M0 tumors	Proctectomy or trans-anal resection for lateral sided tumors <3 cm with good to intermediate histological differentiation or endoscopic resection as per colon cancer	Contact radiotherapy: in case of inoperability, endorectal radiotherapy for patients with T1 tumors providing excellent local control (95.5%), 74% survival rate for T1 tumors, and certain favorable T2 tumors (Papillon and Chassard 1992)
T2 N0 M0 tumors	Proctectomy +/− preoperative radiochemotherapy (oral or IV fluoropyrimidine and 45 to 50 gray over 5 weeks)	Increased postoperative morbidity and mortality with age (13% in patients over 80 years of age vs. 0.5% under 50) (Bhangu et al. 2014) Benefit of neoadjuvant treatment with a complete pathological response rate (pCR) up to 44% before surgery (Isbister 1997)
T3–T4 M0 tumors	**Superior rectum**: rectum and mesorectum surgical resection up to 5 cm under inferior pole of tumor Neoadjuvant chemotherapy recommended for T4 patients **Middle and inferior rectum**: neoadjuvant chemotherapy prior to complete mesorectum surgical resection	Patients ineligible for neoadjuvant radiochemotherapy: preoperative radiotherapy (25 Gy in 5 fractions) and surgery 1 week later. Complication risk raised at 30 days and at 6 months for older patients (Janssen-Heijnen et al. 2007) In some cases: standalone radiochemotherapy, surveillance, or local excisions for unfixed T2–T3 allow prolonged remission (Smith et al. 2015)
pT3–T4 N0	No adjuvant treatment	
pTx N1–2 M0	Adjuvant chemotherapy with 5FU	Less ascertained benefits than in colon cancer management
Stage IV: metastasis	Synchronous metastases resection or radiofrequency when possible Palliative radiotherapy, hemostatic radiotherapy +/− Palliative chemotherapy	

- Balance the benefit of treatment versus its adverse effects considering the life expectancy and the quality of life of the patient.
- Optimize patient reserves with multimodal prehabilitation especially for patients with neo-adjuvant chemoradiation and major surgery.
- Optimize surgery with a minimally invasive approach (laparoscopy and robotic surgery); avoid emergency surgery by anticipating complications.
- Consider chemoradiotherapy to improve local control in locally advanced cancer, but it increases toxicities and may prevent a curative surgery. Contact X-ray brachytherapy can be used alone for early rectal cancer (cT1 <3 cm) or as an adjunction for residual tumors (<3 cm) following external beam radiation therapy. The benefit of adjuvant chemotherapy alone is uncertain, and capecitabine is contraindicated in renal failure.
- Watch and wait could be efficient alternatives for frail patients.
- Remove liver metastasis only with curative intent.

Stage 0 to Stage I (T1–T2 N0 M0) Tumors

Surgery consists of proctetomy or transanal resection for lateral sided tumors measuring <3 cm, with good to intermediate histological differentiation or endoscopic resection as per colon cancer.

Endorectal radiotherapy is an alternative in case of inoperability for patients with T1 tumors providing excellent local control (95.5%) and

survival rate (74%) for T1 tumors and certain favorable T2 tumors (Papillon and Chassard 1992).

Stage II to Stage III (T2–T4 N0–1 M0) Tumors

The surgical treatment of rectal cancer implies a major surgery with anterior resection, complete mesorectal excision, sphincter conservation, and lymphadenectomy.

In locally advanced cancer, this procedure must be completed by pre-surgical treatments like radiotherapy (RT) and/or neoadjuvant chemotherapy to improve local cancer control. Classic protocol is oral or intravenous fluoropyrimidine and 45–50 grays over 5 weeks. However, this treatment is rarely feasible in elderly patients due to comorbidities and limited physiological reserves. Thus, elderly patients are less frequently treated with neoadjuvant radiotherapy or chemotherapy, and non-restorative procedures are more frequently used (Chang et al. 2007). Preoperative radiotherapy showed a benefit for local control compared to postoperative radiotherapy (Kunkler et al. 2014).

The complete pathological response rate (pCR) with neoadjuvant treatment and before surgery is 44% (Isbister 1997). Smith et al. published a study in 2015 evaluating the differences between radical surgery and observation after neoadjuvant treatment in cases of pCR. The study concluded that elderly patients, because of their higher surgical risk, obtained the greatest benefit from the "watch and wait" policy and showed an improved survival at 1 year after treatment (Smith et al. 2015). Another alternative is local resection, a treatment that has shown the same benefit in elderly populations than radical surgery for pT1 stage but an increased mortality in pT2 stage (Bhangu et al. 2014).

However this procedure could be an alternative for palliative management to decrease local symptoms for patients refusing stoma or with comorbidities (Garcia-Aguilar 2013).

The impact of cancer surgery on quality of life is very important in the elderly. Sphincter function, assessed clinically and if necessary after manometry, is an essential element to consider in preoperative assessment and the decision-making process. The delay of surgery following short-course radiotherapy has also been associated with a decrease in postoperative morbidity. But the frequency of postoperative complications and the alteration of quality of life due to poor sphincter function or due to stoma for elderly patients lead to find alternative management strategies.

Stage IV (T3–4 N2 M1): Palliative Treatments

At this stage, all treatments remain possible, but with the aim of limiting symptoms. The first objective is to avoid emergency surgery by trying to anticipate the risk of digestive obstruction and thus limiting the risk of postoperative complications. If the obstruction is located in the proximal rectum, colonic stents can be used. Colonic stents are not recommended for patients planned for chemotherapy without resection. Patients with mid/distal rectal tumors are not eligible for colonic stents and bypass surgery like Hartmann can prevent the digestive occlusion. Patients fit with tumor perforation should be explored urgently and should have peritoneal lavage and digestive or tumor resection. For unfit patients specialized palliative care should be enforced.

Another symptom to consider is rectal bleeding. For this symptom, several therapies are possible: surgical resection for fit patients, hemostatic radiotherapy, or local cauterization for unfit patients with persistent bleeding.

Chemotherapy or palliative radiotherapy may be considered to limit and slow down the local development of the tumor and to prevent especially painful complications (Montroni et al. 2018; Kunkler et al. 2014).

Surveillance

Surveillance consists of clinical inspection with digital rectal examination. The local extension is monitored by echo-endoscopic or pelvic MRI to

screen for local relapses. General extension must include research of pulmonary metastases because they are more frequent than in colon cancer.

Esophageal Cancer

Esophageal cancer is the eighth most common cancer and has the sixth worst prognosis because of its aggressiveness and poor survival rate. This cancer occurs with a median age of 68 years and is associated with a poor quality of life due to feeding difficulties. There are no recommendations for management of esophageal cancer in older patients.

The anatomopathology of this cancer in the elderly population is adenocarcinoma (50%) and squamous cell carcinoma (45%) (Skorus and Kenig 2017).

Curative treatment is based on esophagectomy which is a major thoracic surgery with a high rate of perioperative complications especially in older populations. If surgery is impossible due to an advanced cancer stage or physiological status of the patient, the alternative is chemotherapy +/− radiotherapy depending on cancer stage (Table 3).

Surgery Outcomes for Older Patients

Older patients have poor surgery outcomes. A 2013 systematic review analyzed the outcomes of 9531 and 2573 operations on young and elderly (>70 years old) patients, respectively (Markar et al. 2015). Esophagectomy in elderly patients was associated with increased in-hospital mortality, as well as increased pulmonary and cardiac

Table 3 Management of esophageal cancer in elderly patients (Bollschweiler et al. 2017)

Stage of esophageal cancer	Treatment recommendations	Specificities for elderly patients
Barrett's esophagus : high dysplasia or intramucosis carcinoma	<1 cm no surveillance 1–2.9 cm surveillance after 5 years 3–9.9 cm surveillance after 5 years	If limited life expectancy, no surveillance (Bollschweiler et al. 2017)
pT1a : mucosal infiltration	Endoscopic resection	For patients >70 years old: less perioperative complications and better 2 years survival than esophagectomy (Cummings et al. 2016)
pT1b (esophageal submucosa)-pT2 (muscularis propria)	Surgical resection and selective lymphadenectomy: transthoracic esophagectomy	If significant comorbidities: definitive chemoradiation (Bollschweiler et al. 2017)
Clinical T3: locally advanced cancer or esophagogastric junction	Squamous cell carcinoma or adenocarcinoma: preoperative chemoradiation: 5-FU, platin 40 Gy, or CROSS protocol	Benefit of neoadjuvant chemotherapy 5FU-cisplatin vs. surgery alone on overall survival after 70 years old with acceptable tolerance (Medical Research Council Oesophageal Cancer Working Group 2002) FLOT protocol had major adverse effects in >65 years patients (81.9% NCI-CTC grade 3–4) with no benefit on progression-free survival after 70 years old (Al-Batran et al. 2013)
	Or chemotherapy for adenocarcinoma: 5-FU, platin, or FLOT protocol (5-FU, leucovorin, oxaliplatin, docetaxel)	
	And transthoracic esophagectomy	
Inoperable cancer	Radiotherapy or chemoradiation	Intensity-modulated radiotherapy improves overall survival and cardiac mortality compared to 3-d radiation (Lin et al. 2016)
Metastatic cancer	Palliative chemotherapy: 5-fluorouracile, oxaliplatine, and also irinotecan or taxanes +/− Targeted therapy if HER2 positive: trastuzumab	
Supportive care	Self-expanding metal stent Intraluminal brachytherapy Radiotherapy Rigid plastic tube insertion	

complications. Preexisting comorbidities explain a large part of these increased complications. Indeed, lower pulmonary function and cardiovascular comorbidities are risk factors for higher mortality and morbidity after esophagectomy (Liu et al. 2015). Moreover Nakashima Y et al. showed that sarcopenia had a high prognostic impact after esophagectomy. Sarcopenia was present in near half of patients with esophageal cancer and was an independent risk factor for an anastomotic leak (HR = 2.3; 95% CI: 1.06–5.1, $p = 0.034$) and poor survival (HR = 2.3; 95% CI: 1.50–3.7, $p < 0.001$). The correlations between sarcopenia and surgical outcomes were not observed in the younger group (Nakashima et al. 2018). The age threshold of 80 years showed an even more significant association between in-hospital mortality and elderly age (pooled odds ratio = 3.19; 95% CI: 1.6–6.35; $P < 0.05$). The elderly group had poorer outcomes with a reduction of overall 5-year survival (pooled odds ratio = 0.73; 95% CI: 0.62–0.87; $P < 0.05$) and cancer-free 5-year survival (POR = 0.75; 95% CI: 0.64–0.89; $P < 0.05$) (Markar et al. 2015).

This meta-analysis included studies from 1970 until 2009. It is noteworthy that surgical techniques have evolved over this period with introduction of minimally invasive approaches that reduce postoperative overall complications especially for patients over 70 years of age (37.9% vs. 60.3%, $p = 0.016$) and pulmonary complications (20.7% vs. 39.7%, $p = 0.026$) compared with open esophagectomy (Li et al. 2015). Moreover, introduction of fast-track programs that optimize perioperative parameters reduces lengths of stay and 30-day mortality for patients over 75 years old compared with classic management (Oakley et al. 2016).

Chemotherapy

Neoadjuvant Chemotherapy

Preoperative chemotherapy by cisplatin 5-fluorouracil improves survival, but this gain of survival remains limited and only for patients with a major response (90% reduction of initial tumor). Patients with a minor response had comparable prognosis when compared to patients undergoing surgery only (Bollschweiler et al. 2017).

Palliative Chemotherapy

Almost half of people with esophageal or gastroesophageal junction cancer have metastatic diseases (bones, lungs, nodes) at the time of diagnosis. A recent meta-analysis showed that palliative chemotherapy/targeted therapy compared with best supportive care improved the median survival time by 1 month with more occurrences of severe toxicities. But there is no evidence that chemotherapy and/or targeted therapy decreases quality of life (Janmaat et al. 2017).

The REAL2 study showed the benefit of a first-line treatment with capecitabine, and oxaliplatin was the same as 5-fluorouracil and cisplatin with less toxicities. However, there is an increased risk of febrile neutropenia (Cunningham et al. 2013).

In case of positivity of HER 2, trastuzumab is indicated as a first-line choice, in combination with chemotherapy.

As a second-line choice, if the general condition of the patient allows it, two options are possible: taxanes or 5-fluorouracil and irinotecan.

Radiotherapy

Radiation is the standard therapeutic modality for inoperable esophageal cancer with a dual purpose: to improve local control and survival. For non-metastatic esophageal cancer, intensity-modulated radiotherapy had better outcomes in aged patients (>65 years) compared with three-dimensional radiotherapy on all-cause mortality (HR = 0.8, 95% CI: 0.72–0.95) and cardiac mortality (HR = 0.18; 95% CI: 0.06–0.54) (Lin et al. 2016).

Supportive Care

Most patients with esophageal and gastroesophageal carcinoma are diagnosed at an advanced stage or are ineligible for surgery and require palliative interventions. Palliative therapies for advanced esophageal cancer include surgery, radiation therapy, chemotherapy, endoscopic procedures, and combinations of these. A recent meta-analysis compared these technics.

Dai Y et al. conclude that self-expanding metal stent insertion is safe, effective, and quicker in palliating dysphagia compared to other modalities. However, high-dose intraluminal brachytherapy is a suitable alternative and might provide additional survival benefit with a better quality of life. Some anti-reflux stents and newly designed stents lead to longer survival and fewer complications compared to conventional stents. Combinations of brachytherapy with self-expanding metal stent insertion or radiotherapy are preferable due to reduced reinterventions. Rigid plastic tube insertion, dilation alone or in combination with other modalities, and chemotherapy alone are not recommended to palliate dysphagia due to a high incidence of delayed complications and recurrent dysphagia (Dai et al. 2014).

Nutritional management is the key to supportive care. This management includes oral supplementation if there is no dysphagia or enteral nutrition with a feeding tube or gastrostomy for patients unable to eat. The objective is the optimization of nutritional intake to limit infectious risks and improve prognosis after surgical or radiochemotherapy treatment (Yu et al. 2013).

Gastric Cancer

Gastric cancers have poor prognosis with a median survival of about 10 months and are often diagnosed at an advanced stage (Dai et al. 2014). The triple chemotherapy with epirubicin plus cisplatin and fluorouracil is standard for advanced esophagogastric cancer. The fluorouracil must be infused through an ambulatory infusion pump, which impairs the quality of life; cisplatin, which is nephrotoxic, requires intravenous hydration. In this randomized trial, capecitabine, an oral fluoropyrimidine, plus oxaliplatin, a platinum compound that does not require hydration, was as effective in prolonging overall survival as was fluorouracil plus cisplatin. The principles of gastric cancer management after 75 years old are the same as younger patients, but comorbidities assessed by CGA could impact therapeutic options (Table 4).

Localized Stage

Surgery

Surgery is the only curative treatment in gastric cancer. A population-based evaluation of outcomes in gastric cancer in the elderly showed that if elderly patients can support an oncologic surgery and chemotherapy, the overall survival is comparable between age groups (48% and 49.6% of survival rate at 5 years) (Schlesinger-Raab et al. 2016).

There is no gain in overall survival with extensive lymphadenectomy for gastric cancer in elderly patients. D "1.5" lymphadenectomy is most often realized (without splenectomy and left pancreatectomy).

Even though no study with a high level of evidence has focused on the impact of a rehabilitation protocol in early postoperative gastric cancer care, the limitation of operative shock is the top priority in frail older patients (Li et al. 2014). This should consist of limited pre- and postoperative fasting, limited hypothermia during surgery, effective pain management, and giving preference to minimally invasive celioscopic surgery (Hu et al. 2016).

Neoadjuvant Chemotherapy

There are no specific prospective studies evaluating neoadjuvant or perioperative chemotherapy in older patients; however, subgroup studies hint to their efficacy. Considering stages over IA (T1 N0 M0), 5FU perioperative chemotherapy (four to six cycles prior and posterior to surgery) associated with FOLFOX-type platinum salts is recommended each time patient's health condition allows it (Smyth et al. 2016a). There is no demonstrated benefit of preoperative radiochemotherapy.

Metastatic Stage

HER 2-Negative Tumors

First-line chemotherapy based on REAL2 (Cunningham et al. 2008) and FLO studies should be 5FU (fluorouracil and capecitabine) and oxaliplatin (Al-Batran et al. 2008). The REAL2

Table 4 Management of gastric cancer in elderly patients

Stage of gastric cancer	Treatment recommendations	Specificities for elderly patients
Localized stage		
	Curative surgery: gastrectomy and regional lymphadenectomy (D1 and D2) *D1 adenectomy: lesser curvature nodes and greater curvature nodes* *D2 adenectomy: celiac trunk nodes, hepatic artery nodes, gastric artery nodes*	D2 adenectomy: No gain in survival for aged patients (Passot et al. 2016)
Proximal cancer, corpus cancer, lignite	Complete gastrectomy and reconstruction on a Roux-en-Y loop	
Distal cancer	Partial gastrectomy with omega loop or Y loop	Y anastomosis limits *biliary reflux*
Stage > IA (T1 N0 M0)	Surgery + perioperative chemotherapy: FOLFOX (Smyth et al. 2016a)	
	If patient is unfit: adjuvant chemotherapy with LV5FU2 or abstention	
Metastasis stage		
HER2 negative tumor	1ère line: FOLFOX 4–6 cycles or capecitabine-oxaliplatine	REAL2 (Cunningham et al. 2008) and FLO (Al-Batran et al. 2008)
		If patient is unfit : 5FU alone or no chemotherapy
	2ème line: FOLFIRI or ramucirumab + paclitaxel (Smyth et al. 2016a)	No specific study or only subgroups of older patients with ramucirumab + paclitaxel
HER2 positive tumor	5FU, platin, trastuzumab (Smyth et al. 2016a)	
Palliative care	Palliative surgery for symptomatic tumors (dysphagia, bleeding, perforation) or palliative radiotherapy	

studies have shown that capecitabine with oxaliplatin may replace 5FU with cisplatin as a first-line choice. The FLO study showed longer progression-free survival with 5FU, leucovorin, and oxaliplatin association than 5FU, leucovorin, and cisplatin association in patients aged over 65 (6.0 months vs. 3.1 months). Moreover, oxaliplatin had a better tolerance profile with lessened nausea, vomiting, fatigue, renal toxicity, anemia and thrombosis. It should be noted that 5FU is administered in continuous drip at 2600 mg/m^2, not in bolus.

Second-line chemotherapy should be irinotecan, taxane, or ramucirumab or ramucirumab with paclitaxel (Smyth et al. 2016b) or FOLFIRI.

HER2-Positive Tumors

First-line chemotherapy should be based on a 5FU, cisplatin, and trastuzumab association. In case of contraindication to cisplatin, FOLFOX-trastuzumab or capecitabine-oxaliplatin-trastuzumab will replace it.

Second-line therapy is the same as for HER2-negative tumors.

Supportive Care

The main supportive care concern is nutritional support. Indeed 60% of patients with gastric cancers are undernourished (Hébuterne et al. 2014). Malnourishment increases postoperative complications and chemotherapy toxicity, diminishes response to chemotherapy, and alters quality of life. Consequent sarcopenia is a major prognosis factor of gastric cancers and must be screened for (Zhuang et al. 2016).

Nutritional management must be planned out prior to treatment with a before and after approach. Nutritional assistance must be set up if intakes are below 60% of nutritional needs, whether enteral (feeding jejunostomy) or parenteral so as to

cover nutritional needs (1.2–1.5 g of proteins/kg/day and 30–35 kcal/kg/day).

Immunonutrition is recommended for malnourished patients 7 days prior and after surgery. In case of gastrectomy, feeding must be fractioned into seven to eight meals per day.

Hemostatic radiotherapy is possible in case of intense bleeding.

Hepatocellular Carcinoma

The incidence of hepatocellular carcinoma (HCC) is increasing worldwide; it is currently the third cause of death by cancer in the world. Subjects are preferentially male and, in more than 80% of cases, affected by cirrhosis. Principal risk factors are hepatitis B and C, alcohol, and nonalcoholic steatohepatitis (NASH). There is an augmentation of the incidence of HCC in older subjects. Certain particularities are noteworthy, a greater prevalence in women, due to their long-life expectancy, lesser infections by hepatitis B virus, but more cirrhosis linked to hepatitis C or NASH. Many studies have shown that HCC is often mono- or pauci-focal, associated with lesser fibrosis, and more often encapsulated (favorable prognosis factor).

Treatments are based on Barcelona Clinic for Liver Cancer (BCLC) classification, taking into account comorbidities and patients' general health states. The place of CGA has not been evaluated in the management of HCC. Screening tools such as the G8 questionnaire or the VES13 could allow selection of older patients affected by HCC needing to benefit from a CGA. Only surgery (hepatic transplantation and surgical resections), per-cutaneous ablations such as radiofrequency are potentially curative. Intra-arterial chemoembolization, radioembolization for intermediate stages, and targeted therapy with sorafenib for advanced stages are palliative treatments.

Curative Treatments

Hepatectomy

Surgical liver resection is the curative treatment of early stage HCC (BCLC stage 0). It has been shown to be feasible for older patients since surgical techniques have evolved (Ishizawa et al. 2010). Many studies have shown there is no difference in global survival and progression-free survival in patients aged 70 years and older when compared to younger patients (Huang et al. 2009; Kaibori et al. 2016). Some studies have shown higher incidences of postoperative complications such as confusion and longer hospitalization in older patients (Kaibori et al. 2009; Nozawa et al. 2015). Two other studies have shown hepatectomy to be feasible in patients older than 80 years, with survival rates comparable to younger patients (Nozawa et al. 2015; Yamada et al. 2012). However, Nozawa et al. observed higher incidences of cardiovascular complications and confusion in this population.

Only 1 retrospective study has tried to identify geriatric risk factors linked to postoperative complications, in 70 patients aged over 70 years (Kaibori et al. 2016).

Orthotopic Liver Transplantation

Orthotopic liver transplantation (OLT) is a curative treatment for HCC, but access to OLT is still narrowed due to organ shortage. Lack of donor is frequent. Presence of comorbid conditions such as ischemic heart disease and diabetes, which are known to adversely affect post OLT course, limits transplantation access in older patients $\geq$70 years. An arbitrary threshold of >65–70 years is generally adopted worldwide.

Radiofrequency Ablation

Percutaneous ablative treatment (RFA) is a curative procedure for HCC tumors less than 3 cm. Studies on outcome in elderly patients after RFA showed conflicting results. Sato et al., in a large cohort of 54,145 patients with HCC, found that older age was significantly associated with mortality. Kao et al. showed that older patients had worse overall survival than their younger counterparts (Kao et al. 2012). Conversely, Shiina et al. reported that age was not associated with reduced survival after RFA (Shiina et al. 2012). Overall, RFA may represent an attractive alternative to SR in elderly patients with comorbidities.

Palliative Treatments

Chemoembolization

Transarterial chemoembolization (TACE) is the treatment of choice in intermediate stages of HCC. Studies have shown similar survival rates between young and elderly patients with HCC. Mirici-Cappa et al., in a large cohort study, found no difference in overall survival between the different age groups (Mirici-Cappa et al. 2010). Likewise, Cohen et al., in a prospective study of 102 patients, reported no difference in terms of survival or complication rate (Cohen et al. 2013). Only one large retrospective study, conducted by Yau et al. (2009), showed a significant difference, with a better median overall survival and disease-specific survival (15.2 months vs. 8.7 months, $p < 0.001$). However, there was no difference in terms of TACE-related mortality. This data suggests that TACE is effective with a good safety profile, in an elderly population.

Molecular Targeted Therapy (Sorafenib)

Sorafenib is now the standard care of patients with advanced HCC, but there are few studies regarding the use of sorafenib in elderly patients. There is only one prospective study comparing sorafenib in elderly >70 years versus younger patients ≤70 years (Di Costanzo et al. 2013).

They found surprisingly that elderly patients had a median time to progression and an overall survival rate that was longer than for younger patients, with less severe adverse effects although results were not statistically significant. Other retrospective studies found similar results. Jo et al showed that the median progression-free survival and the overall survival time were similar in older and younger patients even on very elderly (≥ 80 years) (Jo et al. 2014).

Data concerning tolerability and the safety profile of this molecule is lacking in elderly patients with HCC. Morimoto et al., in a retrospective study, reported that the discontinuation of sorafenib therapy due to SAE was more frequent among elderly patients ≥75 years than among younger patients (Morimoto et al. 2011). Likewise, Edeline et al. found similar frequency of dose reduction and occurrences of SAEs in the elderly group (>70 years) (Edeline et al. 2015). There was significantly less frequent definitive discontinuation of treatment due to toxicity in the younger group. However, they found higher incidence of bleeding in the elderly group, which was explained by concomitant platelets inhibitors.

Conclusion

Available data seems to indicate that age is not an independent factor of mortality or toxicity in patients with HCC. However, data is insufficient to conclude, and patients included in these studies are carefully selected. Identifying frail older patients, with appropriately validated tools (G8 scores and CGA), is necessary to offer elderly patients personalized treatment.

Pancreatic Cancer

Operable Stage

Surgery

Surgery is the only lasting cure, but unfortunately only 15–20% of patients are eligible for full resection (Table 5). This proportion diminishes with age; it is of only 8% after 85 years (Higuera et al. 2016). Pancreatic cancer surgery is taxing and requires patients to be selected beforehand. Many retrospective studies, one of which is French (Turrini et al. 2013), have shown there is no increase in morbidity or mortality in older patients compared to younger ones when they have been deemed operable (Frakes et al. 2015; Hayman et al. 2015).

For inoperable patients over 80 years of age, chemotherapy alone has shown survival rates similar to those from surgery (Kinoshita et al. 2015). Stereotaxic radiotherapy associated or not with gemcitabine has also shown results of good local control in a small retrospective study (Kim et al. 2013).

Table 5 Management of pancreatic cancer in elderly patients

Tumor stage	Recommended treatment	Geriatric specificities
Operable	Surgery Adjuvant chemotherapy with FOLFIRINOX (or gemcitabine or fluorouracil or gemcitabine + capécitabine)	High postoperative morbidity requiring rigorous patient selection Specialized center surgery Options: stereotaxic radiotherapy +/− gemcitabine if patient is inoperable or standalone chemotherapy
Borderline	No referential Chemotherapy with FOLFIRINOX or gemcitabine then surgery if operable	Relevance of neoadjuvant treatment to identify patient with rapidly progressive diseases ineligible to surgery Feasible but more studies needed
Locally advanced cancer	Supportive care + chemotherapy +/− Closure radiotherapy	Chemotherapy with gemcitabine Optional stereotaxic radiotherapy
Metastasis cancer	Supportive care + chemotherapy Age < 75 years, PS 0-1 FOLFIRINOX If PS = 2: gemcitabine + nab-paclitaxel If bilirubin >1.5 or comorbidities: gemcitabine If PS > 2: supportive care alone	FOLFIRINOX only for patients PS 0-1 with no comorbidity Nab-paclitaxel + gemcitabine or gemcitabine for patients PS 2 Palliative care if PS > 2 (Higuera et al. 2016)

Adjuvant Treatment

Adjuvant treatment is indicated for all operated patients at all stages and must start within 3 months of surgery. Despite a demonstrated survival gain, adjuvant treatment is only undertaken in 30–50% of older patients (Nagrial et al. 2014; Parmar et al. 2014). Age does not appear to be a prognosis factor (Frakes et al. 2015).

Single chemotherapy can be proposed to older subjects, either by gemcitabine (Oettle et al. 2013) or by fluorouracil, with comparable results. Gemcitabine has a better tolerance profile (Neoptolemos et al. 2010).

Locally Advanced Stages

Borderline

Borderline is defined by patients with local disease spread for whom surgery is still possible.

In these cases the use of neoadjuvant chemotherapy alone or chemoradiotherapy seems possible even in older patients in order to propose surgical resection despite the absence of a current referential and the necessity for more studies (Miura et al. 2015). This treatment also allows the selection of patients with rapid progression who will not benefit from curative surgical treatments.

Inoperable

This stage is defined by a vascular spread of the disease rendering surgery impossible. At diagnosis, 20–25% of patients have a locally advanced stage.

Referential-validated treatment is chemotherapy with gemcitabine (studies are ongoing to validate the same protocols as for metastatic stages) with the possibility of end-line radio-chemotherapy in selected patients (Huguet et al. 2014). This treatment is not often realized for older patients despite a demonstrated survival gain (Krzyzanowska et al. 2003).

Recently the development of stereotaxic radiation techniques for the pancreas has given interesting results with good tolerance and local control gains with a marked analgesic effect. This treatment is not yet recommended because of insufficient evidence but could be an option for older patients (Chuong et al. 2013).

Metastatic Stage

More than half of cases diagnosed at metastatic stages have a 5-year survival rate inferior to 2%.

In young patients referential poly-chemotherapy is FOLFIRINOX, validated by a prospective study showing 11.1 months of global

survival against 6.8 months for gemcitabine alone (Conroy et al. 2011). However, in this study, patients who were OMS >1 or aged >75 years were excluded. Retrospective studies have shown the feasibility and the efficiency of this treatment with adapted dosage in older patients PS 0 or 1 despite an increase in adverse effects (neutropenia and diarrhea) (Baldini et al. 2017; Guion-Dusserre et al. 2016).

Gemcitabine and nabpaclitaxel association has also shown better efficacy than gemcitabine alone (Von Hoff et al. 2013); this treatment could be proposed to patients over 75 years of age who are OMS 2.

For frail older patients, monotherapy with gemcitabine associated with supportive care is still the referent.

Supportive Care

Because of the anatomic relationships, patients regularly suffer from intense abdominal pain requiring morphine treatments. Invasive techniques such as celiac trunk alcoholization can be undertaken with good efficacy, allowing to diminish morphine prescriptions (Nagels et al. 2013).

Moreover, pancreatic tumors can cause biliary duct or duodenum obstructions requiring invasive prosthetic stent techniques. However palliative, these treatments result in quality of life improvement. These patients often suffer from cachexia and require adapted nutritional management.

Conclusions

It seems that age is not the main decision-taking factor in elderly patients suffering from digestive cancers. We would recommend a CGA or shorter screening tools to assess perioperative complications in order to improve decision-making. Prognostic of robust elderly patients seems to be similar to younger patients, but elderly population is still undertreated due to lack of evidence and imprecise geriatric evaluation.

Palliative chemotherapy, in older adults, only increases slightly survival with an increased toxicity, so that this option should be individualized. Decision should be made based on quality of life, compared with best supportive care.

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Musculoskeletal Aging, Sarcopenia, and Cancer

17

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Abstract

The decrease in muscle mass and strength represents one of the most relevant descriptor of physiological aging. Sarcopenia is the term coined to indicate the pathologic loss of skeletal muscle mass and strength/function during aging. The skeletal muscle decline has a multifactorial origin, involving lifestyle habits, disease triggers, and age-dependent biological changes. This phenomenon is part of the geriatric background and is today starting to disseminate in other specialties dealing with the complexity of frail older persons. In the oncology field, the interest in muscle wasting has mostly been focused on the clinical entity of cancer cachexia, a complex metabolic syndrome characterized by severe muscle loss, systemic inflammation, and malnutrition. The study of body composition in the oncological setting is crucial and may become one of the main characterizations of the oncogeriatric field, where clinical and research actions have to be designed taking into account the consequences of the aging process.

Keywords

Physical function · Cachexia · Muscle · Body composition · Aging

Introduction

Cancer is largely a late-life disease. In developed countries, the median age of cancer patients at diagnosis is over 65 (Global Burden of Disease Cancer Collaboration et al. 2016). Moreover, it is expected that more than 70% of all cancers will affect people aged 65 years and older by the year 2030 (Edwards et al. 2002).

Several mechanisms operating at multiple levels (molecular, cellular, systemic) have been invoked to explain the disproportionate incidence of cancer in old age (Balducci and Ershler 2005; Finkel et al. 2007; Campisi 2013). Indeed, aging and cancer seem to share a common pathogenic process consisting in the time-dependent accumulation of cellular damage (López-Otín et al. 2013; Hanahan and Weinberg 2011). This phenomenon results in two apparently opposite processes: an aberrant gain of cellular function (i.e., cancer) versus a progressive and generalized loss of fitness (i.e., aging) (López-Otín et al. 2013). Not surprisingly, the kinetics of tissue/organ degenerative processes and the incidence of cancer show similar trajectories, rising progressively at approximately the midpoint of adult life span (Rozhok and DeGregori 2016).

The decrease in muscle mass and strength represents one of the most relevant descriptor of physiological aging (Justice et al. 2016). In a fairly large percentage of individuals, an accentuated muscle loss takes place leading to adverse health outcomes (e.g., mobility disability, physical frailty, falls and fractures, mortality) (Pahor et al. 2009; Landi et al. 2015). Sarcopenia is the term coined to indicate the pathologic loss of skeletal muscle mass and strength/function during aging (1989). Sarcopenia has a multifactorial origin, involving lifestyle habits, disease triggers, and age-dependent biological changes (e.g., chronic inflammation, mitochondrial abnormalities, loss of neuromuscular junctions, reduced muscle regenerative capacity, hormonal alterations) (Fielding et al. 2011).

Muscle dysfunction also develops across several stages of cancer trajectory (Christensen et al. 2014). In the oncology field, interest in muscle wasting has mostly been confined to the clinical

entity of cancer cachexia, which is characterized by severe muscle loss (Fearon et al. 2011), systemic inflammation (Fearon et al. 2012), and malnutrition (Argilés 2005). Emerging evidence shows that decreased muscle mass is a prevalent condition in cancer patients regardless of disease stage and body mass (Prado et al. 2008; Martin et al. 2013; Shachar et al. 2016). The presence of sarcopenia in adults with cancer has been associated with increased chemotherapy toxicity, postoperative complications, and higher mortality rates (Kazemi-Bajestani et al. 2016), independent of disease stage (Tan et al. 2009; Villaseñor et al. 2012; van Vledder et al. 2012).

In addition, skeletal muscle health affects the risk of developing cancer, being muscle tissue a major regulator of metabolic and inflammatory pathways (Argilés et al. 2016; Whitham and Febbraio 2016). Finally, substantial evidence shows that muscle strength in healthy individuals is a strong independent predictor of cancer mortality risk (Ruiz et al. 2009).

Muscle Aging and Sarcopenia

The age-related loss of muscle mass and function (i.e., sarcopenia) is one of the most pervasive changes that accompany aging. As acknowledged by Rosenberg (1989), "...There may be no single feature of age-related decline that could more dramatically affect ambulation, mobility, calorie intake, and overall nutrient intake and status, independence, breathing...." Sarcopenia is indeed associated with a multitude of adverse health outcomes, among which falls, disability, institutionalization, and mortality are certainly the most worrisome (Rolland et al. 2008). After the age of 35 years, a healthy person loses muscle mass at a rate of 1–2% per year in conjunction with a 1.5% annual decline in strength, which accelerates to approximately 3% per year past the age of 60 (Hughes et al. 2002; Landi et al. 2016a). As a result, the muscle cross-sectional area of the thigh decreases by about 40% between 20 and 60 years of age. The magnitude of decline in fat-free mass is twice as greater in men than in women and is amplified in sedentary individuals relative to physically active peers (Hughes et al. 2002; Landi et al. 2016a). Besides losing muscle mass, an average adult can expect to gain approximately 0.45 kg (1 lb) of fat per year between the ages of 30 and 60 (Forbes 1999). This shift in body composition is often masked by relatively stable body weight and can result in a condition known as sarcopenic obesity, which further increases the risk of disability, morbidity, and mortality (Batsis et al. 2014; Rolland et al. 2009; Kalinkovich and Livshits 2016).

Although the decline in muscle mass and strength with age has been known for long time, only in recent years, sarcopenia has become a hot topic in gerontology. Several processes and mechanisms have been proposed to play a role in the multifaceted pathogenesis of sarcopenia, including lifestyle habits, systemic factors (e.g., inflammatory cytokines and hormones), local environment alterations (e.g., vascular dysfunction), changes in the neuromuscular system, and modifications of intramuscular specific processes (Marzetti et al. 2009). All these factors eventually lead to an imbalance between anabolic and catabolic processes, which results in muscle protein breakdown, loss of myocytes, insufficient satellite cell replenishment, and ultimately declines in muscle mass (in particular, type II fibers) and function (Marzetti et al. 2009). Overall, multiple factors have been indicated at the basis of the sarcopenic phenomenon, each of them following specific, independent, and mutually interacting mechanisms (Table 1) (Buford et al. 2010; Rier et al. 2016).

Lifestyle Factors

Among lifestyle factors, physical inactivity and inadequate nutrition represent the two most important contributors to poor muscle health in older adults (Martone et al. 2015). The relationship among them and sarcopenia is bidirectional. In fact, sedentariness combined with the ingestion of insufficient amounts of calories and specific nutrients (in particular, proteins) promotes the development of sarcopenia. Once sarcopenia starts to develop, the ability to move, shop for

Table 1 Etiological factors and mechanisms at the basis of sarcopenia in older persons. (Modified from Rier and colleagues (Rier et al. 2016))

Etiological factors	Mechanisms
Muscle disuse	Reduced physical activity Cognitive impairment Immobility Neuromuscular transmission impairment
Endocrine changes	Low testosterone concentrations Low growth factor concentrations Low IGF-1 concentrations Increased insulin resistance
Malnutrition	Inadequate food intake Malabsorption Increased catabolism and protein breakdown Decreased peripheral perfusion leading to muscle hypo-oxygenation
Low-grade chronic inflammation	Increased concentration of pro-inflammatory cytokines with direct and indirect negative effects on the skeletal muscle (e.g., TNF-α, IL-1, IL-6)

IGF-1 insulin-like growth factor-1, *TNF* tumor necrosis factor, *IL* interleukin

grocery, and prepare adequate meals may become impaired. The instauration of the consequent vicious circle may lead to severe malnutrition, weight loss, and further worsening of sarcopenia, finally ending into disability and, eventually, death (Evans 2010). Not surprisingly, while no pharmacological treatment is presently available to prevent age-dependent muscle wasting or to restore muscle mass and function, physical exercise and targeted nutritional supplementations represent the only interventions that may offer substantial therapeutic gain against sarcopenia and its negative correlates (Martone et al. 2015).

Endocrine Aging

Aging is marked by progressive, subtle derangements of nearly all biological systems, including endocrine ensembles (Chahal and Drake 2007). The nature and magnitude of age-related alterations in circulating hormones and target tissue responsiveness have taken center stage in sarcopenia research (Sakuma and Yamaguchi 2012a). Studies have indicated that several age-related endocrine defects such as decreases in anabolic hormones (e.g., testosterone, estrogen, growth hormone [GH], and insulin-like growth factor-1 [IGF-1]) (Sakuma and Yamaguchi 2012a), alterations in the renin-angiotensin system (Carter et al. 2005), and vitamin D deficiency (Cesari et al. 2011) may play a role in muscle wasting with aging.

Inflammation

The presence of a state of chronic low-grade inflammation is an established hallmark of the aging process (i.e., inflamm-aging) (Franceschi and Campisi 2014). The persistent elevation of several inflammatory mediators, in particular interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), has been associated with sarcopenia (Jo et al. 2012). These mediators act in a complex and coordinated network involving multiple feedback mechanisms through which the function of individual factors may be modified, replaced, or modulated by others (Calvani et al. 2015). In this context, multivariate analytical strategies have recently been developed to capture the complex interrelation linking circulating inflammatory mediators to body compositional factors during aging (Calvani et al. 2016; Marzetti et al. 2014). Using such approaches, it was possible to characterize the hidden pattern of relationships among small muscle volume, low muscle strength, great intermuscular adipose tissue, and a cluster of inflammatory mediators (including myeloperoxidase, P-selectin, soluble intercellular adhesion molecule-1, and vascular cell adhesion molecule-1) in community-living young and older adults with varying levels of physical performance (Calvani et al. 2016).

For years, the induction of muscle protein breakdown has been considered to be the major pathway underlying the relationship between inflammation and sarcopenia (Combaret et al. 2009). However, a link among inflammation, mitochondrial dysfunction, and oxidative stress has more recently been proposed, possibly

providing a further mechanistic explanation for the association between inflammation and sarcopenia (Marzetti et al. 2013).

Neuromuscular Changes

A reduction in motor unit number secondary to motor neuron loss is considered to be a major drive of age-dependent muscle wasting. Relevant alterations associated with neuromuscular system dysfunction include muscle fiber loss, fiber type grouping due to repeating cycles of denervation-reinnervation, and increased neuromuscular degradation (Marzetti et al. 2009). The functional implications of such changes involve reductions in strength and coordination and increased fatigability (Hepple and Rice 2016). A destabilization of the neuromuscular junction has also been recently indicated as a possible contributor to the generation of the sarcopenic condition (Butikofer et al. 2011).

Oxidative Stress and Mitochondrial Dysfunction

According to the mitochondrial-free radical theory of aging (Miquel et al. 1980), the accumulation of somatic mutations in the mitochondrial DNA (mtDNA) would result in reduced energy production through oxidative phosphorylation (OXPHOS) and redirection of OXPHOS electrons into reactive oxygen species (ROS) generation. The combination of defective bioenergetics and oxidative stress eventually leads to mitochondrial permeability transition and cell dismissal via apoptosis (Wallace 2005). In postmitotic tissues, such as the heart, skeletal muscle, and nervous system, cell loss, in turn, would be primarily responsible for the appearance of age- and disease-associated phenotypes.

The loss of mitochondrial metabolic flexibility and integrity, due to alterations in mitochondriogenesis, dynamics, and removal, is presently believed to underlie many aspects of the aging process as well as several age-related disorders, including sarcopenia (Riera and Dillin 2015). The inability to adapt substrate oxidation to fuel availability impairs the metabolic homeostasis and the capacity to properly respond to metabolic demands. These events, coupled with inefficient mitochondrial biogenesis, are eventually followed by impaired degradation of dysfunctional mitochondria and accumulation of abnormal, ROS-producing organelles (Riera and Dillin 2015).

As a consequence of redox imbalance, mtDNA can undergo quantitative (e.g., large-size deletions and mtDNA content variations) and qualitative alterations (e.g., base modifications, abasic sites, single- and double-strand breaks, point mutations) that affect its structure and function. Recently, mtDNA content and the expression of mitochondrial transcription factor A (TFAM), a histone-like protein for mtDNA, as well as the modulation of TFAM binding to mtDNA have been found to be relevant targets of mitochondrial dysfunction and impaired mitochondriogenesis (Picca et al. 2014; Picca and Lezza 2015).

Derangements of the muscular mitochondrial quality control (MQC) axis have been associated with sarcopenia through either the inefficient removal of damaged mitochondria or the clonal expansion of dysfunctional organelles (Calvani et al. 2013a). MQC is based on a heterarchical network of interacting pathways and processes, including fission-fusion cycles and mitophagy, which tightly link mitochondrial viability/activity to skeletal myocyte functional needs. A relevant consequence of age-related MQC dysfunction is the activation of myonuclear apoptosis, a mechanism believed to represent a final common pathway through which muscle wasting proceeds (Marzetti et al. 2012).

The Operational Definition of Sarcopenia

One of the reasons for which Rosenberg proposed to name the age-related skeletal muscle reduction with the term "sarcopenia" was to promote a better recognition of this condition by the scientific community and research funding agencies (1989; Rosenberg 1997; Rosenberg and

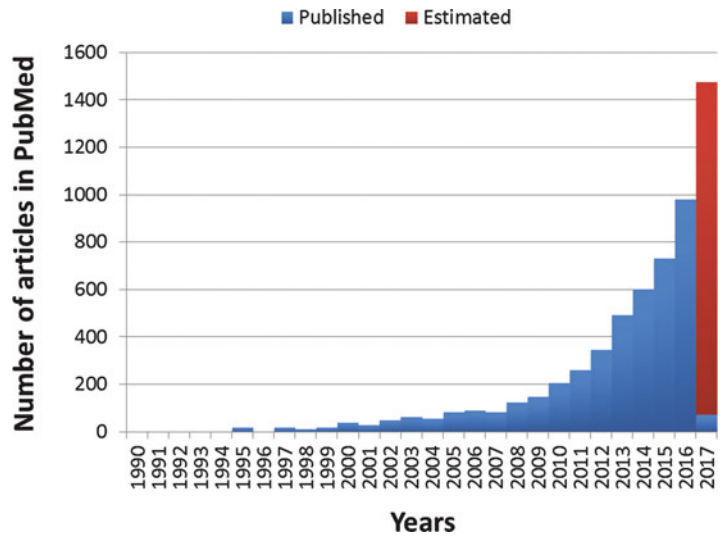

Fig. 1 Number of items retrieved from PubMed using the keyword "sarcopenia" according to year of publication. Updated on January 19, 2017

Roubenoff 1995). Indeed, there has been an exponential growth of interest around sarcopenia over the last two decades (Fig. 1).

From the first theoretical discussions about this universal phenomenon of aging (Herndon et al. 2002), it was necessary to develop operational criteria in order to feed the routine clinical and research practice. The first works in this direction proposed to center the sarcopenia definition on the only quantification of skeletal muscle mass. In particular, Baumgartner and colleagues (Baumgartner et al. 1998) defined sarcopenia as an appendicular lean mass being less than two standard deviations below the mean of a young reference group. Similarly, Janssen and colleagues (Janssen et al. 2004) proposed an index based on the quantification of muscle mass by bioelectrical impedance analysis (BIA) and provided cut points according to the likelihood of developing physical disability.

The fact that adipose tissue influences the muscle physiology via its endocrine properties (Prins 2002) suggested the need of a more holistic approach when defining the body composition profile of an individual. Newman and colleagues (Newman et al. 2003) showed that the quantity of muscle mass alone might not be sufficient to explain physical impairment in specific subgroups. In fact, the adoption of a fat-adjusted measure of appendicular lean mass was able to better explain the participants' physical performance compared with the previously proposed models in the Health, Aging and Body Composition study. Consistent results were also reported in other studies, where it was shown that the amount of fat tissue and intramuscular fat infiltrates might have an important role in the definition of the risk profile, even more relevant than the lean mass alone (Visser et al. 2005; Delmonico et al. 2007). In other words, the idea that the quality of muscle could be more important than its quantity for maintaining a healthy physical status started to go through.

The quality of muscle can be measured by quantifying the production of strength, force, and function. In this context, it is well established that muscle function is a powerful predictor of negative outcomes in the elderly and provides more information about the risk profile of an individual compared with body composition parameters (Cesari et al. 2009, 2015). Moreover, it surely is more relevant for clinicians working in the care of older persons. For this main reason, the different operational algorithms proposed over the years for capturing the condition of interest by several international groups of experts (Cruz-Jentoft et al. 2010a; Fielding et al. 2011; Morley et al. 2011; Muscaritoli et al. 2010) are characterized by a common denominator: all recognize sarcopenia as a bidimensional condition made of a quantitative (i.e., skeletal muscle mass) and a qualitative (i.e., skeletal muscle function)

component. Among the four main consensus definitions, that endorsed by the European Union Geriatric Medicine Society (Cruz-Jentoft et al. 2010a) is probably the one that received most acceptance and largest diffusion. According to this model, sarcopenia is defined by the simultaneous presence of low appendicular lean mass (assessed by dual energy X-ray absorptiometry [DXA]) plus muscle weakness (measured as poor handgrip strength) and/or impaired mobility (captured by slow gait speed). The publication of these consensus papers indicating possible ways for objectively framing a clinically relevant sarcopenia condition has given further boost to the production of scientific evidence in the field (Fig. 1).

Nevertheless, the creation of a bidimensional condition for sarcopenia generated some difficulties and controversies. Mixing variables capturing different aspects of the skeletal muscle could sometimes be perceived as confusing. The age-related decline of skeletal muscle follows a different (and less steep) trajectory than physical performance and muscle strength measures (Lauretani et al. 2003). This may (at least, partially) explain why physical function measures are stronger predictors of negative health-related outcomes than body composition parameters, perhaps because more sensitive to changes. This issue renders the bidimensional algorithms of sarcopenia unbalanced, in that their predictive value is usually driven by function rather than body composition.

Finally, in 2014, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project released a collection of papers that can today be regarded as the reference in the field. Differently from previous consensus papers based on arbitrary choices made by panels of international experts, the FNIH investigators conducted ad hoc statistical analyses in multiple cohort studies with the aim of objectively defining muscle weakness and low lean mass. It is noteworthy that the FNIH initiative followed a rigorous statistical approach based on Classification and Regression Tree (CaRT) models in order to select the best defining criteria from a wide spectrum of candidate variables. The analyses led to the identification of two sets of muscle weakness and low appendicular lean mass parameters, for which sex-specific cut-points were also generated (Table 2) (Studenski et al. 2014). Noticeably, the FNIH definitions conduct to a more conservative approach to sarcopenia compared with other algorithms (Dam et al. 2014), possibly suggesting a fairer balance between the two components.

Table 2 Variables and sex-specific cut points recommended by the FNIH initiative for defining muscle weakness and low appendicular lean mass

	Women	Men
Muscle weakness		
Handgrip strength (recommended)	<16 kg	<26 kg
BMI-adjusted handgrip strength (alternative)	<0.56	<1.0
Appendicular lean mass		
BMI-adjusted appendicular lean mass (recommended)	<0.512	<0.789
Appendicular lean mass (alternative)	<15.02 kg	<19.75 kg

BMI body mass index

When discussing about the controversies existing in the definition of sarcopenia, it cannot be forgotten the still unsolved issue related to the technique for body composition assessment. In fact, although the operational definitions largely rely on measures obtained by DXA or BIA, many methodologies exist for assessing body composition and the skeletal muscle. Each one of the multiple possibilities is characterized by pros and cons (Table 3), and each one defines a different sarcopenia profile (Pahor et al. 2009). In this heterogeneous scenario, efforts have been made to describe the different features of the available instruments. It is not excluded the possibility that different tools might be used with different purposes (e.g., screening vs. diagnosis) according to the setting (e.g., primary care vs. hospital care) where sarcopenia is assessed (Cesari et al. 2012; Beaudart et al. 2016).

Today, researchers and clinicians found themselves in front of a novel condition (i.e., sarcopenia) with some limitations to be clarified:

- Multiple methodologies to assess body composition in the absence of a recognized gold standard

Table 3 Characteristics of the most frequently used methods for the assessment of skeletal muscle. (Modified from Pahor and colleagues (Pahor et al. 2009))

Method	Strengths	Weaknesses
MRI	Best resolution Assessment of muscle quality (i.e., intramuscular fat infiltrates) Quantification of lean and fat mass	Highly expensive equipment Need of special training and expertise Time-consuming Space requirements Results specific of a body district
CT	Assessment of muscle quality (i.e., intramuscular fat infiltrates) Quantification of lean and fat mass	Highly expensive equipment Need of special training and expertise Time-consuming Exposure to radiations Space requirements Results specific of a body district
DXA	Quantification of lean and fat mass Commonly used in the clinical setting Relatively inexpensive exam No special training General and sectorial quantification of body composition components	No muscle quality assessment Space requirements Low-dose radiations Not differentiating water from bone-free lean tissue High costs for the machine
BIA	Relatively cheap device Inexpensive exam Minimal maintenance Portable	Variable body resistance No muscle quality assessment Low accuracy No specific body district
Anthropometry	Easy to assess Inexpensive	Very limited accuracy No muscle parameter assessment
Ultrasound	Low cost for the exam Qualitative assessment of (specific) muscles structure	Relatively high costs for the machine Need of trained personnel Evaluation of a very specific body district Operator-dependent

MRI magnetic resonance imaging, *CT* computerized tomography, *DXA* dual energy X-ray absorptiometry, *BIA* bioelectrical impedance analysis

- A bidimensional definition presenting one factor more relevant than the other in determining the risk profile
- Unclear clinical utility of sarcopenia, especially if framed as a mere screening condition for the identification of individuals at risk of disability (Cesari and Vellas 2012)

Translation of Sarcopenia in Oncology

Prevalence of Sarcopenia

The heterogeneity of operational definitions, methodological procedures, and defining cut-points makes it challenging, if not impossible, to clearly estimate the prevalence of sarcopenia in the general population. Since sarcopenia can be considered as a hallmark of poor health status, its prevalence tends to vary across clinical settings, from the lowest prevalence reported in the community/primary care up to the highest documented in nursing homes.

Consistently, the estimation of sarcopenia in oncology might be perceived as a pure epidemiological exercise lacking a robust clinical and biological rationale. In fact, the existing controversies about the objective assessment of sarcopenia are here further enhanced by the presence of an additional major confounder that is the oncological condition, differently affecting the skeletal muscle according to its site and severity. For completeness but with all the due precautions in the application of these data, it is worth to mention the systematic review conducted by Rier and colleagues (Rier et al.

2016) reporting a prevalence of sarcopenia (defined using computerized tomography) ranging from 5% to 89% in different populations of oncological patients.

Different Objectives

As mentioned, the construct of sarcopenia was originally developed for sustaining research on aging and developing interventions against physical function loss. For this reason, the first applications of sarcopenia have been conducted in community-dwelling older persons. In this context, the interest in measuring sarcopenia was to detect the biological substratum of a condition of risk exposing an older person (even if in apparently good health) to incident disability. Sarcopenia was then a sort of pre-disability condition for promoting healthy lifestyle and successful aging.

These objectives might not completely fit when the quantification of the skeletal muscle is conducted in a person affected by a potentially lethal disease such as cancer. In this setting, priorities may be different. Of course, the preservation of the functional status remains a cornerstone in the definition of the interventions, but the treatment of cancer has equal (if not superior) importance.

Often sarcopenia is incorrectly seen as a condition to screen the most vulnerable elders, a sort of risk assessment tool. Surely, sarcopenia is a strong predictor of negative health-related outcomes, independently of the setting where it is assessed. The prognostic value of low muscle mass is well established in oncology as well as in other specialties (Rier et al. 2016). However, easier, cheaper, and more clinical friendly instruments are available for this purpose in geriatrics as well as in other medical specialties. If the clinician (or public health authorities) does not see the special advantages for his/her practice from the assessment of a certain parameter, then it will never be implemented. It will be perceived as redundant if not useless, especially if time-consuming and/or possible generator of extra costs.

Sarcopenia should instead be considered as a biological marker capable of more actively feeding decisional algorithms in clinics. In particular, body composition may play a relevant role in defining the patient's risk profile for chemotherapy adverse reactions (Gérard et al. 2016). For example, the administration of lipophilic agents to individuals with different body composition profiles but equal body mass/surface may expose them to different levels of risk for adverse reactions. Unfortunately, to date, the use of sarcopenia (and body composition) in the oncology setting is still limited. Sarcopenia is commonly seen as a risk factor for negative outcomes, and body composition-adjusted protocols of chemotherapy are still lacking. Moreover, the paucity of efforts and funding in the area of cancer therapy toxicity (to which sarcopenia and body composition might greatly contribute) has already been evoked in specialized literature (Cleeland et al. 2012). Nevertheless, the conduction of specific research in this field is necessary (Prado 2013). Oncologists do not need additional tools for measuring the risk profile of their patients (Hamaker et al. 2012). At best, collaboration between oncologists and geriatricians might converge in the development of specific and shared screening instruments for frailty.

Different Tools

As mentioned, the definition of sarcopenia is usually based on algorithms measuring skeletal muscle mass via DXA or BIA. These instruments are not part of the oncological routine and might be perceived as burdening the already busy and time-limited schedule of cancer patients waiting for pharmacological and non-pharmacological treatments. In order to diffuse the evaluation of body composition in the oncological setting, it is therefore important to rely on measures that are already included in the diagnostic or therapeutic *iter* of the patient. Thus, some authors have started generating models of sarcopenia pragmatically taking advantage of body composition parameters routinely collected during the cancer staging. For example, Psutka and colleagues (Psutka et al.

2014) computed a skeletal muscle index from CT images obtained at the level of the third lumbar vertebra during abdomen scan. Such legitimate and scientifically valid approach has been growingly used over the last years for introducing discussions and interventions on body composition in oncology (Kazemi-Bajestani et al. 2016; Prado 2013). Certainly, the use of CT scans may deviate from the algorithms and recommendations designed for the community setting, limiting the possibility of comparisons of findings with other realities. However, it can be acceptable to proceed in parallel on the same condition of interest in two contexts because needs and resources are different. Moreover, everything may currently be justified by the lack of gold standard references on the topic.

Sarcopenia Versus Cachexia

One of the major ambiguities to solve when discussing about skeletal muscle wasting in cancer patients is the "sarcopenia and the cachexia" dilemma. Are we sure that when we measure sarcopenia in the oncology setting, we are not instead getting information on the apparently similar but biologically different condition of cachexia?

Cachexia is defined as a complex metabolic syndrome associated with underlying illnesses, generally heart failure, chronic obstructive pulmonary disease, and cancer. It is characterized by muscle wasting with or without loss of fat mass. The most relevant feature of cachexia is represented by weight loss (in adults) or growth failure (in children). It is a wasting disorder finding its biological roots in the commonly associated anorexia, inflammation, insulin resistance, and increased muscle protein breakdown (Evans et al. 2008; Sakuma and Yamaguchi 2012b).

If all these characteristics of cachexia are individually considered, it is possible to realize how close this condition is to the sarcopenia construct. In fact, the biological substratum of the two is largely overlapped. If cachexia and sarcopenia are considered as two conditions placed at different levels in the continuum of muscle decline, it is necessary to identify a clear and objective threshold that differentiates the two. It is possible that cachexia is simply a state of sarcopenia accelerated and accentuated by the massive catabolic stimulus caused by an index disease.

As occurred for sarcopenia, some confusion also stem from the lack of a clear and agreed definition of cachexia. Evans and colleagues (Evans et al. 2008) proposed to base the diagnosis of cachexia on the presence of weight loss accompanied by at least three out of five additional criteria (i.e., muscle weakness, fatigue, anorexia, low skeletal muscle index, and abnormal biochemistry) (Table 4). More recently, Fearon and colleagues (Fearon et al. 2011) described a different diagnostic model for cachexia in cancer. This latter operational definition is largely based on the quantification of weight loss and sarcopenia and differentiates three levels of severity (Table 5).

Table 4 Diagnostic criteria for cachexia in adults proposed by Evans and colleagues (Evans et al. 2008)

Main criterion	
Weight loss	At least 5% reduction of weight occurred within 12 months in the presence of underlying illness, or BMI <20 kg/m^2 if weight loss cannot be documented
Secondary criteria	
Decreased muscle strength	Poor handgrip strength
Fatigue	Physical and/or mental weariness resulting from exertion. Inability to continue exercise at the same intensity with consequent deterioration of performance
Anorexia	Limited food intake (i.e., total caloric intake less than 20 kcal/kg of body weight/day; less than 70% of usual food intake) or poor appetite
Low fat-free mass index	Lean tissue depletion (i.e., low mid-upper arm muscle circumference, low appendicular skeletal muscle index)
Abnormal biochemistry	Increased inflammatory status (CRP >5.0 mg/L; IL-6 $>$ 4.0 pg/mL)
Cachexia is defined by the presence of the main criterion plus at least three secondary criteria	

BMI body mass index, *CRP* C-reactive protein, *IL-6* interleukin 6

Table 5 Diagnostic model of cancer cachexia as proposed by Fearon and colleagues (Fearon et al. 2011)

Stage	Characteristics
Precachexia	Weight loss ≤5% Anorexia Metabolic change
Cachexia	Weight loss >5% over the past 6 months (in absence of simple starvation) BMI <20 kg/m^2 and any degree of weight loss >2% Appendicular skeletal muscle index consistent with sarcopenia and any degree of weight loss >2% Often reduced food intake Systemic inflammation
Refractory cachexia	Variable degree of cachexia Cancer disease both pro-catabolic and not responsive to anticancer treatment Low performance score Less than 3 months of expected survival

BMI body mass index

Looking at the criteria presented in both operational definitions, the overlap between sarcopenia and cachexia becomes evident. Moreover, it is noteworthy how many variables included in the construct of these forms of cachexia can be found in several definitions of the geriatric syndrome of frailty. For example, the symptoms/signs of weight loss, fatigue, and poor physical function are frequently indicated as key features of frailty clinical manifestations (Ferrucci et al. 2004).

Interventions against Skeletal Muscle Decline in Older Persons with Cancer

Methodological Considerations

Overlap between different clinical conditions is frequently observed in geriatric patients. With advancing age, the traditional concept of disease tends to lose its relevance in favor of the more pragmatic construct of function. In other words, the center of the medical action moves from the nosologic condition (traditionally framed within rigid and arguable burdens) toward a more holistic and comprehensive evaluation of the patient. The change in paradigm implies methodological differences to be accepted and implemented in the daily clinical and research routine. To put it simple, it means that sarcopenia in older persons cannot be understood and treated without perceiving it as the "tip of an iceberg." It represents one of the many conditions that might potentially represent the entry door to a multidimensional and multidisciplinary assessment of the individual. This can easily be appreciated by looking at the many etiological causes and mechanisms underlying the onset of sarcopenia (Table 1). As such, the boundaries between sarcopenia, cachexia, and frailty may become of lower relevance. It is instead more important the action following the detection of one of these conditions in which the skeletal muscle decline (and its detrimental consequences) plays a major role (Cesari et al. 2016b).

In a traditional model of care, the identification of a clinical condition is usually followed by a mono-dimensional, direct, and specific treatment. With geriatric conditions, the paradigm works differently. The intervention can here be designed and implemented only after a global and comprehensive evaluation of the individual, an approach that is not only focused on his/her biological and clinical profile but should include the environment where he/she lives (Studenski 2009; Marzetti et al. 2016; Cesari et al. 2016a). It is noteworthy that, consistently with this approach, it is not rare to see sarcopenia considered as a geriatric syndrome in the literature (Cruz-Jentoft et al. 2010b; Landi et al. 2016b). The prioritization of interventions according to the resulting risk profile and resources of the individual will then allow designing a person-tailored action plan, which includes pharmacological and non-pharmacological components.

In general, it is important to contextualize the sarcopenia phenomenon according to the framework of action. If sarcopenia or other risk conditions are simply used to aliment an adapted model of care, their operational definition should be based on the needs and resources of the intervention. Overlap and some degree of inaccuracy could be easily tolerated. Differently, if sarcopenia should serve as the biological substratum

for muscle-specific interventions (or actions affected by body composition), its standardized and rigorous assessment becomes crucial.

Physical Exercise

Physical exercise represents the most powerful intervention against the loss of muscle mass and physical impairment. In the phase III Lifestyle Interventions and Independence for Elders (LIFE) trial, Pahor and colleagues (Pahor et al. 2014) showed that the implementation of a physical activity protocol was able to reduce the incidence of mobility disability in sedentary and frail community-dwelling older persons. Consistent findings have also been reported by similar researches conducted in smaller groups of cancer patients showing the beneficial effects of exercise (Galvão et al. 2007; Adamsen et al. 2009; Galvao et al. 2010). Not surprisingly, physical exercise is today considered to be equivalent to medications, and special attention is devoted to the design and standardization of recommendations for its prescription (Eijsvogels and Thompson 2015).

Nutrition

Nutrition plays a major role in the maintenance of muscle mass and function. In particular, it has been shown that the dietary intake of protein represents the primary source for limiting the age-related loss of lean mass. Recent recommendations provided by international task forces are soliciting clinicians at increasing the minimum daily protein intake of their older patients, from 0.8 g/kg/day to 1.0–1.2 g/kg/day. For conditions characterized by enhanced catabolism (such as cancer cachexia), this threshold is raised up to 1.2–1.5 g/kg/day (Bauer et al. 2013; Deutz et al. 2014).

It is not only important the amount of protein introduced with the diet but also the pattern of their consumption. In fact, a physiological limit in the protein synthetic capacity of the organism has been reported, indicating that a spread feeding of proteins over the day should be preferred over a time-skewed pattern (Paddon-Jones and Rasmussen 2009). The amino acid composition of dietary protein also has a great impact of their muscle anabolic potency. Essential amino acids (in particular, leucine) represent the primary stimulus for protein synthesis and turnover (Calvani et al. 2013b).

Nicholson and Wilson (2003) proposed in 2003 the dynamic "Pachinko model" to describe the nutritional regulation of muscle physiology. Dietary constituents flow through the human system in a probabilistic way, influenced by non-modifiable factors described as fixed pins (e.g., age, gender, race, etc.) and others (e.g., epigenetic and/or transcriptional regulation of genes, hemodynamics) that can be modified by acting on "control knobs" (e.g., meal timing, physical exercise, gut microbiota manipulation). These latter represent the lever on which we can act for optimizing the effects of nutrition of muscle physiology (Calvani et al. 2013b) (Fig. 2).

Pharmacological Interventions

To date, no pharmacological intervention exists against sarcopenia. Multiple agents have been proposed and tested over the years for counteracting the skeletal muscle decline. Unfortunately, even the most promising agents (e.g., testosterone in hypo-androgenic men) (Snyder et al. 2016) and myostatin inhibitors (Woodhouse et al. 2016) have fell short of expectations, only showing partial improvements on secondary outcome measures.

One of the major issues affecting the development of medications targeting skeletal muscle decline is represented by its lack of proper recognition by regulatory agencies. In fact, if sarcopenia is not framed in agreement with the traditional standards of a nosologic condition, regulatory agencies are not in the position to adequately consider it. This is not a minor aspect because it substantially affects the interest of pharmaceutical companies at investing in the field.

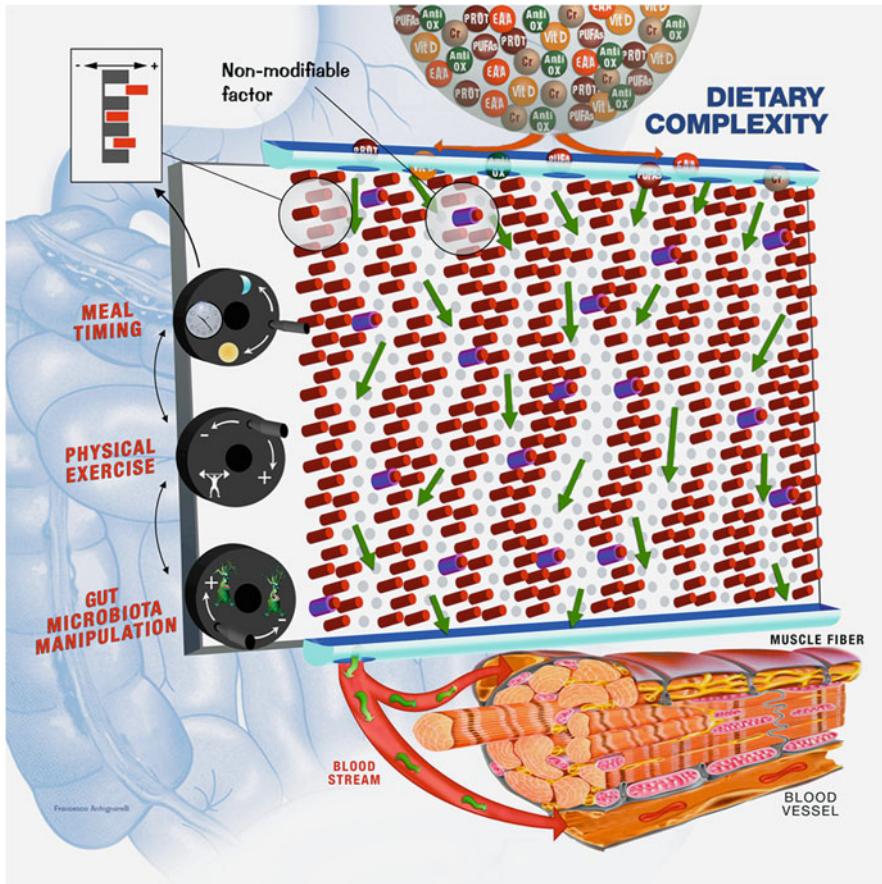

Fig. 2 The "Pachinko model" describing the nutritional regulation of muscle physiology. (Authorized reproduction from Calvani and colleagues (Calvani et al. 2013b))

In 2014, the Innovative Medicines Initiative (an agency of the European Commission mediating between the academic world and the European Federation of Pharmaceutical Industries and Associations) funded the "Sarcopenia and physical frailty in older people: multicomponent treatment strategies" (SPRINTT) project (Marzetti et al. 2015). This is a unique initiative aimed at having all the major stakeholders (e.g., researcher, clinicians, industry, patient representatives, regulatory agencies) involved in the development and validation of a nosologically framed condition of risk centered on the skeletal muscle. Hopefully, the study results will support the framing of a sarcopenic condition acceptable by regulatory agencies (in this case, the European Medicines Agency) and overcome some of the current barriers.

Adapted Model of Care

If the skeletal muscle decline is considered as one of the many risk factors exposing the older person at risk of negative outcomes, its proper identification and management can only occur in the context of adapted models of care. Under this scenario, the oncology and geriatric disciplines have started and intensified bidirectional exchanges over the last years in order to improve care services offered to the aging population of cancer patients (Hurria et al. 2017). The number

of oncogeriatric units is increasing worldwide. They represent the multidisciplinary setting where the specialist approach of the oncologist is supported by the geriatrician's expertise in the multidimensional evaluation of the complex frail elders (Cesari et al. 2013).

Conclusions

Since its origins dated about 25 years ago, sarcopenia has been object of increasing interest in the scientific community. This condition is part of the geriatric background and is today starting to disseminate in other specialties dealing with the complexity of frail older persons. Several controversies have characterized the theoretical framework, operationalization, and treatment of sarcopenia in the geriatric and scientific community settings. These same issues will likely affect the development of sarcopenia in the oncological context, where the study of this condition is challenged by different care priorities, clinical complexities, and biological mechanisms. Nevertheless, the study of skeletal muscle remains crucial for promoting care services aimed at enhancing the proper functioning of the individual, independently of the diseases he/she may present. Future research actions (supported by a pragmatic clinical approach) are necessary for better understanding the causes and contributors to the skeletal muscle decline in older persons with cancer and adapt to this population the growing (but already vast) knowledge that geriatric research has accumulated on the skeletal muscle system over the last couple of decades. The study of body composition in the oncological setting is crucial and may become one of the main characterizations of this interdisciplinary field, where clinical and research actions have to be designed taking into account the consequences of the aging process.

Cross-References

- ▶ Aging and Cancer Biology
- ▶ Biomarkers of Aging (With a Clinical Potential in Oncology)
- ▶ Comorbidity in Aging and Cancer
- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Frailty in Cancer Patients
- ▶ Geriatric Interventions in Oncology
- ▶ Geriatric Screening in Cancer Patients
- ▶ Integrating Geriatric Oncology in Public Health Planning
- ▶ Mitochondria, Oxidative Stress, Cancer, and Aging
- ▶ Normal and Abnormal Aging (General Perspective for the Oncologist)
- ▶ Organizing the Clinical Integration of Geriatrics and Oncology
- ▶ Predictive Tools for Older Cancer Patient Management
- ▶ Research Methods: Clinical Trials in Geriatric Oncology
- ▶ Research Methods: Epidemiologic Research in Geriatric Oncology
- ▶ Research Methods: Outcomes and Survivorship Research in Geriatric Oncology
- ▶ Role of Cell Cycle Control, Checkpoints, and DNA Repair Mechanisms in Stem Cells and Changes with Aging and Cancerogenesis

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Neurological Aging and Cancer

18

Christine Sam and Juan Pablo Negrete-Najar

Contents

Abstract

The effects of aging on the nervous system are widespread and come from changes on molecules, cells, vasculature, and gross morphology. The changes in the brain include decrease in volume, gray matter thinning, abnormalities in proteostasis, apparition of white matter lesions, nerve cell death, dendritic retraction and expansion, synapse loss and remodeling, and glial cell (astrocytes and microglia) reactivity. There are also changes in the autonomous and peripheral nervous system, such as lower sensibility of adrenergic receptors and lower recovery of function after peripheral nerve damage. The mentioned changes can have an impact in the functionality of the person. In general, said impact of these

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changes on a person's functionality is discrete, but combined with other environmental factors such as vascular disease, diabetes, or cancer, it can lead the individual to true impairment. Altogether, even without a disease, these changes put the older individual at higher risk of neurotoxic effects of chemotherapy, such as encephalopathy, neuropathy, and cognitive decline. The risk of developing neurotoxicity is dependent on numerous factors, including dose intensity, baseline neurological deficits, drug interactions, and drug mechanism of action. Early recognition of adverse neurologic effects and differentiation from central nervous system progression of cancer is critical for timely and appropriate adjustments in dosing or discontinuation of the drug, in order to protect the functionality and independence of the older patient with cancer.

Introduction

Aging can be defined as the process of gradual physiological deterioration that most living beings experience with time; it is usually seen as the result of accumulation of molecular and cellular damage. The changes that occur during an organism's lifespan that are categorized as aging are heterogeneous, heterochronic, and dynamic, which is why systematic study of this subject has been difficult and has just exploded in the last few decades (Lopez-Otin et al. 2013; Carmona and Michan 2016).

There is no clear evidence of which molecular, cellular, or physiological changes are the most important drivers of the aging process or how they influence one another, but it seems that the magnitude of an isolated mechanism is usually modest (Trindade et al. 2013). Dr. E. Lakatta once mentioned that "Aging appears not to be a process, but rather a manifestation of a time-dependent, stochastic, molecular disorder that ensues when our natural selection insurance policy expires." (Lakatta 2015)

Aging thus may be conceptualized as a progressive, time-dependent molecular disorder within the systems of an organism, accompanied by reduced complexity and increased entropy, leading to reduced efficiency and efficacy of molecular interactions that regulate cells, tissues, and organ structure and coordinate functions among organ systems, including the nervous system.

The issue of normal aging is a difficult one, given that most of the changes that occur with the passing of years are similar to those that happen in some of the diseases that are common in the elderly. The line that separates "physiological" aging from disease is a blurry and winding one, and in the nervous system, this distinction can be more difficult to make. Everyone will age, but not everyone will have a disease.

The effects of aging on the brain are widespread and come from changes on molecules, cells, vasculature, and gross morphology. Many brain functions reflect the effects of aging. For example, declines in motor abilities (Seidler et al. 2010), sensory function (Brodoehl et al. 2013), and cognitive skills have all been observed with natural aging.

Along with these functional declines, the cerebral levels of neurotransmitters, such as dopamine, acetylcholine, serotonin, and norepinephrine, and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), are dramatically reduced in aging brains (Liu et al. 2017).

These changes will have an impact on the daily life of the elderly, but most of them will be overcome, and the healthy person will adapt to them. Still, even in the healthiest aged individual, there is more neuronal loss, vascular pathology, and changes at the cellular level compared with healthy younger adults (Schott 2017).

Changes in the Brain

It has been widely found that the volume of the brain declines with age at a rate of around 5% per decade after age 40, with the actual rate of decline increasing with age particularly over age 70. It seems that this reduction in volume comes from a decline in neuronal volume rather than number, and as a compensatory mechanism

for any cell death, dendritic sprouting may occur. It is important to mention that this loss of volume causes an expansion of the ventricular system which can be seen in imaging studies.

The changes in the brain have been mainly described in the prefrontal cortex and the hippocampus, and it seems that the least affected region is the occipital. These findings are backed up by the cognitive changes found with aging (Peters 2006).

Population-based autopsy studies of the brains of aged people without neurological diseases consistently report the presence of protein abnormalities (amyloid plaques, neurofibrillary tangles, and Lewy bodies), synaptic dystrophy, as well as the previously mentioned loss of brain volume in most of the brains (Elobeid et al. 2016). The theory behind the proteostasis abnormalities is that of a decline and overwhelming of the phagocytic and lysosome systems in nervous tissue. It is unknown what causes such lesions and whether they are the precursors to neurodegeneration and disease or simply the products of brain aging (Wyss-Coray 2016). An example of this is that in a population-based sample of nonagenarians and centenarians without dementia, almost half fulfilled the neuropathological criteria for Alzheimer's disease (AD) or had a mix of numerous pathologies. Yet, of the nonagenarians and centenarians who had been clinically diagnosed with dementia, 12% were free of pathological features, 23% could be considered to have AD, and 45% had mixed dementia (Kawas et al. 2015).

All of the major cell types in the brain undergo structural changes during aging. These changes include nerve cell death, dendritic retraction and expansion, synapse loss and remodeling, and glial cell (astrocytes and microglia) reactivity. Such structural changes may result from alterations in cytoskeletal proteins and the deposition of insoluble proteins such as tau and α-synuclein inside of cells and amyloid in the extracellular space (Mattson 2008).

There is considerable evidence for synaptic "remodeling" in the brain as we age. For example, there may be decreases in synaptic numbers in some brain regions, but these may be offset by increases in the size of the remaining synapses. In other brain regions, no loss of synapses can be discerned. Some of this remodeling has, as a consequence, the bilaterality of region activity on functional MRI found in older population. An example of this can be seen with cognitive testing. During normal aging, changes occur in the pattern of stimulation of neural networks, causing increased activation in some areas and decreased activation in others. Studies reveal that when an elderly person performs a cognitive task at the same level as that of a young adult, more areas of the former's frontal brain regions "light up," suggesting more brain activity is needed to maintain cognitive performance (Mattson 2008).

As aging happens, especially after the seventh decade of life, a nonlinear and brain-wide trend to gray matter thinning predominant in the parietal and frontal lobes is observed in normal subjects from the second to the eighth decade; this slight frontal atrophy is associated with a decrease in performance on executive and working memory tests (Lyons-Warren et al. 2004).

With the new MRI technologies, the cortical atrophy consecutive to an aging period as short as 1 year can be readily measured, and longitudinal studies have found that the annual atrophy rate varies across the cortex and is about 0.5% per year on average in a group of healthy subjects aged 60–91 years; the hippocampus (–0.84%) is the most affected area. In an AD sample, the annual atrophy rate was higher, with 1% per year change or more, with the widest affectation in the posterior cingulate/precuneus region and lateral temporal cortex (Fjell et al. 2009).

White matter (WM) is mostly composed of bundled myelinated or unmyelinated axons and myelin-producing glial cells, among other glial cell types. WM is essential for the transmission of electrical signals across different brain regions, and WM malfunction can therefore lead to serious neurobehavioral and cognitive impairments (Bennett and Madden 2014).

In normal aging, the changes identified in WM are atrophy, tract disruption, vessel impairments, increased inflammation, and loss of myelination. An estimated 28% of volume reduction happens in WM with aging. This begins around 40 years of

age, peaks at around 50, and decreases rapidly after 60 years and on (Liu et al. 2017).

Brain tissue depends vitally on a constant supply of oxygen and glucose by blood vessels. Aging induces a progressive thickening and stiffening of arteries that alter hemodynamics of cerebral vasculature and the efficiency of the transfer of energy metabolites to glial and neural cells. The vascular alterations can be manifested as WM lesions, also known as leukoaraiosis, which appear on T2-weighed MRI with aging. Depending on the anatomical location, some WM lesions may be responsible for distinct types of functional decline. For example, WM lesions in the frontal lobe are responsible for alterations in the speed of information processing, visual motor function, verbal fluency, and mental sequences (Bartres-Faz et al. 2001).

Animal studies have shown that there is increased splitting of the myelin sheath, myelin balloon formation and separation from the axon (Akiyama et al. 2002), reorganization of ion channels at the nodes of Ranvier, and decreased length of internodal length. These changes cause an increase in the axonal conduction threshold and thus a decrease in the stimulus response, reflecting overall neuronal excitability.

Degeneration of oligodendrocytes and their precursor cells increases with aging, leading to increased myelin breakdown, decreased remyelination, fluctuations in the constituents of myelin, and ultimate disruptions in WM integrity during normal aging (Liu et al. 2017).

Both astrocytes and microglial cells display a senescence-associated secretory phenotype, with the consequence of increased production of inflammatory factors and free radicals. However, this concept was recently challenged by the demonstration of downregulation of neurotoxic pathways and upregulation of neuroprotective pathways in aged microglia (Hickman et al. 2013).

Recent studies suggest that damaged mitochondria are removed and degraded by the autophagic pathway. Autophagic function may be compromised in the aging human brain. This may lead to the accumulation of dysfunctional or degenerating mitochondria, resulting in increased reactive oxygen species (ROS) generation and the release of redox-active iron (Yankner et al. 2008). Oxidative damage of DNA may be mediated by ROS derived from aging mitochondria. DNA damage is repaired efficiently in the young adult brain but persists in the aged brain. During normal aging, this may result in the silencing of genes involved in synaptic plasticity, mitochondrial function, and protein trafficking, potentially contributing to cognitive decline.

Damage to mitochondrial DNA can lead to failure of electron transport and reduced adenosine triphosphate (ATP) production. Moreover, the important calcium sequestering function of mitochondria may be compromised as the result of age-related DNA damage, which may increase neuronal vulnerability to excitotoxicity and apoptosis (Mattson 2008).

Together, the genetic, transcriptomic, and proteomic evidence suggest that changes in inflammation and intercellular communication represent chief aspects of normal brain aging and neurodegeneration. However, it is unclear whether inflammatory pathways simply drive aging and disease or whether aspects of the inflammatory response fulfill reparative and regenerative functions (Coppe et al. 2008).

Altogether, the mentioned changes can have an impact in the functionality of the person. In general, the said impact is discrete, but combined with other environmental factors such as vascular disease, diabetes, or cancer, it can lead the individual to true impairment.

Cognitive Changes

Cognitive aging is a lifelong process of change in cognitive capacity through time. The process is gradual and ongoing, and highly variable, within and between individuals. Cognition, and therefore cognitive aging, is not simply memory but all of its dimensions, including perceptual-motor function, language, executive function, complex attention, and social cognition (McArdle et al. 2009; Sachdev et al. 2014).

Cognitive function declines in parallel across the lifespan with decreasing brain volume,

dopamine receptors, and white matter integrity. At the same time, direct relationships between declining structural measures of the brain and cognitive function are not always observed, and when they are observed, they are of a modest magnitude. White matter hyperintensities appear to have more significance than total brain volume (Park and Reuter-Lorenz 2009).

There are genetic mechanisms associated with age-related cognitive impairment. Transcriptional profiling of the aging human frontal cortex in a group of 30 individuals ranging from 26 to 106 years of age showed that approximately 4% of the genes expressed in the brain are age regulated (Lu et al. 2004). Age-related changes in gene expression become apparent in middle age and are most notable after 70 years of age. Genes involved in synaptic functions that mediate memory and learning are significantly age downregulated, including glutamate receptor subunits and synaptic vesicle proteins (Yankner et al. 2008). Still, most of the information available on cognitive aging comes from neuropsychological testing.

The norms of cognitive function vary across educational levels and lifelong experiences. For these reasons, whenever a cognition examination is done, the most appropriate norm is the person tracked over time (Lin et al. 2017).

As with other changes associated with aging, cognitive abilities may show at least a small decline, but not all, and not all of the healthy individuals. It is important to mention that declining ability does not translate into impairment of daily activities, especially because these changes are subtle with healthy aging. The most consistent change is cognitive slowing. For example, on a writing task in which people were asked to substitute symbols for numbers as quickly as possible, 20-year-olds performed the task almost 75% faster on average than 75-year-olds. Age-related slowing is also evident on attentional tasks, such as trying to learn a telephone number or address if the information is given quickly or trying to understand the prescription of a new medication (Hartshorne and Germine 2015).

In older people, there can be a deficit in attention, particularly associated with multitasking. Processing information rapidly and dividing attention effectively are cognitive skills that peak in young adulthood and decline thereafter. Similarly, the ability to keep multiple pieces of information in mind at the same time is another skill that peaks around ages 18–20 and becomes more difficult at later ages (Caserta et al. 2009).

Quantitative reasoning and perceptual speed, which may be associated with loss of WM volume and integrity in areas such as the prefrontal cortex are usually associated with physiological aging (Caserta et al. 2009). However, verbal fluency and semantic memory do not decline with normal aging, perhaps because these skills are highly dependent on past experience such as education and occupation.

While memory declines for many people over time, the exact nature of the decline depends on the particular type of memory. Episodic memory performance declines from middle age onwards. This is particularly true for recall in normal aging and less so for recognition. The ability to recall new information peaks early and gradually becomes more challenging after age 40, particularly for visual material. Studies show that by age 70, the amount of information recalled 30 min after hearing a story once is about 75% of the amount remembered by an 18-year-old (Hartshorne and Germine 2015). Semantic memory increases gradually from middle age to the young elderly but then declines in the very elderly. Recognizing information by the help of cues is an ability usually well retained throughout the life (Buchman et al. 2014).

Some memory differences with age are due to declines in controlled, but not automatic, processes resulting in poor explicit memory but relatively good memory for gist or versions of stimuli that feel familiar. Consequently, aging memory relies heavily on gist, making it highly susceptible to distortions and misremembering (Park and Reuter-Lorenz 2009).

Normal age-related memory loss is distinguished from pathological memory loss both by the degree of impairment and the rate of cognitive decline. A structural correlate of pathological memory loss is volume loss in the medial temporal lobes, particularly the entorhinal cortex. This volume loss can appear at the earliest stages of

mild cognitive impairment, progressing to severe atrophy in AD, but generally is not observed in normal aged individuals. There is increasing evidence, therefore, that altered brain activation on functional imaging and the appearance of early pathological changes in medial temporal lobe structures may distinguish incipient dementia from normal aging (Hedden and Gabrieli 2004).

Visual perceptual abilities, principally the ability to understand spatial relationships, also decline with age, especially after age 80. Visual scanning ability also can diminish so that, for example, it becomes more difficult to see a misplaced object among other items. These changes can affect the ability to drive or work with the hands.

Executive functioning refers to higher level skills, such as the conceptualization of a problem, making appropriate decisions, and planning and carrying out effective actions. Older adults tend to be slower in conceptualizing problems and less ready to change strategies when circumstances shift. In one study involving decision making, one third of older adults did poorly compared to younger adult (Denburg et al. 2007).

Language and vocabulary are well retained throughout the lifespan. In fact, vocabulary continues to improve into middle age. Recall of general knowledge acquired at a young age and well-practiced skills also peak in middle age and are resistant to age-related decline. In general, these age-resistant cognitive skills have been strengthened by experience, including situations that require reasoning and judgment.

Age limitations interfere with performance when information acquired in an unfamiliar situation needs to be processed quickly or there are distractions that should be ignored, such as in a busy clinic or when receiving bad news. As a result, older adults on average consider fewer bits of information and use less effective decision-making strategies when they are in unfamiliar situations compared to younger adults. And this can have a really important impact while giving a cancer diagnosis or explaining a treatment and its effects and consequences (Tucker and Stern 2011; Hartshorne and Germine 2015).

The notion that cognitive ability and chronological age are not necessarily directly coupled within individuals has led to the concept of "mindspan" (similar to "lifespan" and "healthspan"), which defines the period of time during which intact cognitive ability is maintained. The goal of research on the neurobiology of cognitive aging is to discover the means by which mindspan can be maximized, maintaining the quality of life that is associated with intact cognitive ability (Fortenbaugh et al. 2015).

As stated before, cognitive aging isn't a disease, but it has similitudes to neurological degenerative diseases, for some it can even be a prepathological state. It seems that the healthy aging cognition has ways to adapt to the changes to function almost normally. Converging evidence from a range of studies using different approaches suggests that the additional age-associated neural activation, especially in prefrontal areas, appears to be functional and to enhance task performance. Many researchers and models have described these activation increases as "compensatory" and suggest that the brain reorganizes as a response to neural aging. The compensation is for the structural changes that occur in the brain in terms of both volumetric decrease and white matter integrity. Shrinkage and dysfunction may reach a critical point as pathology increases, and at that point, the reciprocity no longer exists. After that, the cognitive problems can have clinical manifestation (Park and Reuter-Lorenz 2009).

Changes in the Peripheral Nervous System

With respect to the peripheral nervous system (PNS), several clinical and experimental studies have described that normal aging is accompanied by reduction in maximal tetanic force, impairment of thermal, tactile, and vibration sensitivity, and autonomic dysfunction.

In noninjured peripheral nerves, normal aging is accompanied by impairment of cutaneous sensitivity. Thermal, tactile, and vibration thresholds are increased (Navarro et al. 1988). Hot pain thresholds are similar in young and elderly subjects in the hands, but in the feet, the older subjects

are significantly less sensitive to noxious heat (Navarro and Kennedy 1991). Two-point discrimination deteriorates with time, and vibratory sensibility thresholds also increase significantly with age, both in the hand and foot.

Interestingly, animal studies have demonstrated that aged individuals have a lower basal mechanical nociceptive threshold and exhibit more severe tactile allodynia after partial nerve injury compared to younger individuals (Kovacic et al. 2009).

Aging also affects functional and electrophysiological properties of the PNS, including a decline in nerve conduction velocity, muscle strength, sensory discrimination, autonomic responses, and endoneural blood flow (Verdú et al. 2000). On the other hand, conduction velocity of unmyelinated fibers is relatively unaffected in old individuals.

Age myelinated axons undergo atrophy and shape alterations. The myelin sheaths show ballooning, splitting, infolding, and remyelination. These changes may be partially explained by alterations in axonal transportation system which causes a reduction in the energy available for peripheral nerves (McQuarrie et al. 1989). In addition, a progressive reduction of nerve blood flow associated with an increase in nerve vascular resistance (due to a reduction in microvascular caliber) and a normal hyperemic response was observed in aged rats (Kihara et al. 1991).

Several clinical investigations have reported that both the rate and the degree of functional recovery of the peripheral nerves after injury are significantly reduced with aging (Verdú et al. 2000). The impaired functional reinnervation with aging may be also due to a reduction of the number of regenerating axons that succeed to reach their target, and due to a limited capability for terminal regenerative axon sprouting in target tissues. After nerve injury in the elderly, the collateral nerve sprouting, which is crucial for functional recovery, will be reduced in extent and of lower density (Kovacic et al. 2007).

This reduction in functional recovery is crucial to take into mind when giving neurotoxic chemotherapeutic agents to elderly people, because the effects can be more notorious and long lasting in comparison to younger patients. Post injury, the conduction in peripheral nerves tends to be slower, which can be the cause of dysesthesia and not only neuropathic pain.

With respect to peripheral organ function, the main motor dysfunctions reported in aged subjects are a progressive decline of muscle strength and of motor coordination (Greig et al. 1993; Potvin et al. 1980). There is an approximate loss of strength of 1.8–2.8% per year (Verdu et al. 2000). There is some evidence that this reduction can be slowed down or reduced by formal exercise prescription, but most of the evidence comes from younger elderly patients and noncancer population (Klepin et al. 2013).

Clinical and experimental investigations have also reported autonomic nerve dysfunctions with advancing age. In humans, the beat-to-beat heart rate variations in response to postural changes, Valsalva maneuver, and deep breathing are significantly diminished in old subjects compared with young adult subjects. Older people are more prone to hypothermia and heatstroke. Importantly, they are also sensitive to anticholinergic effects of drugs, which can cause rigidity, movement disorders, and even trigger delirium. These changes, if combined with pathologies, injuries, or toxicity from cancer treatments, can impact the quality of life, functionality, or even treatment completion.

Changes in the Autonomous Nervous System

The autonomic nervous system (ANS) is the part of the nervous system that is responsible for maintaining homeostasis. Its regulatory action occurs without involvement of one's conscious. In elderly people, autonomic functions are relatively well maintained at rest, but patients' ability to adapt to environmental or visceral changes are often notably impaired (Parashar et al. 2016). The most notorious clinical effect is seen in arterial tension and maximum heart rate.

The age-related changes in autonomic nervous system activity and regulatory functions are involved in both sustained hypertension and

transient hypotension in the elderly. Sustained increases in resting sympathetic activity, combined with changes in thickening of the arterial wall, contribute to hypertension. With age, there is an increase in systolic arterial tension, while diastolic arterial tension tends to lower, causing an increase in pulse pressure (Lakatta and Levy 2003).

Orthostatic hypotension and postprandial hypotension frequently occur in elderly people as a result of an impairment of the arterial baroreceptor reflex (Joseph et al. 2017). These changes in the baroreceptor reflex may put the older individual at increased risk of cerebral ischemia during hypotensive episodes, because the lower limit of autoregulation shifts to the high blood pressure range with age (Hotta and Uchida 2010).

Sympathetic tone is widely found to increase during aging in many parts of the body. There is an increase with age in plasma noradrenaline concentration and an increase in the burst discharge rate on muscle sympathetic nerve fibers. The age-related changes in sympathetic nerve activity appear to be higher in the heart and liver but lower in the kidneys (Wallin 2007; Seals and Esler 2000).

The sensitivity of alpha- and beta-adrenergic receptors in the heart and blood vessels is reduced. The normal increases in heart rate, cardiac output, and vasodilation after administration of beta-adrenergic receptor agonists are all diminished in elderly people (Lakatta 1993). This has been associated with the lower maximum heart rate and lower exercise capacity found in the elderly (Paneni et al. 2017).

The highly organized cooperative action of autonomic nerves and somatic nerves that control the bladder and urethra is necessary for both continence and micturition. Maximum urethral closing pressure decreases in the elderly. Apoptotic loss of striated muscle fibers in the external urethral sphincter gradually decreases the number of sphincter muscle cells in men and women with age (Strasser et al. 2000). The bladder capacity that generates the initial desire to void remarkably increases in the elderly, suggesting a decline of volume sensation of the bladder with age. This is believed to be because of a reduction in muscarinic receptors in the detrusor muscle (Suskind 2017).

Autonomic aging, combined with aging in the other systems and the high prevalence of polypharmacy, puts the older patient at higher risk of falls, gait impairment, arrhythmia, and treatment intolerance.

Chemotherapy and Cognition

Even though studies associating cognitive changes with chemotherapy have existed since the 1970s, it has been in approximately the last 10 years that pretreatment neuropsychological assessment has been part of some cancer studies. In this time, it has been proposed that superimposed to the age-related cognitive impairment, there are neurologic changes associated with cancer therapy. These changes have been referred to as "chemotherapy-related cognitive impairment (CRCI) or "chemo brain" (Wefel et al. 2015). The American Cancer Society defines CRCI as: increased forgetfulness, trouble concentrating and remembering details, difficulty with multitasking word finding, and taking longer to finish tasks, which are associated with chemotherapy administration (Craig et al. 2014).

CRCI has been reported in up to 12–75% of patients with cancer and is associated with cancer type, treatment, duration of follow-up, type of study design, and definition of cognitive impairment. Most of these published studies assessed the prevalence of CRCI in a heterogeneous group of patients, including both young and old patients (Loh et al. 2016). Severity of CRCI is typically mild to moderate in nature, such that impairments experienced would not typically qualify for a diagnosis of mild cognitive impairment (MCI) or dementia; however, even subtle impairments in cognitive functioning can greatly influence quality of life (Vega and Newhouse 2014).

The cognitive changes associated with chemotherapy are typically subtle (functioning is reduced but often remains in the normal range), and occur across various domains of cognition, including working memory, executive function, and processing speed, but not the retrieval

of remote memories (Ahles and Saykin 2007). Furthermore, although acute cognitive changes during chemotherapy are common, long-term posttreatment cognitive changes seem to persist in only a subgroup (17–34%) of cancer survivors (Ferguson and Ahles 2003).

There are several mechanisms proposed as the cause of chemotherapy-induced cognitive changes, but not a single one can fully explain the findings in tests, and it seems that they depend on the treatment regimens and the particular vulnerabilities of the individual. The most commonly proposed mechanisms are disruption in blood–brain barrier integrity, DNA damage and shortening of telomere length, cytokine dysregulation, estrogen and testosterone reduction, and genetic susceptibility. The interaction of two or more of the proposed mechanisms need to interact to produce a change big enough to translate into problems in cognitive ability (Ahles and Saykin 2007). Interestingly, these mechanisms are also involved in normal aging cognitive changes, which have led to the development of two broader theories about CRCI and cancer-related cognitive impairment, the phase shift theory and the accelerated aging theory.

The phase shift hypothesis postulates that cancer patients treated with chemotherapy will experience greater decline in cognitive function compared to noncancer/chemotherapy-treated persons, and that the trajectory of decline will parallel normal aging and will remain constant over time (Ahles 2012). Alternatively, the accelerated aging hypothesis proposes that treatment with chemotherapy may accelerate the normal aging process (Maccormick 2006). This model predicts that the slope of cognitive decline will be steeper for cancer patients treated with chemotherapy compared to noncancer or chemotherapy-treated patients. These are not mutually exclusive theories, such as that a subgroup of cancer survivors, perhaps the majority, may demonstrate the phase shift trajectory, whereas another vulnerable group may demonstrate an accelerated aging trajectory (Vega et al. 2017).

This framework has potential clinical value because it suggests that the trajectories of cognitive decline are dependent on premorbid cognitive and other system reserves. This idea is supported by a study in which women aged 60–70 years with low baseline cognitive reserve who underwent chemotherapy had lower performance on tests of processing speed compared with those not receiving chemotherapy, younger patients, and controls (Ahles et al. 2010).

Neuroimaging studies have revealed similar changes observed following chemotherapy treatment and in normal aging, including gray and white matter loss, altered white matter connectivity, altered resting state connectivity changes, and brain activation during tasks (Ahles and Saykin 2007; Mandelblatt et al. 2014). This data supports the idea that the biological processes that underlie normal aging, brain response to chemotherapy, cognitive decline, and neurodegeneration overlap, leading to the nonexclusivity of the CRCI theories previously mentioned.

Functional MRI studies have demonstrated the potential for compensatory activation after chemotherapy, which may maintain normal performance on neuropsychological testing, but reflect a change in resource utilization, similar to what is seen in normal aging (McDonald et al. 2012; Ferguson et al. 2007b; Kesler et al. 2011). Such findings suggest that the patient's neuropsychological testing may fall in the normal range despite being associated with additional resource utilization and experienced as more effortful by patients.

Even though most of the evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy, there is growing evidence to suggest that adjuvant endocrine therapy may impact cognitive function, either alone or in combination with chemotherapy (Vega et al. 2017). However, such effects observed may not occur equally with all endocrine therapies (Mandelblatt et al. 2014). This finding has been described primarily in breast cancer patients, but more and more evidence has appeared in patients with prostate cancer that are receiving androgen deprivation therapy (ADT).

Hormonal anticancer therapies can produce effects, such as depression and fatigue, that may indirectly affect cognitive functioning, and

may also directly affect cognitive functioning as studies suggest that lower testosterone and estrogen levels are associated with worse cognitive functioning in healthy older patients (Holland et al. 2011). Particularly in prostate cancer patients, both low testosterone levels and ADT increase the risk of cardiovascular disease, which is a known risk factor for dementia (Tsai et al. 2007).

Targeted therapies also have the potential to either directly affect brain function or indirectly effect cognition through peripheral extra-CNS mechanisms. For example, sunitinib, a tyrosine kinase (TK) inhibitor capable of crossing the blood–brain barrier (BBB) used to treat different types of cancers, has been shown to have deleterious effects on cognitive functioning, specifically to learning, memory, and executive functioning (Mulder et al. 2014). In a study evaluating TK inhibitors, more than 30% of patients developed some sort of cognitive decline (Abdel-Aziz et al. 2016).

There are unfortunately no universally accepted interventions for CRCI. The most promising ones have been the nonpharmacological interventions. Two pilot studies examining cognitive behavioral therapy in breast cancer patients demonstrated improvement on both objective and subjective (self-report) measures of cognitive function (Ferguson et al. 2007a, 2012). Computerized cognitive brain-training studies suggest improvement in executive functioning, and yoga may reduce subjective memory complaints. This kind of interventions is not cheap, is not widely available, and should be tailored to the individual patient (Kesler et al. 2013; Janelsins et al. 2016).

It is important to mention that currently there is no pharmacological treatment that is specific for CRCI. Some drugs used for cognitive impairment not related to cancer have been tried in the oncological environment, but the studies have yielded mixed results. A lot of research is still needed in order to find the best therapeutic approach to CRCI.

Older patients with a cancer history should be routinely asked about their cognitive functioning. If available, informants should be asked to confirm any reports of cognitive decline experienced by the patient. Clinicians should consider using a structured instrument that examines diverse aspects of functional abilities, psychiatric signs and symptoms, and cognitive functioning. Appropriate referrals to memory clinics, geriatricians, or oncogeriatric services should be done, since these integrative services could give better support to the patient with cancer and cognitive impairment.

Neurotoxicity of Anticancer Agents

There has been a rapid increase in the number of anticancer agents in the past decade, including chemotherapeutics, targeted therapies, immunotherapies, and hormonal therapies. There are a wide range of neurologic complications which can arise from these drugs, with side effects such as peripheral/central neuropathies, cognitive deficits, and encephalopathy. Elderly patients are particularly sensitive to these side effects, which can result in downstream effects such as increased fall risk (Ward et al. 2014) and decline in functional status. The risk of developing neurotoxicity is dependent on numerous factors, including dose intensity, baseline neurological deficits, drug interactions, and drug mechanism of action. Early recognition of adverse neurologic effects and differentiation from central nervous system (CNS) progression of cancer is critical for timely and appropriate adjustments in dosing or discontinuation of the drug. These neurotoxicities can be categorized into central, both central and peripheral, and autonomic effects, which are discussed below.

Central Neurotoxicities

Altered mental status (AMS), both acute and chronic, can be seen with certain cancer treatments. Ifosfamide, an alkylating agent used in both solid and hematologic malignancies, has an incidence of encephalopathy occurring in 5–30% of treated patients (Nicolao and Giometto 2003). Elderly patients have a higher

rate of developing encephalopathy, possibly due to lower serum albumin, hepatic or renal dysfunction, or drug interactions. The encephalopathy is reversible in the majority of cases; treatment involves discontinuing the agent, hydration, as well as administration of methylene blue (Brunello et al. 2007).

PRES, posterior reversible encephalopathy syndrome, is a syndrome characterized by the rapid onset of symptoms including encephalopathy, seizures, and other neurologic symptoms, with imaging demonstrating brain lesions with posterior and white matter-predominant distribution (Singer et al. 2015). Anticancer agents which have been associated with PRES include platinums, gemcitabine, methotrexate, and VEGF TK inhibitors (Pavlidou et al. 2016; Zahir et al. 2012; Deguchi et al. 2018; Rajasekhar and George 2007). Clinical and radiographic features of this syndrome are usually reversible with discontinuation of the causative agent.

Blinatumomab and CAR-T are newer biologic immunotherapies for hematologic malignancies that are associated with a cytokine release syndrome that causes acute encephalopathy. Blinatumomab specifically has a 13–22% risk of grade 3 or greater neurologic events. In one study, patients aged >65 with relapsed/refractory acute lymphoblastic leukemia (ALL) had similar hematologic responses to younger counterparts, however did have more neurologic events, although these typically resolved with treatment interruption (Kantarjian et al. 2016). Prophylaxis includes premedication with dexamethasone. CAR-T therapy has been associated with delirium, seizures, and altered mental status as neurologic manifestations of cytokine release syndrome. Treatment is supportive and involves discontinuation of therapy, although tocilizumab, an IL-6 receptor antibody, has been used to ameliorate symptoms in more severe cases (Frey 2017).

Progressive multifocal leukoencephalopathy (PML) is a rare neurologic disease characterized by progressive inflammation of the white matter of the brain. It is caused by infection with JC virus in immunocompromised patients. All anti-CD20 antibodies (rituximab, obinatuzumab, ofatumumab) carry a black box warning for PML after 22 patients developed PML in postmarketing data analysis in 2006. Other agents that have been associated with PML include alemtuzumab, bevacizumab, brentuximb, ibrutinib, and idelalisib (Raisch et al. 2016).

Peripheral Neurotoxicities

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurologic side effect from anticancer agents, affecting 30–40% of patients treated with neurotoxic agents (Staff et al. 2017). Risk factors include age, genetic factors, and drug-related mechanisms such as dose intensity, duration of treatment, and route of administration. The most common agents associated with peripheral neuropathy are vinca alkaloids, epothilones, platinum agents, proteasome inhibitors, and taxanes. In elderly patients, peripheral neuropathy is a common cause of decreased quality of life and falls and needs to be addressed before it progresses to an irreversible stage (Richardson and Ashton-Miller 1996). Even after discontinuation or dose reduction, neuropathy may take months to resolve, and in some cases does not resolve completely. The site of peripheral nerve injury varies between these agents, but generally involve the dorsal root ganglion, nerve terminals, and microtubules (Staff et al. 2017).

There are unfortunately no proven preventative therapies for CIPN. Symptomatic treatment of CIPN includes serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine, tricyclic antidepressants, topical analgesics, gabapentin, and pregabalin. SNRIs such as venlafaxine have been successfully used for oxaliplatin and taxane-induced neurotoxicity – in a retrospective case control study of 206 patients, about 50% of patients reported a greater than 75% improvement in neuropathic pain (Kus et al. 2016).

Platinum agents, including cisplatin, oxaliplatin, and carboplatin, are among the most commonly used chemotherapies that are associated with neurotoxicity. Cisplatin most commonly is associated with peripheral neuropathy and

ototoxicity. The peripheral neuropathy is dose related, and is often permanent. It primarily affects the dorsal root ganglion, with toxic effects on the mitochondria (Siegal and Haim 1990). Carboplatin has less neurotoxicity compared to cisplatin, and is often substituted for cisplatin in elderly patients who have baseline neuropathy. Oxaliplatin can cause an acute cold-induced dysesthesia that persists approximately 2–4 days after infusion (Staff et al. 2017). Elderly patients, especially aged >70, may be more likely to develop peripheral neuropathy compared to younger counterparts (Raphael et al. 2017). Of note, peripheral neuropathy from platinum agents can worsen even months after discontinuing therapy.

Of the vinca alkaloids, vincristine is the most neurotoxic, with primarily a dose-related sensory neuropathy. The pathophysiology involves disruption of microtubules within axons which results in interference with axonal transport (Legha 1986). To limit the potential neurotoxic effects, the usual recommended dose is 1.4 mg/m^2 per dose, with an upper limit of 2 mg total per dose.

Epothilones, such as ixabepilone and eribulin, are non-taxane tubulin-polymerizing agents that are used in metastatic breast cancer, and are also associated with a sensory neuropathy. This is caused by disruption of microtubules in the spindle which results in damage to the ganglion soma cells as well as nerve axons.

Proteosome inhibitors are used in the treatment of multiple myeloma, and are associated with peripheral neuropathy in a stocking glove distribution mediated by a direct toxic effect on the dorsal root ganglion (Cavaletti et al. 2007). Up to 10% of patients can develop motor neuropathy which manifests as distal weakness in lower extremities. The incidence of neuropathy can be decreased by using once-weekly schedules and subcutaneous administration. Another option to minimize neurotoxicity is to use carfilzomib, a second-generation proteasome inhibitor with <1% incidence of grade 3–4 neuropathy (Vij et al. 2012). Ixazomib, an oral proteasome inhibitor, also has rates of low grade neuropathy of 30–40%, but <2% severe neuropathy (Kumar et al. 2015).

Taxanes are a frequently used class of chemotherapy in solid tumors, including breast, prostate, ovarian, and lung cancers. Drugs in this class include paclitaxel, docetaxel, cabazitaxel, and nab-paclitaxel. These antimicrotubule agents can lead to disruption of the mitotic spindle and interfere with axonal transport.

Toxicities of these drugs can be increased in the elderly due to a number of factors. As taxanes are mostly protein bound, the free fraction can be increased in hypoalbuminemic patients, leading to greater risk of toxicity (Wildiers and Paridaens 2004). Additionally, patients with preexisting diabetes are much more likely to develop neuropathy compared to patients without a history of diabetes mellitus. Paclitaxel has a higher risk of neuropathy compared to docetaxel, with incidence of any grade neuropathy about 60% versus 15%, and the neuropathy is primarily dose related, with neurotoxicity typically occurring after 1000 mg/m^2 for paclitaxel, and 400 mg/m^2 for docetaxel (Grisold et al. 2012). Cabazitaxel is a newer taxane used in the treatment of metastatic prostate cancer, and has a much lower incidence of neuropathy, with <1% of grade 3 or 4 toxicity, and may be a good option for elderly patients who are at risk for peripheral neuropathy (de Bono et al. 2010).

Traztuzumab emtansine (T-DM1), an antibody drug conjugate used in HER2 positive breast cancer, has a risk of grade 3 or greater peripheral neuropathy of 2.4% in the EMILIA trial (Dieras et al. 2017). However, the monoclonal antibodies pertuzumab and traztuzumab do not cross the blood–brain barrier due to large molecular weight, and are not associated with significant neurotoxicity on their own. Another antibody–drug conjugate used in lymphomas, brentuximab vedotin, can cause peripheral neuropathy in 30–50% of patients (Gopal et al. 2012).

Elderly patients are more likely to have comorbidities such as diabetes mellitus and hypercholesterolemia that predispose them to cerebrovascular events; thus, the administration of agents that increase the risk of vascular occlusive events must be done with caution. VEGF TKIs, such as sunitinib and sorafenib, are associated with a significant risk of hypertension and significantly

increase the risk of stroke, especially in older patients with renal dysfunction (Jang et al. 2016).

Nilotinib and ponatinib, BCR-ABL TKIs used for the treatment of CML, are associated with an increased risk of vascular occlusive events as well (Gomez-Galvan et al. 2017; Jain et al. 2015). This is thought to be mediated by promoting a prothrombotic state and possibly accelerating atherosclerosis.

Autonomic Toxicity

In addition to central and peripheral toxicities, a number of anticancer agents are associated with autonomic impairment. Autonomic side effects of vinca alkaloids like vincristine often precede other neurotoxicities, especially sensory neuropathy (Legha 1986). Common autonomic neuropathies include constipation, erectile dysfunction, and postural hypotension. These symptoms are often under-recognized as being secondary to treatment, but have a great impact on the lives of elderly patients. Institution of a bowel regimen is recommended for patients using vinca alkaloids to minimize gastrointestinal side effects. Postural hypotension can put elderly patients at risk for falls, and reconciliation of home medications such as antihypertensives should be done on a regular basis to avoid worsening hypotension.

Toxicity Associated with Immunotherapy

Immune checkpoint inhibitors have revolutionized the therapeutic landscape for a number of cancers, but can infrequently cause neurologic sequelae. These have been associated with a wide range of autoimmune-related neurologic toxicities which are rare, but do occur, including CNS demyelination, myositis, limbic encephalitis, optic neuritis, hypophysitis, peripheral neuropathy, Guillain-Barre like syndromes, and cranial nerve palsies. In a recent meta-analysis, the incidence of immune-related neurotoxicity with anti-PD-1 and anti-CTLA4 monoclonal antibodies is 3.8% and 6.1%, respectively, and up to 12% with both. However, many of the nAE included nonspecific symptoms such as headache, and the incidence of grade 3–4 neurologic toxicities was less than 1% overall. The average time of onset was between 6 and 13 weeks (Cuzzubbo et al. 2017). Hypophysitis is the most common, and can occur in up to 5% of patients (Spain et al. 2017). Hypophysitis is diagnosed by low levels of pituitary hormones, and MRI may show enhancement of the pituitary gland. The majority of these adverse effects occur early on in the treatment course, although can happen at any point during treatment. The neurologic toxicities can be effectively reversed with a prolonged taper of high-dose corticosteroids; however, this may be more problematic for an older population with comorbidities such as heart failure or renal dysfunction, as high dose corticosteroids are associated with fluid retention, myopathy, and GI bleeding. Pyridostigmine can be used in combination with low-dose steroids with successful reversal of myasthenia gravis induced by checkpoint inhibitors. IVIG and plasmapheresis can also be used for many of these neurologic sequelae as well, including myasthenia gravis and Guillain-Barre. While the pathogenesis is not well characterized, it is thought to be related to inflammation around endoneural micro vessels and subperineurial edema and inflammation (Manousakis et al. 2013).

Neurotoxicity of anticancer agents remains a major concern for patients and clinicians as it affects both quality of life and functional status. Although there are no reliable preventative strategies, it would be beneficial to identify patient-specific risk factors for these various neurotoxicities, and consider adjusting the regimen or dose intensity. Factors such as hypoalbuminemia, increased body fat percentage, and renal impairment may also increase risk of toxicities from anticancer therapies, and close monitoring of these clinical parameters while on therapy is essential. There are several genetic variants that have been associated with neurotoxic susceptibility to various therapies as well, and more research is needed to develop inexpensive genetic tests to help identify subsets of patients that may be at

greater risk. Finally, we recommend performing a careful geriatric assessment to identify baseline neurological deficits that may not be readily apparent from the initial evaluation to tailor treatment for patients.

Cross-References

- Aging and Cancer Biology
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Decision Making and Safety Issues in Older Cancer Patients
- Drug Interactions in Aging and Cancer
- Normal and Abnormal Aging (General Perspective for the Oncologist)
- Pharmacology of Aging and Cancer
- Predictive Tools for Older Cancer Patient Management

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Hematopoiesis and Aging

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Abstract

It is apparent that hematopoiesis, the formation and differentiation of the cellular components of blood, and bone marrow function are altered with aging, but the physiologic basis has yet to be fully elucidated. Specifically, the aging process is typically characterized by a reduction in functional reserve capacity. Thus, while basal function is normal, the ability to respond to increasing demand and infectious or inflammatory stress is compromised. In this chapter we provide a brief overview of normal, healthy bone marrow regulation and function and discuss changes observed with aging. These changes affect both intrinsic (e.g., pluripotent stem cells and committed hematopoietic precursors) and extrinsic (e.g., stroma and cytokines) factors of bone marrow function. The idiopathic acquisition of somatic mutations that occur in elderly individuals, termed clonal hematopoiesis of indeterminate potential, is also discussed. We conclude with a discussion of the functional changes in immune function, mediated by bone marrow B and T cells, that are observed in aging individuals.

Keywords

Hematopoiesis · Bone marrow · Aging · Clonal hematopoiesis · Stem cells · Cytokines · CFU-S · CHIP

Introduction

The aging process is characterized by alterations in the functions of many organ systems. Changes occur in the cardiovascular, endocrine, and immune systems and have been studied extensively. Changes in bone marrow function are also evident, but the physiologic basis for these alterations is less well understood. Clearly, the bone marrow plays an important role in normal homeostasis, producing cells responsible for maintenance of oxygen delivery, hemostasis, and host defense against infection. The bulk of evidence favors preservation of normal homeostatic bone marrow function with aging in healthy individuals, although functional deficits are apparent under conditions of hematopoietic stress. Which of these observed cellular alterations are normal physiologic responses and which are consequences of coexistent disease processes remain under debate. In order to place published experimental data in perspective, an understanding of the regulation of normal hematopoiesis is essential.

Normal Bone Marrow Function

The production of mature peripheral blood cells from primitive precursors within the marrow results from a complex interaction between primitive hematopoietic stem cells, the stromal microenvironment, and a set of soluble regulatory cytokines produced locally. The orderly development of the hematopoietic system requires that a strict balance be maintained between self-renewal, cell differentiation, and cell death. Continued production of terminally differentiated peripheral blood cells occurs, while a balance is maintained between amplification of immature precursors and maturation with transit into the peripheral blood compartment. Most immature precursors go unrecognized by traditional light-microscopic examination. The earliest morphologically recognizable myeloid, erythroid, and megakaryocytic precursors are actually relatively mature progeny of a cell found at low numbers within the marrow. This self-renewing cell is referred to as the primitive hematopoietic stem cell (Fig. 1).

The concept of a primitive hematopoietic stem cell was introduced by Till and McCulloch (1961) in the early 1960s. They analyzed the number and nature of cells giving rise to trilineal spleen colonies in an irradiated mouse model and noted that each colony was derived from a single clonogenic precursor. Furthermore, these precursors were capable of continuously repopulating (Becker et al. 1963; Wu et al. 1968). The cell type giving rise to the spleen colonies was termed a colony-forming unit-spleen (CFU-S). This same cell was later shown to also be capable of giving rise to peripheral blood and thymic lymphocytes (Abramson et al. 1977; Visser and Van Bekkum

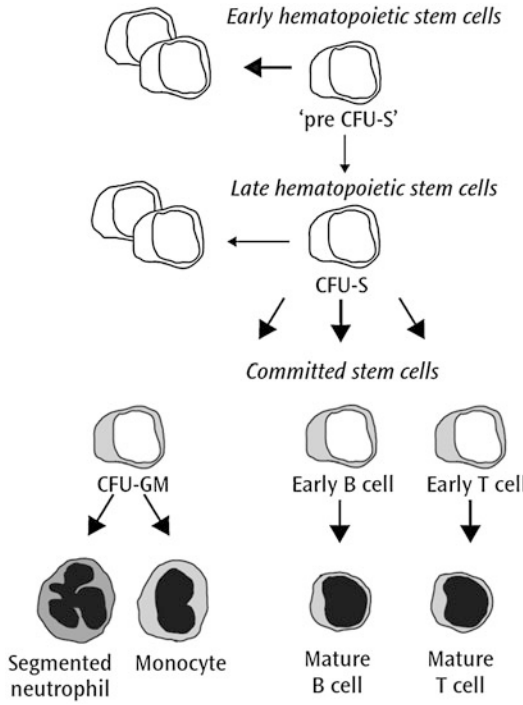

Fig. 1 Early hematopoietic stem cells have a high proliferative potential, with more limited differentiation kinetics. Their progeny, the late stem cells, undergo preferential differentiation to form stem cells committed to the various hematopoietic lineages. These undergo terminal maturation to form the recognizable peripheral blood and lymph node elements. Each stage of stem cell differentiation is antigenically characterized by a constellation of surface antigens which can be readily measured by flow cytometry. *CFU-S*, colony-forming unit-spleen; *CFU-GM*, colony-forming unit-granulocyte/macrophage

1990) and, thus, became the prime candidate for the then-elusive pluripotent stem cell. Since this initial description, a series of cell types has been characterized, and both early and late stages of stem cell differentiation are identified. It is now known that pluripotent stem cells are short-lived (Harrison et al. 1988; Micklem et al. 1987) and represent only a small fraction of cells within the bone marrow and fetal liver. They can be defined by their maximum differentiating and repopulating ability as measured by competitive repopulation assays (Harrison 1980; Harrison et al. 1993). Such assays measure the long-term functional ability of stem cells (Fig. 2). Using this methodology, competitor and donor hematopoietic populations are derived from mice that carry allelic variants of genes specifying quantifiable cellular markers. One population, termed the competitor, is an aliquot of fresh bone marrow cells that serves as an internal standard for repopulating potential. In each experiment, different donor populations containing unknown stem cell contents are measured relative to the repopulating ability of the internal standard competitor pool. Thus, various donor cell populations and bone marrow fractions can be compared (Jordan et al. 1995).

Hematopoietic stem cells have been subfractionated based on size, density, and the expression of cell surface molecules (Visser and Van Bekkum 1990; Lu et al. 1987; Terstappen and Lund-Johansen 1994). There is a general consensus that most human stem cells are contained within the cell population expressing surface CD34 (where "CD" refers to the international nomenclature for antigens, the so-called clusters of differentiation). CD34-positive (CD34+) stem cells represent a spectrum of stages of differentiation and lineage commitment, with variable functional properties, in vitro laboratory properties, and surface antigen expression (Table 1). The majority of CD34+ bone marrow cells are "late stem cells," already committed to either the hematopoietic or stromal cell lineages (Civin et al. 1984; Simmons and Torok-Storb 1991). The most immature progenitors within the CD34+ population are further fractionated by the differential expression of CD38, CD45RA, CD71, CDw90 (Thy-1), and HLADR (Baum et al. 1992; Brandt et al. 1990a; Huang and Terstappen 1994; Lansdorp et al. 1990; Terstappen et al. 1991; Verfaillie et al. 1990). A newly identified population of stem cells in both mice and humans has been characterized as CD34− but capable of multi-lineage repopulation in experimental models. The precise relationship between these CD34− stem cells and traditional CD34+ stem cells is not well understood (Bonnet 2001).

The establishment of hematopoiesis during embryonic development, as well as the continued maturation and differentiation of bone marrow precursors in vivo, requires an interaction with both cellular and soluble factors. Observed changes in stem cell numbers coincide with

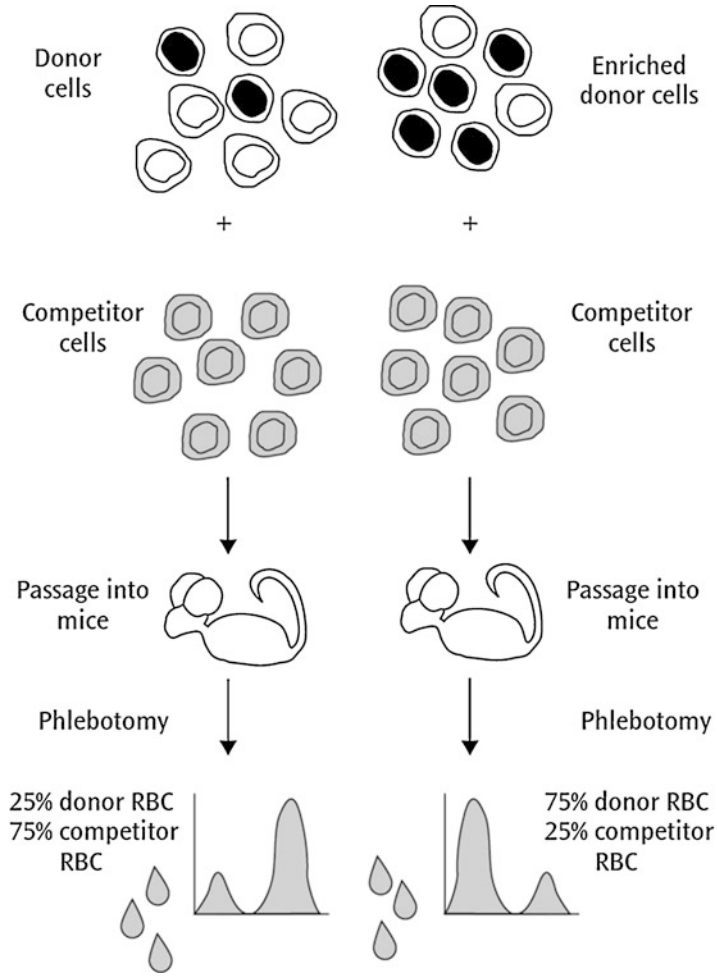

Fig. 2 Primitive hematopoietic stem cells are defined by their maximal differentiating and repopulating abilities, as measured by a technique called competitive repopulation. Donor and competitor cells are chosen from mouse strains to express different surface allelic markers. The mature progeny are assayed for the proportion of cells expressing each marker, and this value is used to estimate the stem cell number (relative to a standard dose of competitor cells) and evaluate for stem cell enrichment efficiency. In this example, the enriched donor sample is three times as efficient as the original sample and, therefore, reflects an increased proportion of functional stem cells. *RBC* red blood cells

alterations in the stromal cell content of the yolk sac, liver, spleen, and bone marrow when these sites become active in hematopoiesis (Klein et al. 1983; Van den Heuvel et al. 1987). In the liver, spleen, and bone marrow, increased numbers of fibroblastoid colony-forming units (CFU-f) precede the onset of hematopoiesis (Van Den Heuvel et al. 1991). When re-cultured in vitro, CFU-f are capable of maintaining hematopoiesis in both human and mouse long-term marrow cultures (Cappellini et al. 1984; Van Den Heuvel et al. 1988). This suggests a close interaction between stem cell proliferation/maintenance and stromal cell support. CFU-f are primarily fibroblastoid stromal cell types and are assayed by plating bone marrow in soft agar in vitro. However, normal hematopoietic stroma in vivo is heterogeneous and, in addition to CFU-f, is composed of macrophages, endothelial cells, and fibroblast (reticular) cells, with many of the fibroblasts converting to adipocytes over time (Allen 1981; Laver et al. 1986; Tavassoli and Friedenstein 1983; Wang and Wolf 1990; Westen and Bainton 1979; Xu et al. 1983). The mechanism for stem cell dependence on stromal cell layers is most likely an interaction of stem cell membrane proteins with adhesion molecules present on the surface of stromal cells (Fig. 3). Such adhesion is postulated to activate the stromal cell components, with resultant production of cytokines (Anderson et al. 1990; Huang et al. 1990; Ploemacher et al. 1986; Williams et al. 1990; Wolf 1978; Wolf et al. 1995; Zsebo et al. 1990).

The most primitive pluripotent stem cells do not appear to respond to any one cytokine given

Table 1 Definition of hematopoietic stem cells

Properties	Early stem cells (pre-CFU-S)	Late stem cells (CFU-S)	Lineage-committed stem cells
Functional	Self-renewal; long-term radioprotection of the host	Production of myeloid, erythroid, and lymphoid elements	Radioprotection of the host
Laboratory	CFU-S formation in secondary transplantation into lethally irradiated mice (long-term repopulation)	Secondary spleen colony assays (CFU-S) Long-term liquid Dexter	Methylcellulose colony formation for multipotential lineage growth
Antigenic	Mouse: Sca-1 (stem cell antigen) positive, Thy-1.1 weakly positive, Lin (lineage markers) negative, KDR receptor (vascular endothelial growth factor receptor II) positive Human: CD34 positive, Rh123 (rhodamine dye) weakly positive, CD38 negative, CD71 (transferrin receptor) negative, HLA-DR negative, c-Kit receptor positive, CD45RO positive, CD45RA weakly positive, CDw90 (Thy-1) weakly positive		Human: CD34 positive, RH123 (rhodamine dye) strongly positive May express variable CD33 (myeloid), CD10/CD19 (B lymphoid), CD38, and HLA-DR

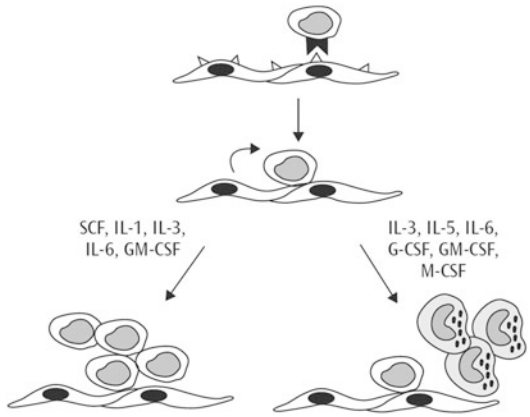

Fig. 3 Binding of hematopoietic stem cells to stroma via surface adhesion molecules results in the release of multiple cytokines by the activated stromal cells. The relative levels of these cytokines and the efficiency with which they can bind to receptors on the stem cell allows for a balance between stem cell replication and differentiation. *SCF*, stem cell factor (c-Kit ligand, Steel factor); *IL*, interleukin; *GM-CSF*, granulocyte/macrophage colony-stimulating factor; *G-CSF*, granulocyte CSF; *M-CSF*, macrophage CSF

alone. Colony growth in soft agar can be seen when these cells are incubated with interleukin-3 (IL-3) in combination with a variety of other growth factors (Heimfeld et al. 1991). Committed myelomonocytic precursors and lymphoid progenitors have been demonstrated to respond to the early-acting growth factors, stem cell factor (SCF, also known as c-Kit ligand and Steel factor), Flt-3/FIt-2 ligand thrombopoietin (TPO), and IL-1, as well as IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte/l-macrophage CSF (GM-CSF), macrophage CSF (M-CSF), IL-7, IL-5, IL-11, IL-12, and leukemia inhibitory factor (LIF) (Ogawa and Matsunaga 1999). Commitment to the erythroid lineage requires both early-acting growth factors and erythropoietin (EPO). Megakaryocytic differentiation is less well understood but requires many of the same early-acting growth factors. TPO induces differentiation in vitro (Bartley et al. 1994; Kaushansky et al. 1994), and ex vivo megakaryocytic expansion is now possible (Maurer et al. 2000).

The Effect of Aging on Bone Marrow Function

A multitude of alterations in hematopoiesis have been ascribed to the aging process, when studied in mice (Table 2). No major changes in basal hematopoiesis, however, are noted with aging (Coggle and Proukakis 1970; Everitt and Webb

Table 2 The physiologic basis of aging in the hematopoietic system of mice

Observed aging phenomenon	Probable physiologic mechanism
Myeloid abnormalities	
Increased proliferative capacity of late stem cells (CFU-S)	Unknown
Increased differentiative capacity of late stem cells (CFU-S), with production of more committed stem cells	Altered stromal cell regulation and increased demand for mature cells
Decreased resynthesis of cytokine substances in bone marrow	Altered stromal cell regulation, with increased fibroblast content of bone marrow
Decreased ability of early stem cells to repopulate the bone marrow of lethally irradiated mice	Decreased marrow graft content of activated stromal cell components capable of cytokine secretion and initiation of hematopoietic reconstitution
Decreased in vitro CFU-GM colony formation	Decreased sensitivity of CFU-GM to exogenous IL-3, G-CSF, and GM-CSF
Reduction in hematopoietic reserve	Blunted proliferative response to stress, most likely secondary to abnormal cytokine regulation
Reduced cycling of committed stem cells (CFU-GM)	Increased demand for mature cells and increased complement of CFU-GM
Increased spontaneous chromosomal abnormalities	Decreased DNA repair mechanisms; altered telomerase activity
T-lymphoid abnormalities	
Blunted T-cell proliferative response to mitogens	Increased content of mature T cells in bone marrow, with shortened duration of response to cell activation accompanied by a decrease in bone marrow-derived thymocyte progenitors; decreased local cytokine production by macrophages and stromal cells
Increased T-cell content of bone marrow	Compensatory increase in infiltrating effector T cells secondary to blunted T-cell proliferative response
B-lymphoid abnormalities	
Increased autoantibody production	Cytokine dysregulation, most notably increased IL-6; restricted VH gene usage
Decreased production of normal immunoglobulin-producing cells	Cytokine dysregulation, most notably IL-7 and IL-4; abnormal T-cell regulation; decreased B-progenitor content of bone marrow
Restricted V_H gene usage	Decreased B-cell precursors and increased peripheral selection; progression decline in *RAG-1* gene activity

IL, interleukin; *G-CSF*, granulocyte colony-stimulating factor; *GM-CSF*, granulocyte/macrophage CSF; *RAG-1*, recombination-activating gene 1

1958). The aging process is typically characterized by a reduction in functional reserve capacity. Thus, while basal function is normal, the ability to respond to increasing demand and infectious or inflammatory stress is compromised. This compromise may involve all lineages within the bone marrow and is the most frequently cited mechanism for the anemia of aging. Older mice and humans recover hemoglobin values more slowly after phlebotomy than do their younger counterparts (Boggs and Patrene 1985), and a less than optimum increase in hemoglobin level is noted during transitions to high altitude (Udupa and Lipschitz 1984).

The fragility of the aging hematopoietic system is further highlighted by studies of mice approaching their maximal life expectancy (Williams et al. 1986). The median lifespan of the experimental mouse line C57BL/6 is 24 months, and the maximum reported life expectancy is 48 months. Mice at 48 months of age have been used in experiments in which they are housed either individually or in groups of five or more animals. Under experimental conditions where

crowding occurs, a significant alteration in bone marrow function results, and the majority of animals become anemic. Examination of their bone marrow shows decreases in the number of countable stem cells and morphologically recognizable mature progeny. Therefore, when viewed globally, these experiments support the clinical impression that minor stresses that may not affect hematopoiesis in younger individuals can cause significant abnormalities in aged animals. Since no abnormalities in basal hematopoiesis can be detected, it is probable that these clinically apparent effects are secondary to blunting or suppression of cell proliferation and function during inflammatory or other physiologic stresses. This is most probably a consequence of cytokine mediation.

There is general consensus that aging causes decrements in the proliferative potential of some cell types (Goldstein 1990; Hayflick 1976; Norwood et al. 1990). There may be blunting of the proliferative response of normal marrow hematopoietic cells, resulting in inadequate amplification of myelopoiesis. This could potentially lead to neutropenia (Finkelstein et al. 1983; Weinstein et al. 1983) or could be manifested as a slow recovery from myelotoxic chemotherapy (Begg and Carbone 1983). Age-related deficits in compensatory myelopoiesis have also been ascribed to changes in the number of bone marrow progenitors, alterations in the responsiveness of these progenitors to regulatory cytokines (Lipschitz et al. 1984), decreased production of cytokines (Gillis et al. 1981; Nagel et al. 1988; Buchanan and Rothstein 1989), or defects in the bone marrow microenvironment (Lee et al. 1989).

The majority of studies to delineate the effects of aging on hematopoietic cell proliferation have been performed in rodents, predominantly mice or senescence-accelerated strains of mice. Contradictory studies exist, and alterations in the function of the hematopoietic system during the aging process are not universally accepted. It is likely that some of the confusion results from differences in experimental procedures, differences between strains of laboratory mice, or inherent differences between rodent models and normal human physiology. For example, bone marrow cellularity in rodents increases with increasing age, while cellularity in humans decreases. Such basic differences in physiology may significantly impact the extrapolation of results from experimental animal studies. However, despite some limitations, many lessons can be learned from in vitro evaluations. In the following sections, the specific effects of aging on each stage of normal stem cell differentiation will be discussed. As will become obvious, a multitude of laboratory abnormalities are found. Most of these are minor alterations or are poorly reproducible. No consistent patterns have been found, and the effect of aging on stem cell function remains a debated topic.

Pluripotent Stem Cells (Pre-CFU-S and CFU-S)

It appears that pluripotent stem cells have a finite replicative capacity (Lipschitz and Udupa 1986). Nonetheless, it is evident that stem cells can function far longer than the lifespan of the host, such that the physiologic consequences of this finding are unclear. In serial transplantation studies in W/W-anemic recipient mice, stem cells from healthy C57BL/6(B6) donors generated normal hematopoiesis for at least 100 months, which is 3–4 times the lifespan of normal mice (Zaucha et al. 2001). In human allogeneic bone marrow recipients, hematopoiesis is sustained for at least 20–30 years after transplantation. Evidence exists, however, that stem cells are heterogeneous in self-renewal capacity; young CFU-S (pre-CFU-S) show a high self-renewal capacity and give rise to older CFU-S with diminishing self-renewal and increasing differentiation potential (Fig. 3) (Schofield and Lajtha 1973; Schofield et al. 1980). During the aging process in mice, hematopoietic stem cells appear to accumulate (Sudo et al. 2000). These repopulating cells retain their self-renewal potential but develop a more restricted myeloid differentiation preference and less lymphoid differentiation potential. This anomaly has been postulated to result from repeated hematopoietic stem cell self-renewal and symmetric division, which may gradually

produce intrinsically defective stem cells. In addition to defects in lymphoid lineage commitment, functional efficiency in homing and engraftment is also affected (Morrison et al. 1996).

Basal hematopoiesis shows no significant change, yet a significantly reduced reserve capacity is evident during stress or intercurrent illness. In order to understand why elderly people appear to possess less hematopoietic reserve than their youthful counterparts, early stem cell function has been evaluated in aging mice. Several studies have attempted to quantitate the number of pluripotent stem cells in the bone marrow (Schofield et al. 1986; Sharp et al. 1989). In the majority of cases, no differences could be detected in the absolute number of late stem cells (CFU-S) or committed multi-lineage stem cells (CFU-mix) when comparing bone marrows obtained from young or old mice. Marginal differences in proliferative potential, however, have been found (Sharp et al. 1989). There is a suggestion that cells originating from older bone marrows proliferate to a greater extent and produce more committed stem cells than those from younger donors. This leads to a three- to fourfold increase in the relative and absolute numbers of the most primitive stem cell subsets. It has been proposed that these precursor cells proliferate in the older animal to compensate for their age-specific functional abnormalities (Globerson 1999). This finding appears to be somewhat confusing, and its relevance to physiologic stem cell functioning during aging is uncertain. A direct relationship between increased stem cell pool and murine strain-specific lifespan has been suggested. The basic mechanism for this observation clearly involves many factors extrinsic to the stem cell itself and appears to be a result of stromal cell dysregulation.

It is generally accepted that the function of marrow stem cells, when these cells are transplanted into other animals or studied in culture, does not change significantly with age, although alterations in accessory cells occur (Schofield et al. 1986). Resynthesis of cytokines appears to be slower in older mice, suggesting abnormalities in cytokine regulation or stromal cell function. However, while stromal cell dysfunction and abnormalities of stem cell proliferation can be demonstrated in vitro, these abnormalities do not appear capable of resulting in a significant decrement in stem cell function in vivo. As an exception to these findings, a single study (Sletvold and Laerum 1988) identified a decrease in absolute CFU-S number using a novel chronobiological approach. The authors suggested that both circadian and seasonal variations in stem cell number exist. Using a calculation of mean CFU-S number, as identified by day-8 spleen colony assays, older mice appeared to have a slight decrement in absolute stem cell number. They also demonstrated less variability by season and time of day than younger littermates. The magnitude of this change, however, was quite small. It is probable that normal physiologic variations in stem cell number contributed to the difficulty in interpreting these data.

Applying these findings to elderly human patients is problematic. Whether or not small changes in in vitro stem cell number lead to in vivo abnormalities is unclear. In order to answer this question, functional studies are needed. Using serial transplantation into lethally irradiated mice, stem cells show a gradual loss of self-replicative ability (Schofield et al. 1980). While early evidence suggested that CFU-S from young donors were better able to repopulate the marrow of irradiated mice than stem cells obtained from older donors, this difference was probably related to stromal cell content and induced cytokine secretion. There is evidence suggesting that many of the early published serial transplant studies had significant methodologic artifacts (Harrison et al. 1978; Ross et al. 1982). Furthermore, as noted above, any defect in stem cell number or function is marginal. Therefore, in summary, it appears that the CFU-S have sufficient reserve capacity to produce adequate numbers of hematopoietic cells for periods that far exceed the maximum life expectancy of the host (Harrison 1973). Furthermore, although functional defects are evident, most observed abnormalities of stem cell function are likely secondary to alterations in stromal cells or stem cell/stromal cell interactions.

Committed Hematopoietic Precursors

Studies have examined the effect of aging on the number of both committed hematopoietic stem cells [CFU-granulocyte/macrophage (CFU-GM), CFU-erythroid (CFU-E), burst-forming units-erythroid (BFU-E), etc.] and differentiated bone marrow cells (Williams et al. 1986). In mice, the results are similar for late and early stem cells. Most studies show no age-related reduction in the number of erythroid (BFU-E and CFU-E) or granulocyte/macrophage (CFU-GM) progenitor cells. Furthermore, there appears to be no age-related differences in the proportion of CD34+ marrow cells or of more mature CD34+ subsets, defined as CD34+/CD33+ cells (Chatta et al. 1993). Maximum colony formation by primitive CD34+ cells stimulated with combinations of cytokines, including G-CSF, GM-CSF, and IL-3, is also similar in young and old subjects. However, an inverse correlation between the number of CD34+ stem cells isolated from peripheral blood and age has been documented (Egusa et al. 1998). It is possible that this results from a similar functional homing defect as described for early stem cells, although this hypothesis has not yet been tested directly. Also, similar to early stem cells, the kinetics of the proliferative response may be altered, although no consistent pattern of abnormalities is found. Alterations appear to be growth factor-specific and thus do not represent a generalized stem cell defect. For example, dose-response studies have identified a decrement in the sensitivity of cells obtained from elderly subjects to G-CSF, but not to IL-3 or GM-CSF. Similarly, the ability of early erythroid-committed progenitors (CFU-E) to respond to EPO and IL-3 is unchanged (Hirota et al. 1988). When using a similar strategy to evaluate the mature progeny of committed stem cells (Sletvold et al. 1988), no significant decrement in mature peripheral blood neutrophils, erythroid cells, or platelets can be identified.

Progenitor Cell Cycle Kinetics

Another explanation for changes in marrow reserve during aging is an abnormality in the ability of stem cells to maintain proliferation, either temporally or in response to a stimulus. Several subtle abnormalities in both early and committed stem cell proliferation have already been discussed. Interestingly, it has been shown that the bone marrows of aged mice accumulate stem cells and that these mice contain stem cells that are abnormal in cycle (Globerson 1999). They replicate on addition of cytokines, but maintenance of the cycling rate of CFU-GM, as measured using the thymidine suicide technique (Lord and Schofield 1985), is lower in elderly than in young adult mice (Iscove et al. 1970; Tejero et al. 1984). Data suggest that the reduced cycling of CFU-GM in older mice may be due to a constant demand for mature cells and an increased complement of CFU-GM modulated by stromal regulation (Tejero et al. 1989).

Stem Cell Integrity

The proliferative lifespan of the stem cells that sustain hematopoiesis throughout life is not clearly delineated. It has been proposed that the sequential loss of telomeric DNA from the ends of human chromosomes during cell division eventually reaches a critical point that triggers cellular senescence (Vaziri et al. 1994). This occurs because of the absolute requirement for DNA synthesis to begin at the binding site for the DNA replicative enzyme DNA polymerase (a process called priming) and the fact that this enzyme causes unidirectional DNA synthesis only. This unidirectional process results in incomplete replication of the terminal ends of the linear chromosomes distal to the DNA polymerase binding site (Olovnikov 1973; Watson 1972). In order to compensate for this replicative defect, eukaryotes have evolved a specialized rescue mechanism involving both chromosomal nucleoprotein modifications and a novel enzyme known as telomerase (Fig. 4). Eukaryotic chromosomes end in specialized nucleoprotein structures called telomeres, which in humans contain tandem repeats of the nucleotide TTAGGG. Telomeres are critical for chromosome stability and function, and the loss of telomeres signals cell cycle arrest and

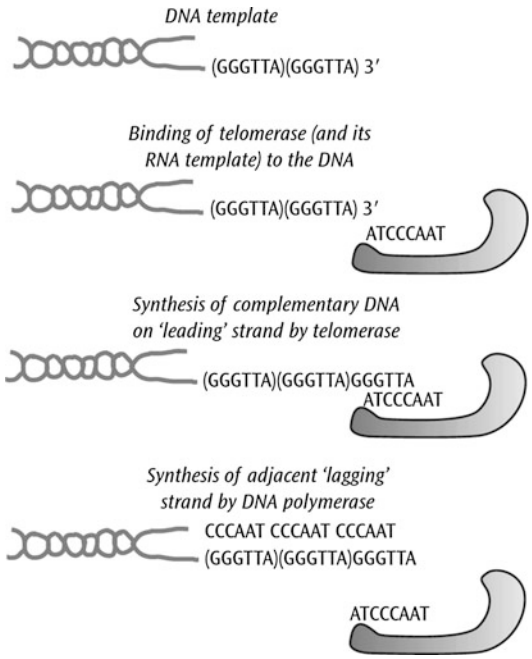

Fig. 4 Linear chromosomal DNA cannot be fully replicated by DNA polymerase. Therefore, special DNA sequences, called telomeres, have evolved at the ends of human chromosomes. A special enzyme called telomerase contains an integral RNA template. It is capable of adding nucleotides to the replicating (leading) end of the chromosome in an attempt to extend its 3′ end, allowing replication to be completed. DNA polymerase fills in the adjacent (lagging) strand but uses telomeric DNA as a site of initiation of synthesis (primer). If telomerase is not present, the chromosomal ends become progressively shortened until chromosomal replication can no longer proceed

chromosomal loss in yeast (Lundblad and Szostak 1989). Shortening of telomeres during mammalian aging in vivo has been observed in dermal and epidermal cells, peripheral blood leukocytes, and colonic epithelium, but not in sperm DNA (Allsopp et al. 1992; Hastie et al. 1990; Vaziri et al. 1993). There is evidence suggesting that early (pre-CFU-S) human stem cells (CD34+/CD38dim/-) from bone marrows of adult donors have shorter telomeres than similar cells obtained from fetal liver or umbilical cord blood (Vaziri et al. 1994). This finding suggests that the proliferative potential of hematopoietic stem cells may indeed be limited. To support this contention, telomeric shortening has been studied in stem cells after they have been induced to undergo excessive replication cycles. Shortened telomeres are well described in peripheral blood leukocytes following allogeneic bone marrow transplantation, in some bone marrow failure syndromes, and following some cytotoxic chemotherapy regimens (Robertson et al. 2000). The telomeric shortening after bone marrow transplant corresponds to approximately 15 years of aging, yet acquired bone marrow failure has not been described. Thus, telomeric shortening as a cause of suboptimal marrow responsiveness to proliferative stimuli or altered hematopoiesis appears unlikely.

Stem cell utilization, as measured by X-chromosome inactivation, also appears to be independent of telomere length. It has been known for some time that clonality assays in healthy elderly women can be unreliable owing to an acquired progressive skewing of X-chromosome inactivation (El Kassar et al. 1998). It was postulated that this could be the result of a decreased stem cell pool, and telomeric senescence was implicated as the primary cause. However, it has become clear that factors other than telomeric senescence (random stem cell loss or X-allelic exclusion) are important in altering hematopoiesis with aging. Evidence in laboratory-bred safari cats (Abkowitz et al. 1998) suggests that this skewing is a result of inherited genetic factors that cause a selective advantage to certain cells carrying one or the other X chromosome. Thus, hemizygous selection appears to be the cause of the age-dependent skewed hematopoiesis that characterizes the bone marrows of elderly individuals.

The process of aging is also associated with a general loss in the biologic competence of both single cells and the individual as a whole. At the cellular level, this loss is seen as a decrease in the ability of proliferating cells to replicate and of postmitotic cells to function effectively. When cytogenetic analysis was performed on the dividing bone marrow of rats (Sen et al. 1989), the incidence of chromosomal abnormalities (predominantly hypodiploidy) increased gradually with aging. Other abnormalities, such as polyploidy or changes in mitotic index, were not significant. The overall DNA content remains constant owing to the small number of

hypodiploid cells present (6.57% in males and 5.99% in females). When other tissues outside of the bone marrow are examined for similar abnormalities, an increase in univalency and nondisjunction are found in the ovaries of females (de Boer and van der Hoeven 1980). No significant alterations in sperm chromosome number or structure could be identified in even the very oldest males, although the division frequency did decline sharply at the extremes of aging (Sen et al. 1989).

Evidence for possible abnormalities of DNA repair and chromosomal dysregulation during aging was found in studies in which cytogenetic alterations were examined following exposure to mutagens (Singh et al. 1986). Older animals developed a higher frequency of micronuclei, reduced metaphase indices, and lower sister chromatid exchange per cell when compared with younger counterparts. Treatment with mutagens will significantly increase micronuclei and sister chromatid exchange in most strains of mice at all ages. The important point to note, however, is that the magnitude of this change increases significantly in older animals. When strain-dependent genetic predispositions are taken into account, sensitivity to mutagens and a decreased ability to repair abnormalities appear to characterize the aging animal.

The Effect of Aging on Stem Cell Clonality

The discovery of age-associated clonal hematopoiesis arose from studies exploring the phenomenon of X-inactivation skewing in elderly individuals (*discussed above*). Age-associated skewing of X-chromosome inactivation, which is particularly common within the myeloid compartment of stem cells, was hypothesized to be a result of somatic mutation acquisition, subsequently conferring a growth advantage and a clonal hematopoietic state. In fact, Busque et al. demonstrated that somatic *TET2* mutations were highly enriched in the peripheral blood of elderly women with X-inactivation skewing and that the variant allele frequencies of the mutations were highly concordant with the degree of skewing (Busque et al. 2012). There were no differences in the hematologic parameters between individuals with and without *TET2* mutations. This presence of stem cell clonality in the absence of an overt hematologic phenotype has been confirmed in multiple additional studies.

Clonal hematopoiesis, or clonal hematopoiesis of indeterminate potential (CHIP), is currently defined by the presence of somatic mutations, with variant allele frequencies between 2% and 20%, in genes commonly associated with myeloid neoplasms (e.g., *DNMT3A, TET2,* and *ASXL1*) but without overt signs of hematologic malignancy (Steensma et al. 2015). Three concurrent studies first described the phenomenon of age-associated clonal hematopoiesis in large cohorts (Genovese et al. 2014; Jaiswal et al. 2014; Xie et al. 2014). The studies demonstrated that clonal hematopoiesis is an age-dependent genetic event that occurs in up to 10% of individuals over the age of 70 years and in virtually no individuals under the age of 40 years. The presence of CHIP is an unfavorable risk factor that has been associated with a significantly increased risk for hematologic malignancy (HR 12.9), reduced overall survival (HR for death 1.4), and increased risk of coronary heart disease (HR 2.0) when compared to individuals without CHIP (Genovese et al. 2014; Jaiswal et al. 2014).

Studies using alternative parameters to define CHIP have reported even higher frequencies in elderly individuals. Using error-corrected sequencing to detect variants at frequencies as low as 0.03%, Young et al. demonstrated that 95% of healthy individuals (50–60 years old) harbored CHIP mutations (Young et al. 2016). Interestingly, the mutations were frequently (76.9%) present in multiple hematopoietic compartments (i.e., lymphoid and myeloid) and stable over time (27.5% of individuals had the same mutation 10 years apart). The clinical significance of very low-frequency variants or the hematopoietic compartment of the variants has yet to be elucidated. Using whole-genome sequencing and barcodes of mosaic somatic mutations (down to 1% allele frequencies), Zink et al. reported that over 50% of individuals over the age of 85 years

demonstrated clonal hematopoiesis, whereas less than 0.5% of individuals less than 35 years old were classified as having clonal hematopoiesis (Zink et al. 2017). This was also the first study to report that a germline mutation (*TERT,* telomerase reverse transcriptase, rs34002450) predisposes individuals to clonal hematopoiesis (OR 1.37).

Clonal hematopoiesis has been demonstrated to confer significant risks in the setting of cancer. First, there is an approximately 5% absolute risk for hematologic cancer development for individuals with CHIP (Genovese et al. 2014; Jaiswal et al. 2014). Second, individuals with CHIP who are treated with chemotherapy for non-hematologic malignancies have a significantly higher incidence of lethal secondary cancers, known as therapy-related myeloid neoplasms (median survival 6–11 months), than individuals without CHIP (Gillis et al. 2016; Takahashi et al. 2017). Likewise, individuals with CHIP who receive autologous stem cell transplants for lymphoma are at a significantly increased risk of developing therapy-related myeloid neoplasms (Gibson et al. 2017a). Case series also suggest that CHIP can be transferred to recipients through allogenic stem cell transplantation (Gibson et al. 2017b). Interestingly, the prevalence of CHIP is higher in individuals with solid cancers (approximately 25%–30%) than in non-cancer cohorts; however, as in healthy individuals, the prevalence in cancer patients is also significantly associated with increased age, with an approximate 6% increased odds of CHIP for every 10 years of age (Gillis et al. 2016; Coombs et al. 2017).

Clonal hematopoiesis also increases the risk of cardiovascular disease by promoting the development of atherosclerosis, ultimately resulting in coronary heart disease. Using mouse models prone to atherosclerosis (*Ldlr*$^{-/-}$), Fuster et al. demonstrated that partial bone marrow reconstitution with *Tet2*-deficient cells (to model clonal hematopoiesis) was sufficient for clonal expansion and resulted in a significant increase in atherosclerotic plaque size (Fuster et al. 2017). *Tet2*-deficient macrophages increased the expression of pro-inflammatory cytokines, including interleukin (IL)-6 and 1β, which likely exacerbated atherosclerosis. This effect could be reversed with IL-1β blockade (Fuster et al. 2017). These findings were confirmed in a large case-control study, which demonstrated that individuals with CHIP have an increased risk of coronary heart disease and early-onset myocardial infarction (1.9-fold and 4.0-fold, respectively) (Jaiswal et al. 2017). These increased risks were attributed to increased coronary artery calcification (a marker of coronary atherosclerosis burden) and cytokine release, and the mechanism was validated in mouse models of CHIP.

In summary, it is established that clonal hematopoiesis occurs increasingly with age; however, the etiology is unknown at this time. There are genes that most commonly harbor clonal hematopoiesis mutations (e.g., *DNMT3A, TET2, ASXL1*, and *PPM1D*); however, the translational significance of each gene has yet to be elucidated. One study reported an association of *TET2*, but not *DNMT3A*, mutations with age (Buscarlet et al. 2017). While there is no clear cutoff defining clinically significant variant allele frequencies for CHIP mutations, it is known that the risks of cancer and coronary heart disease are significantly increased (49-fold and 2.2-fold, respectively) in individuals with higher variant allele frequencies ($\geq$ 10%) (Jaiswal et al. 2014, 2017). Data suggests that progression from CHIP to coronary heart disease may be precipitated through inflammatory processes, but the mechanism for clonal expansion from CHIP to overt hematologic malignancy is unknown at this time.

The Effect of Aging on Bone Marrow Stroma

Age-related variations in hematopoiesis are well documented, but, as noted previously, it is sometimes difficult to distinguish between the influence of extrinsic (marrow microenvironment) and intrinsic (genetic or stem cell) factors. Bone marrow stroma is an important source of extrinsic signals necessary for the maintenance of both in vitro and in vivo hematopoiesis. Direct-contact signaling between stem cells and stromal cells via adhesion receptors and secretion of cytokines has been documented (Williams et al. 1990; Wolf

et al. 1995). Serial transplantation studies in aging mice have suggested that defective secretion of cytokines and decreases in the ability of bone marrow stroma to maintain stem cell replication are the major factors responsible for the decreased cell proliferation that characterizes aging. This deficiency has been further evaluated in other experimental models (Boggs et al. 1991), where a variety of latent deficiencies of the hematopoietic microenvironment have been documented. No change in the capacity of stromal cells to bind stem cells has been identified. However, when colony formation in culture is studied during aging (Sidorenko et al. 1990), an increase in the bone marrow content of stromal precursor cells forming fibroblast colonies (CFU-F) is noted. This increase in bone marrow stroma is not associated with changes in bone marrow stem cell content, although a relationship between stromal cell number and bone marrow cellularity is apparent. The changes in stromal cell content, cell number, and cellular organization (Schofield et al. 1986; Sidorenko 1985; Sidorenko et al. 1986) point to an age-related reorganization of the bone marrow microenvironment.

How stromal cell reorganization influences stem cell physiology is not well understood. This most likely reflects a general paucity of experiments designed to evaluate the contribution of stroma to cell proliferation and function. The few functional studies in the literature are generally not well controlled. A single report suggests decreased neutrophil function when granulocytes are grown in long-term cultures of stroma from older as opposed to younger donors (Udupa and Lipschitz 1987). In this study, neutrophil function following stimulation by mitogen 4-phorbol-12-myristate-13-acetate (PMA) was decreased in cultures initiated from the bone marrow stroma of older mice. However, neither cytokine production nor variability in culture conditions was evaluated.

The Effect of Aging on Cytokine Production and Release

Although the steady-state blood cell levels are normal, many older persons appear to have an impaired ability to accelerate hematopoiesis in response to physiologic stress. This impairment, in large part, appears to be due to a disordered cytokine regulatory network. Abnormalities in both constitutive expression and induced expression have been described (Baraldi-Junkins et al. 2000). The majority of evidence documents alterations in both cytokine secretion and cellular responses to cytokines in vitro, and few of these proteins have been measured directly in vivo (Table 3). No published studies have identified decreases in the serum levels of cytokines necessary for myeloid proliferation or differentiation (Li et al. 1988). However, an age-related decline in secretion of human IL-3 and GM-CSF by phytohemagglutinin (PHA)-stimulated peripheral blood mononuclear cells has been demonstrated in elderly persons and centenarians when compared with young adults (Bagnara et al. 2000). Furthermore, a paradoxical increase in serum SCF was noted, illustrating the complexity of this system and suggesting the presence of an as-yet uncharacterized compensatory mechanism to maintain the stem cell pool.

Of the cytokines studied in some detail in the literature, the most consistent results have been with measurements of IL-2, IL-6, and IL-7 (Fong and Makinodan 1989; Holbrook et al. 1989). Levels of IL-2 show a consistent decrease, likely contributing to abnormalities of T-cell function. Likewise, several studies (Stephan et al. 1998; Updyke et al. 1993) have evaluated the contribution of decreased production of IL-7 on altered B-lymphoid differentiation during aging. IL-7 is produced by bone marrow stromal cells and is required for pre-B-cell development (Namen et al. 1988). Whether alterations in cytokine secretion or production in vitro will translate into meaningful in vivo phenomena remains to be seen. Decreases in IL-2 and IL-7 production correlate with clinical data showing decreased immune function in elderly individuals.

Perhaps the most important cytokine for gerontologists is IL-6 (Ershler 1993). IL-6 is a multifunctional protein (Fig. 5) produced by a wide variety of cells under varied conditions. It is the critical factor in the acute-phase inflammatory response and appears to be involved in such diverse activities as induction of B-cell proliferation and maturation, regulation of protease

Table 3 A variety of cytokine abnormalities (in vivo and in vitro) that have been associated with aging

	Mouse	Human
In vivo abnormalities	Decreased serum IL-3 Decreased serum IL-2 Increased serum IL-6	Increased serum IL-6 Increased serum SCF
In vitro abnormalities Abnormalities in cytokine production and/or secretion	Decreased production of IL-1, IL-6, and TNF by LPS-stimulated peritoneal macrophages Decreased production of IL-7 by long-term bone marrow cultures	Decreased production of IL-2 by anti-CD3-stimulated T cells Decreased production of IL-3 and GM-CSF by PHA-stimulated PBMC Decreased production of IL-4 and IFN-γ by conA-stimulated mononuclear cells Increased production of IL-6 by PHA-stimulated lymphocytes
Abnormalities in cellular responses to cytokines	Decreased responsiveness of B precursors to IL-7 Decreased responsiveness of bone marrow stromal cells to PDGF and IGF-I	Decreased responsiveness of marrow progenitors to G-CSF

IL, interleukin; *SCF*, stem cell factor (c-Kit ligand, Steel factor); *TNF*, tumor necrosis factor; *LPS*, lipopolysaccharide; *GM-CSF*, granulocyte/macrophage colony-stimulating factor; *PHA*, phytohemagglutinin; *PBMC*, peripheral blood mononuclear cells; *IFN-γ*, interferon gamma; *conA*, concanavalin A; *G-CSF*, granulocyte colony-stimulating factor; *PDGF*, platelet-derived growth factor; *IGF-I*, insulin-like growth factor I

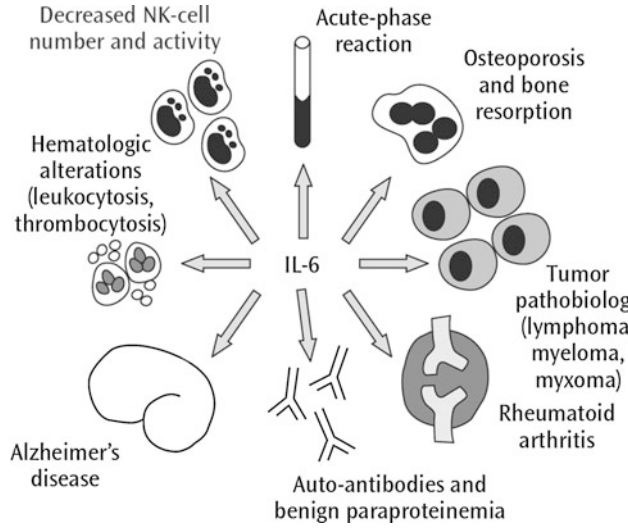

Fig. 5 Interleukin-6 (IL-6) exerts a number of important effects on many organ systems. Increases in IL-6 during normal aging are thought to contribute to the pathogenesis of several neoplastic and non-neoplastic (predominantly inflammatory) disorders

inhibitors such as α1-antichymotrypsin and α2-macroglobulin, and stimulation of bone resorption in vitro. Dysregulation of IL-6 expression has been implicated in the pathogenesis of a variety of neoplastic and non-neoplastic disorders, including multiple myeloma (Kawano et al. 1988; Klein et al. 1989), non-Hodgkin lymphoma (NHL) (Merz et al. 1991; Nachbaur et al. 1991), rheumatoid arthritis (Ganter et al. 1989; Garman et al. 1987), Castleman's disease (Brandt et al. 1990b; Yoshizaki et al. 1989), and cardiac myxoma (Jourdan et al. 1990).

The regulation of IL-6 gene expression is complex, with low to absent levels found in the serum of normal individuals. With aging, however, there is a gradual increase in the level of measurable IL-6, even in the absence of documented inflammatory stimuli (Daynes et al. 1993; Foster et al.

1992; Tang et al. 1991). It has been postulated that changes in IL-6 regulation may constitute one of the fundamental aging processes and could conceivably contribute to a broad spectrum of age-associated diseases (Ershler 1993). Because of the known effects on B-cell proliferation, dysregulation of IL-6 gene expression may well be related to the appearance of autoantibodies and perhaps the benign paraproteinemias that occur in aging mice (Radl 1990; Radl et al. 1975). Furthermore, since α1-antichymotrypsin and α2-macroglobulin may adversely alter the breakdown of amyloid precursor proteins, IL-6-induced increases in these protease inhibitors may contribute to the pathogenesis of Alzheimer's disease (Abraham et al. 1990; Bauer et al. 1991; Vandenabeele and Fiers 1991).

When administration of recombinant human IL-6 was tested in vivo in rhesus monkeys, a number of alterations in hematologic and immune parameters were observed (Sun et al. 1993). IL-6-treated animals lost an average of 10.9% of their body weight over a 28-day period of IL-6 administration. In addition to weight loss, there was a decrease in hemoglobin and hematocrit without evidence of peripheral hemolysis or obvious bone marrow suppression. A transient leukocytosis and a sustained thrombocytosis were also noted. Decreases in natural killer (NK)-cell activity and number were identified. Such changes are transient when normal young adult monkeys are studied but are sustained in elderly animals. A similar dichotomy is noted when examining serum protein. In normal adult monkeys, total protein levels rise after administration of IL-6, secondary to increases in acute-phase reactants and the appearance of a hypergammaglobulinemia. However, unlike the young adult animals, older subjects show a fall in serum total protein, which remains depressed for up to 1 week after the administration of IL-6 is discontinued. Thus, IL-6 clearly has a multitude of diverse effects on metabolism and homeostasis, and these effects may be variable during aging.

Perhaps the most extensively studied effect of IL-6 on aging is that related to osteoporosis. Osteoblasts are among the many cell types that secrete IL-6, and IL-6 stimulates bone resorption in vitro (Ishimi et al. 1990). Increasing levels of IL-6 with aging may contribute to postmenopausal osteoporosis (Roodman 1992). Decreasing estrogen levels result in a decrease in IL-6 gene expression (Girasole et al. 1992) with increased bone resorption and osteoclast activation. The system is complex, however. In addition to IL-6, at least two other cytokines are implicated in the generation of osteoporosis. Both insulin-like growth factor I (IGF-I) and platelet-derived growth factor (PDGF) have been identified as mitogens for marrow stromal cells (Tanaka and Liang 1995; Tanaka et al. 1994). They enhance cell growth and bone turnover through their actions on bone formation and bone resorption and appear to be less potent in older individuals. This lack of stimulation may result in decreased progenitor cell proliferation and subsequently a diminished expansion of new osteoblasts.

The Effect of Aging on Immune Function

Bone Marrow T Cells

The reported decline in immune responses during aging has been largely attributed to reduced functioning of the T-cell compartment (Fig. 6) (Pawelec et al. 1999). The majority of studies designed to investigate the biologic basis for the T-lymphocyte changes utilize mouse models. Sharp et al. have shown an increase in the proportion of T lymphocytes in bone marrow with age (Sharp et al. 1990). When these cells were sorted by flow cytometry and studied for proliferative response to mitogen (concanavalin A), T lymphocytes from bone marrow of older mice showed a significantly lower response than those obtained from younger donors. When adjusting the cultures for the presence of equal numbers of T lymphocytes, older bone marrows appeared to initially manifest a higher level of proliferation. However, the response was maintained for a shorter duration, suggesting a functional deficit. Thus, there are greater numbers of effector T lymphocytes in the bone marrow of older animals, but they show a proliferative response of shorter duration.

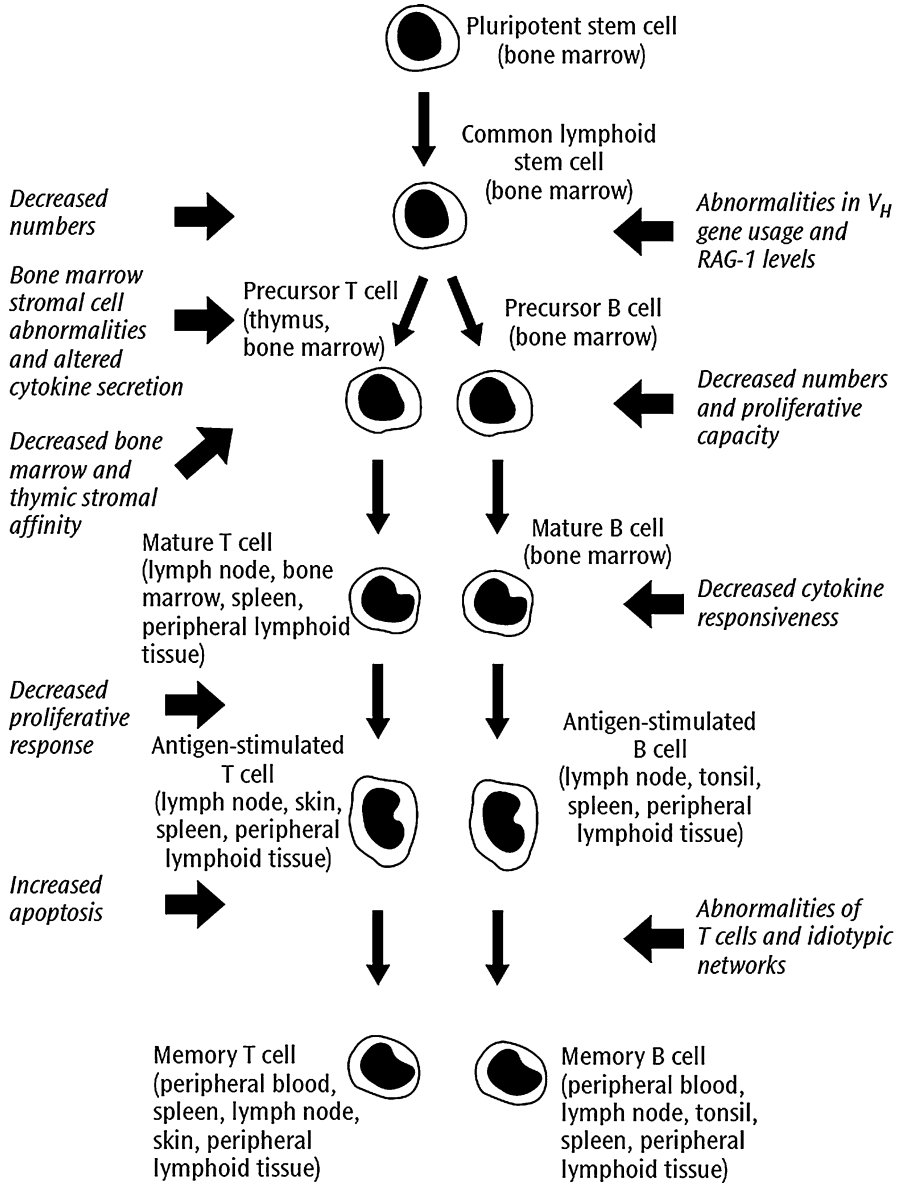

Fig. 6 A multitude of abnormalities in both T- and B-cell differentiation and proliferation have been ascribed to the aging process. These defects occur at all stages of T- and B-lymphocyte development

Concomitant with the increase in mature T cells, Globerson et al. have identified a decrease in the number of bone marrow-derived thymocyte progenitor cells with aging (Globerson et al. 1992). It was suggested that this decrease may be a normal function of aging that accompanies involution of the thymus. The proportion of mature T cells (CD4+/CD8+ ratios) derived from bone marrow of both young and older individuals appears similar. Since these mature T cells are long-lived and can continue to proliferate in response to immunogenic stimuli, the observed decrease in thymocyte progenitors may have little functional impact.

Thymic involution, however, imparts additional functional abnormalities to T-lymphocyte proliferation and function during aging. Sustained cell production by the thymus depends on the

continued migration of bone marrow thymocyte precursors to the thymus. As previously demonstrated (McCormick and Haar 1991), the ability of bone marrow-derived prothymocytes from aged individuals to migrate in response to thymic supernatants is grossly defective. Preincubation of these same bone marrow cells with neonatal thymic epithelium dramatically improves the ability of the aged bone marrow stem cells to migrate in vitro. Growth hormone and IGF-I stimulate thymopoiesis, and their levels decrease with age (Montecino-Rodriguez et al. 1998). It is apparent that thymic factors, hormone levels, and bone marrow cytokines are necessary for the function and differentiation of prothymocytes in the bone marrow, and alterations in either their levels or the cellular response influence T-cell production during aging.

When bone marrow-derived T lymphocytes are studied by flow cytometry (Hozumi et al. 1993), the majority are CD3+ cells possessing a cytotoxic/suppressor phenotype (CD8+), although both CD8+ and CD4+ cells do increase numerically with aging. These T lymphocytes are thymic-derived and are not biased for any usage of specific T-cell receptor (TCR) β chains. Their proportions differ from T-cell subsets within the spleen and peripheral blood, suggesting that this population of T lymphocytes preferentially proliferates in the bone marrow microenvironment. Their proliferation appears to be dependent on the surrounding bone marrow non-T-cell population (Hozumi et al. 1993). Direct contact between bone marrow T cells and non-T cells leads to inhibition of T-lymphocyte proliferation after addition of exogenous mitogen. Whether or not this inhibition prevents cytotoxic T cells from recognizing homologous bone marrow hematopoietic elements and proliferating (autoimmunity) is unknown at this time but certainly appears feasible. Globerson identified an additional mechanism responsible for abnormal T-cell differentiation and function in aging mice (Globerson 1994). Bone marrow cells from young and old mice were co-cultured with lymphoid-depleted fetal thymic explants. Although the proportion of total T cells developing from older bone marrow donors was significantly lower than that of younger bone marrow donors, there was no difference in the ratio of T-cell subsets or reactivity to mitogen. Unlike previous studies, which implicated only thymic-derived defects, this study suggested an intrinsic lesion in the bone marrow-derived T-cell precursors. Whether this reflects abnormal differentiation or an increase in programmed cell death has not yet been established. It was noted that the frequency of thymocyte progenitors in older bone marrow donors is reduced by approximately 40% during aging. If the older cells were cultured in the presence of fetal thymic explants for 24 h longer than those of younger donors, T-cell development was normalized. This suggests the possibility that bone marrow-derived T cells of older donors have a decreased affinity for thymic stroma. Thus, there are multiple defects that accumulate in the bone marrow T-cell compartment with aging. Decreased affinity for stroma, in addition to decreases in migratory activity and cell replication during aging, can be of major impact.

Bone Marrow B Cells

B-lymphocyte development is modulated by a complex network of positively and negatively acting cytokines, as well as by cell-to-cell interactions. T-lymphocyte function appears to exert a major role in B-cell development. Few abnormalities of aging have been directly attributed to defects in B-cell development or function within the bone marrow (Fig. 6). An age-related decrease in the number of pre-B lymphocytes in the bone marrow has been confirmed (Schulze and Goidl 1991). These cells were identified by cell surface phenotyping as CD19+/CD10+ dual-positive cells. The decrease in early B-cell precursors is accompanied by a decreased capacity to generate surface immunoglobulin-positive mature B cells. Neither the presence of inhibitory factors nor increases in suppressor T cells could be identified as the cause of these effects.

Development of B-cell precursors into mature immunoglobulin-bearing B cells depends on soluble factors such as IL-4 and IL-7, as well as cellular interactions provided by stromal cells

and T cells (Kincade 1987). During the aging process in mice, stromal cell function appears to become altered. Release of IL-7 by stromal cells requires cell-to-cell contact with B-cell precursors. Evidence suggests that the secretion of IL-7 by aged stromal cells is delayed when compared with stromal cells from young donors (Stephan et al. 1998). Since marrow stromal cells are the only local source of IL-7, this delayed secretion may have a profound effect on the generation of new B lymphocytes in the marrow. Furthermore, there may also be a decreased overall response to cytokine-induced proliferation. Jonsson and Phillips identified a two- to fivefold lower response to IL-7 in mice over 20 weeks of age when compared with younger animals (Jonsson and Phillips 1993). This decrease appeared to be secondary to a reduced frequency of IL-7-responsive pro-/pre-B cells in the bone marrow of the older mice, and could not be overcome by the addition of large amounts of IL-7. Despite these intrinsic defects, most of the age-related changes in B lymphocytes appear to be reflective of aging T lymphocytes. There is a constant decrease in the amount and affinity of antibody produced by aged animals (Price and Makinodan 1972), accompanied by age-associated increases in autoantibody production (Viale et al. 1994). The decline in antigen responsiveness associated with aging has been characterized in both qualitative and quantitative terms (Schulze and Goidl 1991; Price and Makinodan 1972). The magnitude of responses to both thymic-independent and thymic-dependent antigens are depressed. Furthermore, in the aged, the expressed antibody repertoire is principally composed of low-affinity antibodies with a decrease in, or absence of, medium- and high-affinity antibodies. Along with this lack of maturation in antigen affinity, there occurs a concomitant change in the expressed repertoire of antibodies to a given antigen. Auto-anti-idiotypic antibodies produced during the normal immune response of the aged animal are markedly enhanced when compared with those seen in the immune responses of younger adults. This abnormality is accompanied by a rise in titers of autoantibodies and a gradual increase in total serum immunoglobulin concentration.

Some of the molecular genetic abnormalities responsible for these alterations have also been described. Aging mice have been found to have higher frequencies of peripheral mature B cells utilizing restricted variable gene (VH) families. This suggests that older animals express less diversified antibody repertoires as a consequence of reduced B-cell precursors and increased peripheral selection (Viale et al. 1994). This restricted gene usage may contribute to the increase in autoimmunoreactivity noted during aging. Although CD5+ B cells have been associated with immunereactive populations, no significant differences in the frequency of CD5+ B cells have been observed during aging.

A mechanism postulated for the decrease in VH gene usage is the progressive decline in expression of recombination-activating gene 1 (*RAG-1*). This gene is expressed in early pre-B lymphocytes, where it is involved in the process of recombination and rearrangement of immunoglobulin gene segments to produce mature immunoglobulin. *RAG-1* messenger RNA is expressed by B-cell precursors and in mouse bone marrow increases during the first 2 months of life to reach a maximum level at 2 months of age (Ben-Yehuda et al. 1994a). This level is maintained until adulthood, where levels progressively decrease. A decrease in *RAG-1* gene expression is directly correlated with a loss of antigen diversity within the immunoglobulin gene family (Ben-Yehuda et al. 1994b). This may explain why, with increasing age, the antibody response becomes progressively more dominated by IgM and low-affinity antibody, with decreased immunoglobulin class switching and decreased somatic mutation. This abnormality also affects T-cell function, as shown by studies in nude mice (Ben-Yehuda et al. 1994a). Transfer of young T cells is capable of restoring full antigen diversity and *RAG-1* gene expression to bone marrow cells.

Thus, both extrinsic and intrinsic changes in bone marrow B cells occur with aging. The number of B-cell progenitors is decreased. Changes in regulatory mechanisms, predominantly stromal cell and T-cell function, are the major factors responsible for the major decline in the B-cell immune response with age (Ghia et al. 2000).

The interactions of B-cell production and differentiation and thymic involution remain to be elucidated.

Conclusions

While many defects in hematopoiesis have been ascribed to the aging process, their specificity remains controversial. The difficulty in assessing functional abnormalities is in part related to the coexistence of other disease processes in the aging population. However, more importantly, it is the complex interactions between normal stem cells and their progenitors, the bone marrow stroma, and the immune system (both T and B lymphocytes), as well as the multitude of cytokines produced, which contribute to a vast interactive network. While multiple studies in mice and other rodents have attempted to dissect this complex process, human studies must confirm these findings. The importance of these studies cannot be underestimated, since an understanding of the physiology of hematopoiesis is paramount to the construction of less toxic and more effective therapies for the aging patient population.

Cross-References

- Acute Myeloid Leukemia in Older Adults
- Aging and Cancer Biology
- Chronic Lymphocytic Leukemia in Older Adults
- Chronic Myelogenous Leukemia and Myeloproliferative Disorders in Older Adults
- Decision Making and Safety Issues in Older Cancer Patients
- Hematopoietic Stem Cell Aging and Malignant Hemopathies
- Immunosenescence and Cancer Immunotherapy at Old Age: Basics
- Principles of Chemotherapy in Older Adults
- Role of Cell Cycle Control, Checkpoints, and DNA Repair Mechanisms in Stem Cells and Changes with Aging and Cancerogenesis
- The Biologic Interconnections Between Aging and Lymphoma
- The Evolving Role of Transplant for Older Adults

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Pharmacology of Aging and Cancer

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Contents

Abstract

Advanced age is the number one risk factor for the development of cancer. As a result, older adults (≥65 years old) represent the majority of patients with cancer globally. By 2030, around 70% of all cancer diagnoses will be made in adults 65 years and older. Older patients are often less fit and, in general, tolerate medical therapies poorly. Advanced age is accompanied

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by many physiologic changes which can impact the pharmacology, pharmacokinetics, and pharmacodynamics of medications. Moreover, older patients tend to accumulate medications over time, leading to polypharmacy (PP). Polypharmacy is a "disease" that has many risk factors and causes which can potentially lead to poor outcomes. Deprescribing, or the process of systematically reducing or discontinuing drugs, has been deemed an effective "cure" for PP. Older patients with cancer are particularly susceptible to adverse outcomes from PP and potentially inappropriate medications (PIMs). This chapter describes the impact of aging and cancer on geriatric pharmacotherapy as well as the incidence and definitions of PP and PIMs in the context of geriatric oncology. Finally, processes and models of deprescribing that can be applied to older patients with cancer are discussed.

Keywords
Deprescribing · Polypharmacy · Geriatrics · Geriatric oncology

Introduction

Advanced age is the number one risk factor for the development of cancer (McIntyre 2016). As a result, older adults (≥65 years old) represent the majority of patients with cancer globally. By 2030, around 70% of all cancer diagnoses will be made in adults 65 years and older (NCCN 2015). Older patients are often less fit and, in general, tolerate medical therapies poorly. Advanced age is accompanied by many physiologic changes which can impact the pharmacology, pharmacokinetics (PK), and pharmacodynamics (PD) of medications. Moreover, older patients tend to accumulate medications over time, leading to polypharmacy (PP). Drugs for chronic disease management, symptomatic management, and prevention of treatment induced toxicities are often used alongside anticancer therapies. The complex interplay between PP, physiologic changes of aging, and competing comorbidities all add to the risk of chemotherapy toxicities, poorer quality of life, and less than ideal patient outcomes.

Polypharmacy is a geriatric syndrome that has been defined many ways. The most commonly used definition of PP is the use of five or more medications on a regular basis (Maggiore et al. 2010). This definition is easily incorporated into daily practice but may not capture the true impact of PP on patient care and outcomes. Other terms commonly used to define PP include potentially inappropriate medications (PIMs), medication overuse, medication related problems, and medication underuse. Polypharmacy, especially in the setting of comorbidity, can lead to adverse drug effects, drug-drug interactions, drug-nutrient interactions, nonadherence (i.e., early discontinuation of chemotherapy), and increased health care utilization (Maggiore et al. 2010). The use of medication screening tools to assess PP in older patients with cancer has recently been summarized in detail (Whitman et al. 2016a). The 2015 Beers Criteria, Screening Tool to Alert Doctors to Right Treatment/Screening Tool of Older Persons' Prescriptions (START/STOPP), and the Medication Appropriateness Index (MAI) have each been endorsed by the American Geriatrics Society and discussed within the National Comprehensive Cancer Network's (NCCN) Clinical Practice Guidelines for Older Adult Oncology. There is a lack of consensus on the best method to define and evaluate PP and PIMs in older patients with cancer.

Currently, health care providers are challenged with managing patients' chronic disease states in the setting of cancer. Patients with diabetes, hypertension, chronic obstructive pulmonary disease (COPD), arthritis, gastroesophageal reflux disease (GERD), and other complex disease states are provided medication therapies that are guideline-driven and often managed by specific providers. Drugs given for chronic diseases often interact unpredictably with chemotherapy and can result in increased toxicity. Moreover, considerations for reducing PP and pill burden in older patients with cancer and in patients with a limited life expectancy are often overlooked. An effective geriatric model that can be applied to older patients with cancer has been developed. The

authors describe a framework of evaluating each medication by considering the time-to-benefit, patients' life-expectancy, goals of therapy, and purpose of therapy (curative versus palliative) (Holmes et al. 2006). Furthermore, deprescribing has been touted as an effective way to minimize PP, especially for older patients with cancer; deprescribing will be discussed and explored later in this chapter.

This chapter will review basic tenants of pharmacology, PK, and PD that are specific to geriatric patients. Additionally, the definitions, incidence, assessment, and management of PP and PIMs in older cancer patients will be extensively reviewed. Finally, the role of deprescribing will be discussed in the context of geriatric oncology.

General Pharmacotherapy Considerations in Geriatric Oncology

Both chronological age and functional age have been used to define elderly patients. Regardless of this definition, as individuals age they have expected physiological changes that can impact drug therapy. These progressive impairments and reduced functional reserve impact multiple systems and organs such as the gastrointestinal (GI) tract, kidneys, liver, cardiovascular, musculoskeletal, and central nervous system (CNS). Older patients with cancer, in particular, may have accelerated changes in these parameters due to a number of reasons (e.g., chemotherapy exposure, antimicrobial use, PP, frailty) (Shi et al. 2008). Moreover, older patients with cancer with comorbid conditions have exaggerated changes in PK and PD. These age-related changes can significantly impact the way our bodies handle medications (i.e., PK) and the way medications impact our bodies (i.e., PD). All of these changes affect choice, frequency, and dosing during drug administration. Common PK considerations in medication therapy include drug absorption, distribution, metabolism, and elimination (i.e., ADME). Each of these factors can impact or be impacted by chemotherapy, supportive medications, and preventative drug use. Additionally, PP and PIM use add an additional layer of complexity due to unclear interactions with physiologic changes from aging and drug adverse effects; the risks of adverse drug effects increase exponentially with the number of medications. Specifically, the risk of an older adult experiencing an adverse drug effect is 35% and 82% when exposed to $\geq$5 and $\geq$ 7 medications, respectively (Cashman et al. 2010; Sokol et al. 2007). Many adverse effects can be mistaken as symptoms from an existing malignancy or perceived as cancer progression (Riechelmann et al. 2009). Physiologic changes, PP, and PIM use all need to be considered when evaluating older patients with cancer.

Absorption

Changes associated with absorption are primarily driven by alterations in the GI tract. Gastric pH tends to increase with aging due to natural changes (i.e., reduced secretion of digestive enzymes and gastric acid) or due to chronic use of acid suppressive therapies (e.g., proton pump inhibitors [PPI], antacids); chronic PPI use is common in older cancer patients who may have GI symptoms associated with their underlying malignancy. Moreover, numerous medications used in the setting of cancer require an acidic pH for optimal absorption. For example, oral chemotherapy agents such as dabrafenib, dasatanib, erlotinib, gefitinib, and vismodegib all require acidic environments for absorption and it is recommended to avoid chronic acid suppressive therapy; this is particularly significant because poor absorption can lead to suboptimal drug levels and poor outcomes (Segal et al. 2014). Likewise, other supportive medications used in oncology requiring an acidic pH include some azole antifungals (i.e., itraconazole) and ferrous sulfate. Intestinal atrophy can be a contributor to decreased gastric acid secretion but also may lead to a general decrease in bowel surface area resulting in less drug absorption (Shi et al. 2008).

Other factors contributing to a decrease in GI absorption include reduced splanchnic blood flow, decreased GI motility (impaired peristalsis and colonic transit), and slightly delayed gastric emptying (Shi et al. 2008). Changes in motility

along many sites of the GI tract can be troubling in older adults, especially in the setting of added PP and adverse effects. For example, older cancer patients taking opioids for cancer-related pain can expect additional decreases in GI motility resulting in constipation. This, in turn, can lead to greater time for drug accumulation in the stomach and small intestines possibly resulting in higher drug levels and an amplification of PD drug effects.

In general, passive diffusion of smaller drug therapy molecules remains unchanged in the elderly, but there may be a decrease in active transport resulting in a decrease in bioavailability. Absorption of the nutrients calcium, vitamin B-12, iron, and glucose may be reduced with aging (Mangoni and Jackson 2004). In general, drug transport effects seem to be minimal and of no particular clinical significance (McLean and Le Couteur 2004).

Finally, considerations relating to drug absorption that are particularly relevant to older adults with cancer include transdermal and subcutaneous drug administration, swallowing difficulties, poor nutrition, and the impact of feeding tubes on drug variability (Wooten 2012). Age-related skin changes, reduced muscle mass (sarcopenia), and general frailty can all impact transdermal and subcutaneous absorption. Older cancer patients are offered therapies such as transdermal opioids (e.g., fentanyl patches), hormone therapies, anticoagulation, and other topical therapies. Poor muscle tone and cachexia can prevent use of these therapies because of erratic or insufficient drug absorption. There is also the potential for both local and systemic reactions due to changes in absorption (Shi et al. 2008). Swallowing difficulties is also a barrier for drug therapy adherence and attainment of appropriate drug levels; this can lead to poor outcomes, especially for anticancer therapies. Poor nutrition may lead to decreases in drug transport cofactors that assist in active transport across GI mucosa; the significance of these changes remains unclear. Feeding tubes can be a barrier to drug absorption due to inappropriate drug-tube binding (e.g., phenytoin). Likewise, patients that administer medications via gastrostomy tubes or jejunostomy tubes may have issues with losing dignity and embarrassment, especially if drug administration occurs frequently throughout the day without much privacy.

Distribution

Drug distribution is determined by factors such as drug clearance, dose, plasma protein binding, red blood cell viability, and changes in the body's adiposity, total body water, and muscle tone. Body fat generally increases by about 20 to 40% and total body water and lean body mass decrease by 10% with advancing age (Shi et al. 2008). As a result of this change in fat-water distribution, drugs that are more lipophilic (e.g., diazepam) may have a larger volume of distribution into tissues resulting in a longer drug half-life; lipophilic drugs with actions in the CNS in elderly patients may be particularly troublesome. In contrast, hydrophilic drugs such as digoxin and atenolol have smaller volumes of distribution; thus, these drugs concentrate in the plasma requiring lower doses in elderly patients. Of note, patients with cancer can have altered drug distribution due to edema from their cancer therapies or from their malignancy (e.g., third spacing). Older cancer patients typically have less bone marrow fat and bone marrow reserve (Hurria and Lichtman 2008). This is often due to myelosuppressive cancers (e.g., acute myeloid leukemia), chemotherapy, and/or radiation. As a result, older patients are at an increased risk of myelosuppression and its accompanied complications.

Changes in plasma protein binding associated with aging are generally insignificant. Though coupled with drug interactions and changes in plasma protein due to comorbidities (particularly cancer and malnutrition), physiological changes become relevant (doxorubicin, etoposide, and taxanes are highly plasma protein bound). Albumin is the most common site of plasma protein binding for medications. Albumin concentrations typically decrease by about 10% or stay the same with aging while alpha-1-acid glycoprotein tends to increase with age; alpha-1-acid glycoprotein changes are likely due to increased inflammation associated with aging. Decreased albumin can

increase unbound drug and increase toxicity, especially for drugs with a low therapeutic index (Shi et al. 2008). Anemia and poor nutrition in elderly cancer patients can effects quantity and quality of red blood cells. This is important in the chemotherapy context because agents such as anthracyclines and taxanes are transported by red blood cells; therefore, effects from chemotherapy could be unpredictable (i.e., increased toxicity and/or decrease efficacy) (Hurria and Lichtman 2008).

Metabolism

A change in the ability of older adults to hepatically metabolize medications is the second most clinically meaningful of the PK effects, after renal elimination. Older adults tend to have a decrease in hepatic mass and blood flow of about 20–30% and 20–50%, respectively. These changes lead to reduced "first-pass" metabolism (Mangoni and Jackson 2004). Metabolism of drugs in the liver is primarily dependent on metabolizing enzymes and hepatic perfusion. Protein binding also plays a role in drug metabolism; more unbound drug (due to reduced plasma protein binding) increases the amount of drug clearance through the liver. The majority of drugs metabolized in the liver undergo phase I metabolism through the cytochrome (CYP)-P450 system (i.e., oxidation, hydrolysis). A smaller but still significant percentage of medications undergo phase II metabolism. In phase II metabolism, polar molecules are added to drugs (i.e., glucoronidation) in order to increase molecular weight, hydrophilicity, and, ultimately, clearance through the kidneys (Wooten 2012).

Phase I metabolism is more likely to be impaired in the elderly with as much as a 30% reduction in metabolizing enzymes; this is due to possible decreased enzyme synthesis as well as reduced liver volume and blood flow (McLean and Le Couteur 2004). Drugs that undergo phase I metabolism can have several negative consequences in older patients with cancer. Firstly, anticancer agents can have reduced clearance and an extended half-life, leading to increased toxicities. For example, paclitaxel is metabolized by CYP3A4, the major phase I drug metabolism enzyme. If there are less enzymes as a result of aging or less metabolic activity due to drug-drug interactions or pharmacogenomic changes, paclitaxel-induced toxicities, such as neuropathies, can be exaggerated. Secondly, anticancer agents that require activation by phase I enzymes ("pro-drugs") can be impacted. Tamoxifen requires activation by CYP2D6 to an active metabolite, endoxifen. Reduction in this conversion to an active metabolite may reduce efficacy. Though in vitro testing has not provided reasonable evidence that CYP2D6 activity is reduced with aging, this still may be clinically meaningful (McClean and Le Couteur 2004). There are inadequate data regarding anticancer dose adjustments in the setting of hepatic impairment and age-related changes.

Efflux transporters that are vital to drug clearance should also be considered. P-glycoprotein (P-gp) is an essential efflux transporter that is expressed in intestinal tissue, hepatocytes, and in the blood-brain barrier. These transporters act as gate-keepers to prevent inappropriate xenobiotics from entering vital organs and tissue spaces. It is unclear whether there are significant age-related changes in P-gp concentration. Drug interactions and pharmacogenomic changes in P-gp can still impact drug therapy, particularly in older patients (McClean and Le Couteur 2004).

Elimination

Aging also has a significant impact on kidney function. Older patients have a decrease in renal mass, blood flow, and the size and number of functioning nephrons. Also, older patients are sensitive to drug therapies, such as beta blockers and vasodilators, which can reduce blood flow to the kidneys. Renal mass decreases by 25–30% with aging. No clearly defined cut-point has been established to describe specific time points in renal mass decline; each individual patient's renal function is somewhat variable. In contrast, renal blood flow consistently declines about 1% or 0.75 to 1 ml/min per year after the age of 40 (Hurria and Lichtman 2008; McLean and Le

Couteur 2004; Shi et al. 2008). Age-related changes are important, but confounders like hypertension, vascular disease, diabetes mellitus, and nephrotoxic drug therapies most likely play a more important role (McClean and Le Couteur 2004). Prediction of renal function in elderly patients may also be difficult due to changes in muscle mass and falsely elevated creatinine levels; therefore, serum creatinine should not be used as the sole marker for renal function in elderly patients (Lichtman and Boparai 2008). Various PK equations have been developed to predict renal function in the general population; age-related changes confound the applicability of these equations. Examples of common tools include Cockcroft/Gault, Jelliffe, Wright, and the modification of diet in renal disease (MDRD) (Charhon et al. 2012).

Impairments in renal function can impart difficulties in anticancer drug administration. Many chemotherapy and targeted agents require adjustment with renal impairment (i.e., cisplatin, carboplatin, capecitabine, melphalan, and methotrexate). There are some established guidelines for specific drugs, but the majority of recommendations are not evidence-based and drug labeling lacks clear guidance. Again, PP and comorbidities can add to drug toxicities when considered alongside older adults' progressive decline in renal function.

General Pharmacodynamic Principles

Pharmacodynamics is defined as the science of how drugs affect the body (Wooten 2012). Medications exert their effects through drug receptors resulting in a therapeutic response. Older patients with cancer are susceptible to adverse effects due to PD changes associated with aging. As with PK, the presence of multiple comorbidities, frailty, drug-drug interactions, and PP can potentiate pharmacologic responses in negative ways. Older patients become more sensitive to particular medication classes such as cardiovascular and CNS acting agents. As the body ages, there may be fluctuations in drug affinities at particular receptor sites, changes in postreceptor signals, and disruption of physiologic equilibrium (i.e., baroreceptor reflex). Likewise, the number of receptor sites may change (Shi et al. 2008). Both drug efficacy and toxicities are impacted by PD changes.

Specific adverse effects are notable and worth mentioning in older adults. Administration of anticholinergic or antimuscarinic agents (e.g., diphenhydramine, amitriptyline, doxepin, oxybutynin) to older patients can result in dizziness, orthostatic hypotension, dry mouth, falls, urinary retention, tachycardia, agitation, and delirium. The negative consequences of these classes of medications can predispose older patients with cancer to poor tolerance to anticancer therapies. Cardiovascular medications, particularly antihypertensives, can also increase older adults' risk of adverse drug effects such a fatigue, dizziness, orthostatic hypotension, and falls. Beta-blockers are reported to be less effective in terms of heart rate and blood pressure control due to changes in receptor selectivity (Rossello et al. 2015). Though, older patients on beta-blocker therapy still commonly report bothersome side effects, such as fatigue. Medications that act through the CNS are commonly used as supportive therapies in older cancer patients (i.e., benzodiazepines for anticipatory nausea and vomiting; prochlorperazine for nausea; diphenoxylate and atropine for diarrhea). Older adults can be extremely sensitive to these therapies and caution is warranted. It is important to monitor for falls, excessive sedation, and other geriatric syndromes for patients taking CNS medications (Mangoni and Jackson 2004).

Pharmacologic effects in older adults can be unpredictable; therefore, starting with lower doses and titrating as appropriate is always good practice. Significant morbidity can result from inappropriate drug therapy in older adults. Likewise, studies have shown that long term use of anticholinergic medications, particularly in older adults, may result in increased brain atrophy, dysfunction, and general clinical decline (Risacher et al. 2016). Moreover, in the context of older cancer patients, response to anticancer therapies may be exaggerated as well. Tools looking to predict chemotherapy toxicity utilize patient specific variables that overlap with PK and PD principles (e.g., anemia). Finally, information on PK, PD,

Table 1 Summary of pharmacokinetic changes in older cancer patients

Parameter	Change
Absorption	Increased gastric pH Intestinal atrophy Reduced bowel surface area Reduced splanchnic blood flow Decreased GI motility Slightly delayed gastric emptying Decreased active drug transport Reduced absorption of vital nutrients (calcium, vitamin B12) Reduced subcutaneous tissue and muscle mass Swallowing difficulties Poor nutrition (reduced active transport cofactors) Presence of feeding tubes
Distribution	Increased body fat Decreased total body water Decreased lean body mass Increased general edema (cancer or drug related) Reduced bone marrow fat and reserve Decreased albumin Increased alpha-1-acid glycoprotein Anemia (reduced quantity of red blood cells)
Metabolism	Reduced hepatic mass Decreased hepatic blood flow Decreased "first-pass" metabolism Reduced phase I metabolizing enzymes (CYP450) Variability in efflux transporter expression (P-glycoprotein) Pharmacogenomic effects (single nucleotide polymorphisms)
Elimination	Reduced kidney mass Reduced renal blood flow Decreased size and function of nephrons Decreased creatinine clearance

PP, and potential chemotherapy toxicities should be used in conjunction with a comprehensive geriatric assessment (CGA) for older cancer patients (Decoster et al. 2015) (Table 1).

Polypharmacy in Older Cancer Patients

In comparison to the general geriatric population, there is currently a paucity of data describing PP and PIMs in older cancer patients. With an increase in complex pharmacotherapy and the advances in targeted therapies and immunotherapies in oncology, the concepts of PP are becoming ever more important. While the definitions of PP will be described extensively below, it is important for readers to view PP as a "disease" (Garfinkel et al. 2015). As with other disease states, PP has risk factors, causes, and requires appropriate assessment and treatment. Likewise, PP can result in impaired "normal" functioning and is distinguished by signs and symptoms (e.g., drug-drug interactions, falls). This section describes PP and PIMs in the context of geriatric oncology and serves to guide clinicians when evaluating their patients holistically, especially in alignment with a CGA (Image 1).

Definitions and Incidence of Polypharmacy

In a recent review, Bushardt et al. (2008) provide 24 definitions of polypharmacy that are currently described in the literature. This variability in definitions sheds light on the lack of consistency in the general population. The incidence of PP in general community-dwelling older patients ranges from 13% to 92% (Maggiore et al. 2010). Based on studies in older cancer patients, PP incidence is about 60% (range, 29–96%); Table 2 summarizes the literature on PP and PIM incidence in older cancer patients. Currently, there is no concrete, agreed upon definition for PP in older cancer patients. Specifically, LeBlanc et al. (2015) have emphasized the need for standardized measures and definitions of PP for this population. Maggiore et al. (2010) also highlighted the importance of developing a geriatric oncology-centric definition. The studies described here help to fill this gap of uncertainty and guide clinicians in practice. Table 3 provides a compilation of specific definitions for PP that have been published in the geriatric oncology literature.

As discussed above, the most commonly referenced definition of PP in older cancer patients is the regular use of five or more medications (Park et al. 2016). This number includes prescription, over-the-counter (OTC) products, dietary

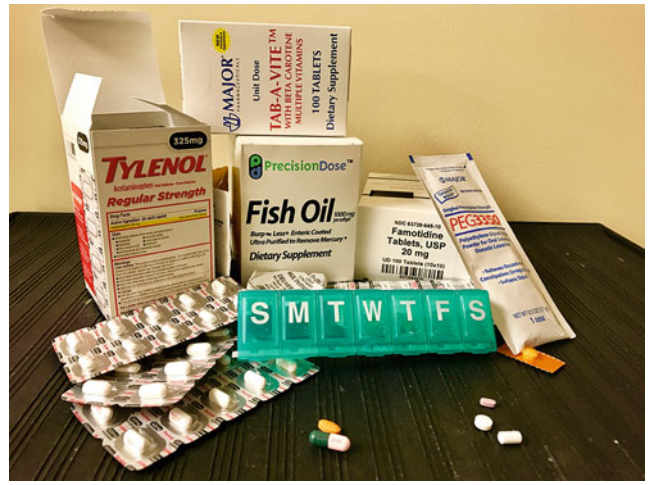

Image 1 Illustrative representation of polypharmacy. Ms. K takes a total of 13 different medications and 20 "pills" daily. She spends on average 7 h each week sorting and taking her medications

supplements, and complementary and alternative medicines (CAM). Using a specific medication cut-point to define PP has many advantages and disadvantages. Firstly, the use of a specific number is easily incorporated into clinical practice. Also, it has been shown that medication number itself is a good indicator for nonadherence versus patient age alone (Corcoran 1997). The risk of drug-drug interactions and adverse drug effects increase exponentially with the number of medications (Sokol et al. 2007). Several studies looking at PP and their relationship to specific outcomes found associations between the use of five or more medications and the presence of frailty, comorbid conditions, and impaired physical functioning (Turner et al. 2014). Moreover, in a study evaluating PP in cancer patients over the age of 65, the authors found that in patients taking four or more medications, their understanding of drug indication, dose, and frequency of use was impaired (Si et al. 2012).

A landmark study looking at PP cut-points in older cancer patients helps to establish a PP definition, particularly for clinicians wanting to use PP as a referral trigger. This study was designed to assess whether PP could predict clinically important adverse events. The authors found that taking 3.5 or 5.5 medications correlated with increased patient exhaustion and falls, respectively. Moreover, taking 6.5 medications or more predisposed patients to frailty, impaired physical functioning, and reduced performance status. The authors note that they did not look at specific medication classes and their associated risk (i.e., anticholinergic burden) or the presence of comorbid diseases (Turner et al. 2015). Nevertheless, this study does provide reasonable evidence to use a cut-point of five or more medications in this population.

In contrast, a disadvantage to using medication quantity for the sole marker of PP has been alluded to in the previously described study. Medication appropriateness, or the use of unnecessary medications, may be an even better predictor of negative patient outcomes. For example, if an older patient with metastatic colon cancer is taking diphenhydramine for insomnia, many would consider this PP due to its inappropriateness, even if this was their only medication. Diphenhydramine increases the risk of falls, sedation, and other anticholinergic effects. Therefore, medication quantity does not always predict poor outcomes. Considering appropriateness encourages the clinician to evaluate the risk versus benefits, particularly when safer alternatives may exist. Likewise, a quantitative definition disregards the potential for harm in an extremely vulnerable population (Sharma et al. 2016). A recent study found a statistically significant association with PIM use (as defined by the Beers Criteria) and the presence

Table 2 Summary of polypharmacy and potentially inappropriate medication incidence

Study	Date	Definitions	PP %	PIMs %	Pertinent results/outcomes	Other
Sokol et al.	2007	NR	NR	NR	Average number of medications = 9.1	NR
Riechelmann et al.	2009	PIMs as unnecessary or duplicate	NR	22	Assessment by palliative care team reduced PIMs by 2%	NR
Flood et al.	2009	NR	NR	21	32% of patients took 9 or more medications	NR
Puts et al.	2009	PP ≥5 meds Drug related problems or PIMS – *Vigilance Sante criteria*	56.3	47.6	PP and age ≥ 76 were associated with having one or more potential drug problem; half of the problems were found to be of moderate severity	As needed medications were not included
Prithviraj et al.	2012	PP ≥ 5 meds PIMS based on Beers Criteria (present or not present)	80	41	Average number of medications = 7.3; PP linked to IADL disability; score ≥ 3 on VES-13; having ≥5 comorbidities; and to be prescribed a Beers list medication – being underweight was also associated with PP	Patients with a new cancer diagnosis
Jorgensen et al.	2012	PP – no (0–1), minor (Barnett and Jabraj 2017; Bergen et al. 2016; Bjerre et al. 2015), or major (≥5)	34.7	NR	More PP up to 18 months prior to cancer diagnosis compared to controls – Analgesics, acid suppressive therapies, and antibiotics	NR
Yeoh et al.	2013	Drug-related problems (DRPs) or PIMs	NR	91.5	3 drug related problems per patient; 92% of the DRPs were resolved by the MTM pharmacist; increase in general understanding of treatment goals occurred post-MTM	NR
Turner et al.	2014	PP ≥ 5 meds	57	NR	Association between PP and frailty (pre-frail and frail); PP associated with Charlson Comorbidity Index and impaired physical functioning	Mean number of drugs 5.7
Saarelainen et al.	2014	PP ≥ 5 PIM – Use of a Beers Criteria med	NR	26.5	PIM user more likely to be female, age 75–79, use ≥5 meds, be frail, high distress score ≥ 5, and falls in previous 6 months; 52.5% of frail patients were using ≥1 PIM (association between PIM use and frailty); 82.4% PIMs using taking ≥5 meds	Mean number of meds 5.7; mean PIMs 0.31

(*continued*)

Table 2 (continued)

Study	Date	Definitions	PP %	PIMs %	Pertinent results/outcomes	Other
Maggiore et al.	2014	PP – 0-3;4–9;≥10 Beers 2012, Zhan Criteria, 2011 DAE; 6 high risk	NR	29, 11, 13	No significant association between number of med and chemotherapy toxicity; no association between PIM use and chemotherapy toxicity and hospitalization	Grade 3 toxicity or higher Mean 7 meds
Kierner et al.	2016	PP ≥ 5	96	NR	No outcomes measured. This was listed as a limitation of the study	Median number of 9 meds
Nightingale et al.	2015b	PP ≥ 5 EPP ≥ 10 PIMs Beers, STOPP, HEDIS DAE	PP 41 EPP 43	51	Association with PIM use were PP and increased comorbidities	Mean age 79.9; mean number of meds =9.23
Park et al.	2016	PP ≥ 5 (rx, OTC, herbal); PIMs – Beers 2012	29.3	24	Treatment toxicities; duration of hospitalization; noncancer health events (readmission with 2 years) – Benzos associated with PH	H&N cancer; 1.7% EPP
Delien et al.	2016	PP ≥5 meds; PIMs based on START/ STOPP	73	52	STOPP – 50 PIMs for 29 patients (32%) at admission compared to 16 PIMs for 14 patients (16%) at discharge – Most common findings for STOPP – CCB and constipation; duplicate drug classes	Mean number of drugs 6.73; 19% used 10 or more drugs

PP polypharmacy; *PIMs* potentially inappropriate medications; *NR* not reported; *START/STOPP* Screening Tool to Alert Doctors to Right Treatment/Screening Tool of Older Persons' Prescriptions; *IADL* instrumental activities of daily living; *VES-13* vulnerable elders survey; *MTM* medication therapy management; *HEDIS DAE* Healthcare Effectiveness Data and Information Set Drugs to Avoid in the Elderly; *EPP* excessive polypharmacy; *Rx* prescription; *OTC* over-the-counter; *PH* prolonged hospitalizations; *CCB* calcium channel blockers

of frailty. The most common PIMs in this study included benzodiazepines, tricyclic antidepressants, alpha blockers, and pro-kinetic agents (Saarelainen et al. 2014).

Factors Influencing Polypharmacy in Older Cancer Patients

The "disease" of PP has many risk factors. Older patients with cancer often have many concomitant comorbid conditions. More than 80% of older cancer patients have at least one chronic disease at the time of their diagnosis (Corcoran 1997). Of the patients who take preventative medications, half report having adverse effects attributable to these drugs (Lees and Chan 2011). One study in older palliative cancer patients found that, on average, patients took seven preventative medications (Lindsay et al. 2014). Along the same lines, older patients often see a plethora of physicians for their other, noncancer conditions. Specialists often prescribe based off of clinical practice guidelines that have a one-disease, one-drug focus. Over 50% of older cancer patients receive prescriptions by more than one provider and 31% use more than one pharmacy (Sokol et al. 2007). Prescriptions obtained from several pharmacies can lead to incomplete medication lists, duplication of therapies, and increased costs. Particularly relevant to older cancer patients is the lack of primary care provider coordination (Balducci et al. 2013).

Table 3 Common definitions of polypharmacy

Definitions of polypharmacy in geriatric oncology[a]
Simultaneous use of two drugs or more
Long-term concomitant intake of two or more medications
Use of four or more medications
Use of five or more medications
Use of ten or more medications (excessive polypharmacy or hyperpolypharmacy)
Use of a large number of medications
Taking more drugs than clinically warranted
Use of several drugs concurrently for the treatment of one or more coexisting diseases
Unnecessary or inappropriate medications
Medication underuse (the indicated drug is not used)
Medication duplication (similar medications are used)
Medications without a clear indication
Presence of drug-drug interactions

[a]These definitions should not be restricted to prescribed medications. Over-the-counter (OTC), herbal medicines, and supplements should be included

Primary care providers can serve as a medication "hub" where the patients' whole clinical picture is evaluated. The lack of a primary care provider may potentiate PP, miscommunication between patients and providers, and patients' poor understanding of their drug therapies.

Transitions of care are large contributors to PP in this population. In a study evaluating prescription knowledge among older cancer patients, only 5% after hospital discharge could accurately identify drug names, indications, doses, and frequency. Also, up to 40% of patients were discharged on a medication no longer clinically indicated (e.g., PPI while no longer on steroids). Moreover, during subsequent office visits, almost a third of patients failed to report at least one medication and two-thirds of patients did not review for any regimen changes associated with their new prescriptions (Si et al. 2012).

Patients with cancer are exposed to anticancer agents and supportive care medications that often interact with preventative therapies. Also, 30–50% of older cancer patients use at least one CAM therapy, which also adds to PP and potential medication-related problems (LeBlanc et al. 2015; Nightingale et al. 2015a; Prithviraj et al. 2012). Prescribing cascades are common in elderly cancer patients. This occurs when medication adverse effects go unrecognized and are subsequently treated with additional drug therapies. Figure 1 reviews a common prescribing cascade in older cancer patients. The oncologist should adopt the motto, *assume every symptom is a drug adverse effect until proven otherwise*, into every day practice. Obtaining the root cause of adverse effects and new symptoms can be difficult due to their nonspecific nature. Providers can mistake adverse drug effects as cancer-related symptoms and, even more importantly, patients may perceive new symptoms as cancer progression (Riechelmann et al. 2009).

In a study of newly diagnosed older cancer patients, 62% experienced a drug-related problem (Turner et al. 2014). Similarly, a study in elderly Danish cancer patients found that there was a significant increase in PP up to 18 months prior to a cancer diagnosis. Notably, PP was due to an increase in opioid therapies, acid-suppressive agents, and antibiotics within 6 months prior to diagnosis. The authors stratified PP in no PP (0–1 medications), minor PP (2–4 medications), and major PP ($\geq$5 medications). Minor PP occurred in 34% of patient cases versus 29.9% of controls. Likewise, major PP occurred in 24.3% of patient cases versus 17.4% of controls. A diagnosis of lung cancer had a strong association with PP (40.9% for cases versus 24.9% for controls). The phenomenon of PP preceding a cancer diagnosis is likely due to treatment of nonspecific cancer-related symptoms (Jorgensen et al. 2012). Therefore, the presence of PP, in addition to the standard cancer work up, could be utilized as an additional tool in patient assessment.

A number of other factors influencing PP include patient nonadherence, drug costs, hoarding medications, and medication "catch-up." Nonadherence can result in poor therapeutic response (e.g., elevated blood pressure); as a result, drug doses may be inappropriately increased. Supra-therapeutic doses can result in untoward adverse effects (e.g., orthostatic hypotension and falls in the case of antihypertensives). Other factors affecting medication adherence include patients' health literacy, hearing acuity, vision, memory, and poor medication scheduling (Corcoran 1997). Cost may be a factor leading

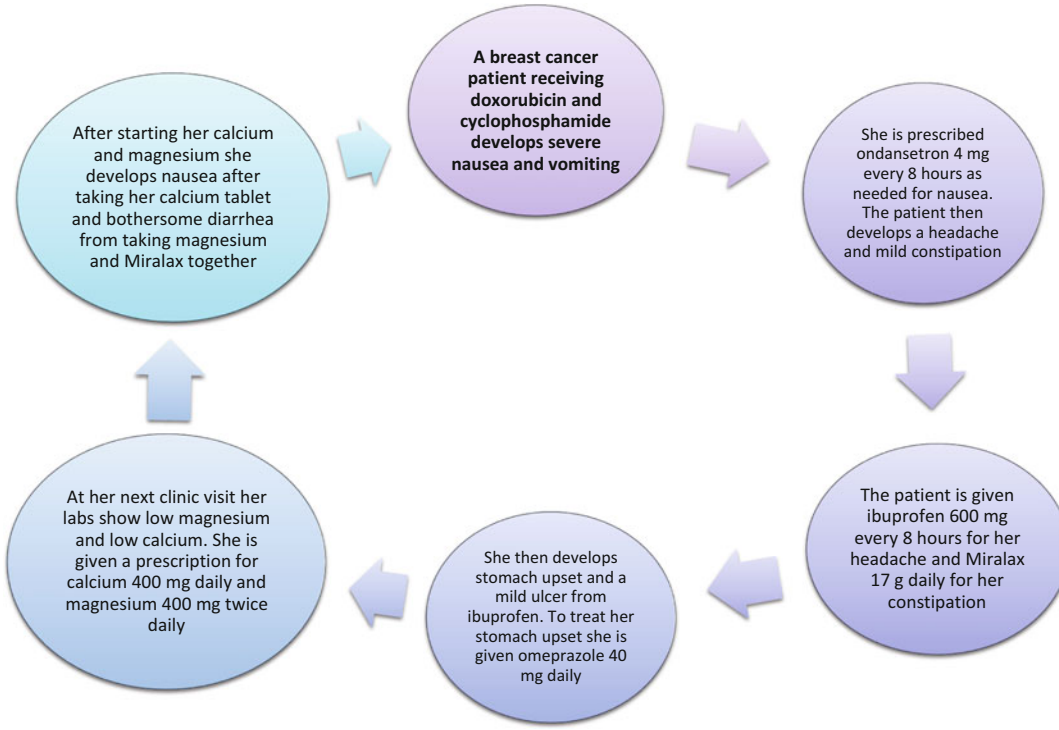

Fig. 1 Geriatric prescribing cascade

patients to either not take their medications as prescribed or "hoard" medications and subsequently take excessive doses or combinations at times when symptoms become prevalent (i.e., dose "catch-up" phenomenon) (Corcoran 1997). For example, patients taking long acting opioids can deviate from their suggested schedule and, during times of pain crises, patients may take extra doses of long-acting and short-acting opioids; this can lead to constipation, falls, sedation, and even respiratory depression (Marvin et al. 2017).

Medical culture and direct-to-consumer advertising has created the notion of "a pill for every ill" (Corcoran 1997). This is particularly important for older cancer patients who have comorbid conditions, are vulnerable to adverse effects, are frail, and have a high symptom burden from their underlying malignancy and cancer therapies. Patients often expect a new prescription during each encounter, but providers should attempt to rule out other causes prior to starting new therapies (e.g., prescribing cascades, other iatrogenic causes, temporary side effects of treatment) (Straand and Sandvik 2001). In addition to common geriatric slogans (e.g., "start low and go slow"), the philosophy of "*primum non norcere*" could be interpreted as "do not rush to treat when no treatment is needed." This philosophy should be adopted within the older cancer population. Finally, clinicians' unawareness of their lack of knowledge regarding PP and medication use represents the highest level of risk for their patients (Garfinkel et al. 2015).

Evaluating Polypharmacy and Potentially Inappropriate Medication Use

An accurate medication list is the first step in identifying PP and PIMs. While no one study has determined the ideal individual to complete a comprehensive medication review in this population, studies support the involvement of a clinical pharmacist in the multidisciplinary

team (Balducci et al. 2013; Delien et al. 2016; Grodzicki-Korc et al. 2014). A medication history should include a "brown bag" assessment where patients bring all of their prescription, OTC, and CAM therapies for physical review (Corcoran 1997). The clinic environment is ideal for this type of review. Clinicians should obtain information on the number of prescribers, number of pharmacies utilized, and barriers to drug adherence. A medication review should occur prior to initiation or modification of anticancer therapies, during times of transitions of care, or in the case of new comorbid conditions. There are a number of existing geriatric screening tools to help identify PP and PIMs. A geriatric oncology specific tool has yet to be developed (Whitman et al. 2016a). When screening for PP and PIM use, the overall goal should be to identify medications that are causing side effects, impairing the patient's quality of life, or not improving outcomes. Once identified, the clinician should work alongside the patient and their caregivers to determine the best way to reduce inappropriate medication use. Polypharmacy assessment and management should not be a "one-size fits all" approach and using a combination of screening tools may be required.

Medications Screening Tools for the Older Cancer Patient

A review by Whitman et al. (2016a) describes several implicit and explicit screening tools and how they could be applied to older patients with cancer. Table 4 provides an expanded list of the existing geriatric screening tools (Bulloch and Olin 2014; Whitman et al. 2016a). The NCCN guideline for Older Adult Oncology supports the use of the Beers Criteria, START/STOPP, and the MAI concurrently. Use of certain tools or models, such as the MAI, require a more comprehensive understanding of the patient's current clinical picture, their treatment goals, and the prescribed indication for each therapy (McNeil et al. 2016; Turner et al. 2016). For example, the MAI takes into account aspects such as medication indication, effectiveness, drug-disease interactions, and cost of therapies. A study evaluating PIMs in palliative cancer patients considered several situations as inappropriate: statin therapy without a cardiovascular event in the preceding 12 months; gastric protectants without a history of a GI bleed, peptic ulcer, gastritis, or chronic NSAID use; antihypertensives if blood pressure was less than 90/60 mmHg or symptoms of hypotension; antidiabetic medications used with a fasting blood glucose less than 50 mg/dL or signs of hypoglycemia; or use of a medication without a clear medical indication (Fede et al. 2011). Another implicit medication screening model is the "Good Palliative- Geriatric Practice" (GP-GP) algorithm (Garfinkel and Mangin 2010).

Table 4 Geriatric medication screening methods

Implicit tools
Medication Appropriateness Index (MAI)[a]
Unnecessary Drug Use Measure
Balducci et al. Geriatric Oncology Framework (2013)[a]
Maggiore et al. Polypharmacy Review (2010)[a]
Good Palliative-Geriatric Practice (GP-GP) algorithm
Assessing Care of Vulnerable Elders-3 (ACOVE-3)
Assessment of Underutilization (AOU)
Screening Medications in the Older Drug User (SMOG)
Assess, Review, Minimize, Optimize, Reassess (ARMOR) Tool
Tool to Improve Medications in the Elderly Via Review (TIMER)
Systematic Tool to Reduce Inappropriate Prescribing (STRIP)
Prescribing Optimization Method
Explicit tools
Beers Criteria 2015[a]
Screening Tool to Alert Doctors to Right Treatment/ Screening Tool of Older Persons' Prescriptions (START/ STOPP)[a]
Healthcare Effectiveness Data and Information Set Drugs to Avoid in the Elderly (HEDIS DAE)[a]
Fede et al. Model (2011)[a]
Oliveira et al. Criteria of Futility (2016)[a]
Zhan Criteria[a]
Drug Burden Index (DBI)
Anticholinergic Risk Scale (ARS)
Improved Prescribing in the Elderly Tool (IPET)
Fit for the Aged (FORTA)

[a]Tools that have been applied to older cancer patients

This algorithm has not been specifically applied to older cancer patients, but many of the concepts are relevant; this model will be discussed further in the deprescribing section of this chapter. Drawbacks of implicit tools include more time commitment and less intra-rater reliability (Whitman et al. 2016a).

The goal of each medication assessment should be to ensure that every medication therapy fits the individualized needs and circumstances of the patient (Balducci et al. 2013). Balducci et al. (2013) and Maggiore et al. (2010) describe concise lists of questions to assess PP and PIMs in older cancer patients:

1. Is there a proper indication for each medication?
2. Is the medication achieving the desired effect (e.g., for a pain medication, is the pain controlled?)
3. Does the patient present with nonspecific symptoms (e.g., fatigue, impaired cognition) that may be ascribed to some of the medications?
4. Are the medications prescribed at an appropriate dose?
5. Is there potential for clinically important drug-drug interactions?
6. May some of the drugs interfere with the antineoplastic treatment?
7. What is the risk of drug-tumor interactions?
8. Does the patient adhere to the treatment plan?
9. Are there conditions that needed treatment and at present are left untreated?

A. Perform a careful review of the patient's list of medications, including indications and dosages
B. Directly inquire about over-the-counter and herbal/complementary agents
C. Evaluate in advance the potential interactions between the chemotherapy regimen and other medications to minimize drug interactions and subsequent toxicity; discuss with pharmacy staff where appropriate
D. Consider use of electronic drug databases that may help identify at-risk drugs, drug classes, dosages, and schedules, bearing in mind the limitations of such tools, especially if pharmacy-based support is not readily available or accessible
E. Maintain an open and active line of communication with the patient's other medical providers regarding changes or additions to medication lists
F. Continue to perform routine medication reconciliation at every clinical visit in conjunction with pharmacy and/or nursing staff where appropriate

This nine-question framework and recommendations for PP assessment should be used alongside explicit screening tools to identify the greatest incidence of PP, PIMs, and other medication-related problems. Other useful implicit tools include the Assessing Care of Vulnerable Elders-3 (ACOVE-3), Assessment of Underutilization (AOU), Screening Medications in the Older Drug User (SMOG), Assess, Review, Minimize, Optimize, Reassess (ARMOR) tool, Tool to Improve Medications in the Elderly Via Review (TIMER), and the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) (Bulloch and Olin 2014). Currently, existing evidence supports use of the Beers Criteria, START/STOPP, and the MAI sequentially (Whitman et al. 2016b). Finally, an important question to ask when evaluating for PP and PIMs is "why is the patient on a PIM in the first place? Is it because they have previously failed a safer alternative or because no alternative medication exists?" (Prithviraj et al. 2012).

Consequences of Polypharmacy in Older Cancer Patients

Polypharmacy and PIM use can lead to a number of untoward adverse effects and other negative

Table 5 Polypharmacy and associated outcomes

Potential risks associated with polypharmacy in geriatric oncology	
Impaired physical functioning	Postoperative complications
Grade III-IV chemotherapy toxicities	Cognitive impairment
Frailty	Delirium
Falls	Pill burden
Reduced adherence to oral chemotherapy	Patient financial toxicity
Reduce adherence to essential drugs	Increased global health care costs
Drug-drug interactions	Compromising anticancer therapies (failure of treatment)
Drug-disease interactions	Poor lower extremity function
Increased rate of outpatient visits	Increased mortality
Weight loss	Hip fractures
Impaired balance	Increased length of hospital stay
Increase nursing home admissions	Early discontinuation of anticancer therapies

outcomes. These poor outcomes are the consequence of the "disease" of PP. Table 5 sums up the potential risks associated with PP in the older cancer population. A recent study evaluated the association between PP and PIM use among older adult oncology patients undergoing chemotherapy and their risk of chemotherapy toxicities. The authors found no significant association between the number of medications and chemotherapy toxicities but did see a higher incidence of hospitalizations and early cessation of chemotherapy (Maggiore et al. 2011). Though, a similar study failed to find an association between PP, chemotherapy toxicity, and hospitalization rate (Maggiore et al. 2014). In a population of elderly head and neck cancer patients, PP and PIMs occurred in 29.3% and 24% of patients, respectively, and were associated with clinically meaningful outcomes. Specifically, use of benzodiazepines and calcium channel blockers increased the risk of prolonged hospitalizations and increased the rate of hospital readmission within 2 years (Park et al. 2016).

Health care utilization may increase as a result of PP and PIM use. Patient office visits due to adverse drug events occur in about 60% of patients between the ages of 65 and 74 (Sokol et al. 2007). Likewise, inappropriate medication use in this population has led to an increased rate of nursing home admissions, increased hospital length of stay, more frequent emergency department visits, and an increased rate of visits to outpatient oncology clinics (Lees and Chan 2011). A considerable financial burden is imposed on the patient as well as the health care system as a whole. The term "financial toxicity" has been used to describe real and perceived distress to older cancer patients undergoing active treatments (Lees and Chan 2011; Souza et al. 2014).

A study examining comorbidities in older cancer patients found that the majority of patients experienced anguish due to a side effect of treatment or were inconvenienced in their daily lives to due drug-therapy monitoring. Over 80% of patients in this study took at least one of the following drug classes: antihypertensives, lipid lowering agents, antiplatelets, or bisphosphonates. The most commonly reported adverse events were dizziness on standing (i.e., postural hypotension secondary to low blood pressure), muscle aches, easy bruising, and indigestion or reflux. Patients reported dissatisfaction with drug therapy monitoring (e.g., monthly cholesterol checks, weekly INR monitoring, and daily blood pressure measurements) that resulted in a poor quality of life (Cashman et al. 2010).

Other significant outcomes of interest include falls, frailty, impaired physical functioning, and cognitive impairment (Mossello et al. 2015). Polypharmacy often results in an increased serotonergic and anticholinergic burden. As a result, patients are more likely to have impaired balance and falls. Falls result in significant health care costs and are a leading cause of fatal and nonfatal injuries in older adults (Bergen et al. 2016). As described previously, PP (defined as taking $\geq$5 medications) resulted in a four times higher likelihood of being frail, having impaired physical functioning, and experiencing exhaustion (Turner et al. 2014).

Finally, PP may also be a risk factor for poor adherence to essential therapies. Excessive pill burden and complex dosing may limit patients' willingness to stick to their prescribed regimen,

especially for oral chemotherapy. Oral chemotherapy is effective *only* if patients adhere to their therapy. Rates of oral chemotherapy adherence range from 17% to 98% for patients with breast cancer and hematologic malignancies to 97% for patients with ovarian cancer. Likewise, adherence to other anticancer therapies can be impacted by PP and PIMs in instances when adverse effects cause patients to miss clinic appointments (e.g., falls, hip fractures) or when patients have intolerable side effects from preventative medications (e.g., prescribing cascades) that result in early discontinuation of anticancer therapies. Finally, patients with baseline cognitive impairments are more likely to develop delirium from anticancer therapies and other supportive care medications (McIntyre 2016).

Deprescribing in Older Cancer Patients

Deprescribing has been deemed an effective "cure" or "antidote" for the "disease" of PP (Cassels 2017; Frank and Weir 2014). Deprescribing has been defined several ways but most commonly as the process of reducing or discontinuing drugs, aimed at minimizing PP and improving patient outcomes (Todd et al. 2016b). Importantly, deprescribing should consider existing or potential harms of medications, especially in the context of individual patient values and goals (Scott et al. 2015). The "good prescribing continuum" should consider initiation of drug therapy, monitoring, adjustment, and appropriate medication discontinuation. Clinicians are encouraged to assign drug therapies a "best before" date when initiating drug therapies; this practice serves as a reminder to continuously re-evaluate the necessity and appropriateness of pharmacotherapy (Scott et al. 2015).

Deprescribing studies specific to older adults with cancer are lacking. The majority of studies looking at medication cessation are in patients with limited life expectancy, palliative cancer patients, or in the general geriatric population. One deprescribing-focused study specific to older patients with cancer was conducted in a large academic cancer center. This study evaluated a clinical pharmacist-driven deprescribing model that used several implicit and explicit medication screening tools simultaneously to identify PIMs (Whitman et al. 2016b). Nevertheless, the majority of existing deprescribing frameworks and models can be applied to older cancer patients. The philosophy of deprescribing can be psychologically daunting for both patients and providers. There is often a mismatch of expectations between patients, general care providers, and specialists; therefore, it is essential to review barriers and individual perspectives in regards to deprescribing (Reeve et al. 2013).

Deprescribing Models

Currently, there are three well-validated models that serve to guide clinicians in the deprescribing process. An additional model exists that is specific to the older cancer population that also deserves review. Effective use of these models requires a broad understanding of a patient's full clinical picture. Likewise, simultaneous use of explicit medication screening tools is supported by the literature. Other medication management and deprescribing frameworks exist but are specific to palliative care and patients with terminal illnesses in the end stages of their disease (Lees and Chan 2011; Lindsay et al. 2014; Riechelmann et al. 2009). Moreover, the Choosing Wisely Initiative is an organization aimed at practicing evidence-based medicine, minimizing duplicative therapies, and maximizing the use of truly necessary test procedures, and medications (Sharma et al. 2016). The efforts from this organization are in alignment with the practices of deprescribing and PP reduction. One recommendation by the Choosing Wisely Initiative (2013) advises against prescribing lipid-lowering medications in patients with limited life expectancy. Policy-driven efforts, such as the Choosing Wisely Initiative, are good adjuncts to practice-based deprescribing models.

The first deprescribing model of interest was developed by Holmes et al. (2006). Four factors should be considered when evaluating drug

therapy continuation: the remaining life expectancy of the patient, time until benefit of drug therapies, individual goals of care, and the target of the treatment (e.g., preventative versus palliative). Prognostication of a patient's remaining life expectancy can inform decisions about both prescribing and deprescribing. Patients with a limited life expectancy or advanced illnesses, such as dementia, may have a limited opportunity to obtain benefits from certain medications and medication classes (e.g., statins, bisphosphonates, antihyperglycemics) (Steinman and Hanlon 2010; Stevenson et al. 2004). Likewise, in a study evaluating deprescribing in the last 48 h of life, it was shown that preventative medications were more likely to be discontinued by geriatricians who expected a patient's death. This adds to the evidence that better prognostication can lead to easier decisions about deprescribing. In the same study, it was determined that patients dying from an oncologic disease were also more likely to have medications discontinued compared to patients with general frailty or dementia (Van Den Noortgate et al. 2016). Goals of care assessment should include medication-related goals and overall goals of their disease state. Older patients with cancer are often faced with the choice of using life prolonging medications (i.e., antibiotics) that may impact their quality of life versus medications that only provide comfort. Prioritizing goals such as extension of longevity, reduction in symptoms, minimizing drug therapy costs, and reducing pill burden is an important part of the deprescribing assessment (Steinman and Hanlon 2010). Additional evidence supports the addition of time to harm or number needed to harm (NNH) for a particular medication to this model; this concept is the essence of looking at overall risk versus benefit of individual therapies (Todd et al. 2016b).

The second model uses a five-step process that guides deprescribing. The authors emphasize that deprescribing should not be about denying effective treatment and that the process of deprescribing should be positive and patient-centered. They note the uncertainties and discomfort expressed by many clinicians, especially in regards to stopping chronic medications. They re-iterate the notion that PP is a "disease" and that clinicians should aim to alter the natural history of the "disease" by diagnosing the problem (i.e., PP) and making a therapeutic decision (i.e., withdrawal drug therapies). The authors emphasize that deprescribing conversations may be best accomplished in concordance with a palliative care team (Todd et al. 2016b). The five step process is listed below:

1. Ascertain all drugs the patient is currently taking and the reasons for each one
2. Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention
3. Assess each drug for its eligibility to be discontinued
4. Prioritize drugs for discontinuation
5. Implement and monitor drug discontinuation regimen

The third model is the Good Palliative-Geriatric Practice (GP-GP) algorithm. Application of this algorithm in clinical practice has provided key evidence that reduction in PP by deprescribing resulted in improved outcomes. This model uses a series of statements to frame discussion with patients and guardians (Garfinkel and Mangin 2010). The algorithm use a "Yes," "No," or "Not sure" framework that guides the clinician. Factors taken into account include evidence-based consensus for drug therapy based on indication, dosing, and possible side effects; the validity and relevancy of the indication based on patient specific factors; known adverse effects that possibly outweigh the benefits of therapy; adverse effects attributable to drug therapy; alternative therapies; and dosing frequency. Based on answers to selected questions, the provider can continue with the same dosing rate, reduce the dose, stop drug therapy, or shift to another drug. In a study applying this algorithm to 64 older adults, it was found that out of 311 medications identified as inappropriate,

286 (92%) were subsequently discontinued. No significant adverse drug events were reported after stopping medications and 84% of patient reported an improvement in general health. Likewise, several patients who stopped unnecessary drug therapies reported improvements in cognitive function, as determined by a Mini-Mental State Examination. An average of 4.2 drugs were stopped per patient and only 2% of medications were restarted.

Finally, a study evaluating deprescribing in a geriatric oncology clinic provides evidence supporting the feasibility of this practice in the older cancer population. A total of 17 older cancer patients (≥65 years old) underwent a comprehensive medication assessment by a clinical pharmacist. Potentially inappropriate medications were identified by applying the 2012 Beers Criteria, STOPP criteria, and the MAI sequentially. The authors utilized medication-condition matching, adverse effects, drug-drug interactions, patient goals, and life expectancy as factors in PIM discontinuation. Patients were taking an average of 11.4 medications and, overall, a total of 73 PIMs were identified. A total of 55 PIMs or three medications per patient were deprescribed by the clinical pharmacist and geriatric oncologist. Upon patient follow-up, the authors noted improvements in several patient reported outcome measures: reduction in fatigue after stopping statins, a decrease in episodes of dizziness and orthostasis after tapering antihypertensives, and subjective reports of improved quality of life. A limitation of this study was that it did not use standard outcome measures. Nevertheless, this is the first study to display real time deprescribing in the older cancer population (Whitman et al. 2016b).

Prioritizing Deprescribing Interventions

One of the most difficult decisions for clinicians is deciding when discussions regarding deprescribing should occur. A study evaluating deprescribing in palliative care patients, caregivers, and health care providers found that patient and caregiver perspectives about medication continuation changed based on the stage of their disease. Prognosis, or patient understanding of their remaining life expectancy, served as a tipping point or "transition" where less importance was placed on certain medications (i.e., preventative versus symptom-focused) (Todd et al. 2016b). This concept has also been named the "brink," or optimal time to discontinue specific medications (Garfinkel and Mangin 2010). Having discussions about deprescribing before the patient has reached this point may result in poor outcomes (Todd et al. 2016b). It has also been shown that focusing on improvement in quality of life and reducing symptom burden is more effective than focusing on pill burden and cost (Steinman and Hanlon 2010). Other studies report that the volume of drug therapy (i.e., pill burden) is in fact an issue, especially in the setting of dysphagia (Todd et al. 2016b).

A number of "red flags" can be considered to help the clinician prioritize which therapies to deprescribe. The most common are the lack of a clear indication or duplicate indications. Matching each medication to a respective condition is an easy way to determine inappropriate medication use. Likewise, this "match" should not be solely based on guideline appropriateness but should also consider how continuing a particular medication will help the patient obtain their goals (Steinman and Hanlon 2010). Another good marker is if the patient or caregiver questions the ongoing indication or benefit of the drug (Farrell et al. 2015b). A study evaluating patient and caregiver attitudes toward deprescribing found that 92% of individuals would be hypothetically willing to have a medication stopped, especially if it were ineffective or they had a general dislike of medications (Reeve et al. 2016).

Medications causing obvious adverse effects should be considered for deprescribing (Steinman and Hanlon 2010). Likewise, patients with end-stage diseases, terminal illnesses, dementia, or extreme frailty should have a PP review with the goal of minimizing drug therapies (Graham 2015; Scott et al. 2015). One review of deprescribing in older patients notes that the presence of frailty should always be a catalyst for deprescribing (Frank and Weir 2014).

Additionally, the presence of "prescribing inertia" or a "repeat prescription syndrome" in which there is automatic renewal of every medication without a clear understanding of appropriate use or indication should be considered a trigger for deprescribing (Straand and Sandvik 2001). Finally, it has been emphasized that deprescribing discussions are appropriate during any patient interaction, especially when new medications are initiated (Frank and Weir 2014).

The revised patients' attitude towards deprescribing questionnaire (rPATD) is an effective tool used to obtain beliefs and attitudes about deprescribing from older adults and caregivers. Having this information prior to broaching the topic of deprescribing could be helpful in prioritizing patients who are willing to have these conversations; this could help alleviate providers' concerns regarding clinic consultation time. The questionnaire could also be used to target patients who may require education regarding medication management and rationales for appropriate drug discontinuation (Reeve et al. 2016).

Barriers to Deprescribing

There are a number of barriers to deprescribing. One of the most pressing barriers is the lack of clear evidence of the deprescribing process and the dearth of randomized trials evaluating patient outcomes. Tables 6 and 7 list common barriers experienced by providers and patients. Both providers and patients can be psychologically impacted by decisions to stop or change medication therapies. Patients are often told that they will be required to take a medication "for the rest of their lives." When life changing events occur, such as a diagnosis of a metastatic cancer, the notion of discontinuing a drug therapy may come as a surprise to patients. Mismatched expectations about indefinite medication use occur commonly in situations of terminal illness diagnoses but can also occur when general practitioners and specialists have differing opinions and recommendations. This fragmented care and inconsistent advice among multiple providers can lead to patient mistrust of health care (Stevenson et al. 2004). Similarly, deprescribing discussions may result in a patient's confrontation with their mortality, especially when they were told they would take a particular medication until they died. Moreover, patients may feel a sense of futility of previous efforts in maintaining their health (i.e., regular glucose checks daily, strict vegetarian diet) (Maddison et al. 2011). Feelings of abandonment by the medical community and a loss of self-worth may occur when patients are

Table 6 Common barriers for providers

Provider barriers to deprescribing in geriatric oncology
Difficulty determining life expectancy
Difficultly discussing with patients how reduced life expectancy can impact treatment goals
Suboptimal communication between family physicians and specialists resulting in polypharmacy
Providers reluctant to stop medications initiated by another prescriber
Lack of ownership of deprescribing efforts (i.e., family physicians believe specialists should take the lead)
Hesitation to compromise patient hope by stopping chronic medications
Lack of confidence to deprescribe medications safely (i.e., safe taper)
Lack of comprehensive evidence of benefits or harm of deprescribing in this population
Underappreciation of the scale of polypharmacy-related harm
Concern for legal ramifications of not following clinical practice guidelines

Table 7 Common barriers for patients

Patient barriers to deprescribing in geriatric oncology
Patients feeling "abandoned" or not worthy of treatment
Difficulties in understanding the concept of medication discontinuation
General reluctance of patients and families to change medications
Underappreciation of the scale of polypharmacy-related harm
The belief that taking a medicine to prevent or treat a disease is always needed ("pill for every ill")
Fear of poor response by their providers
Belief that adverse drug events are due to natural aging processes
Fear of drug withdrawal

told their preventative medications are no longer needed.

Another significant barrier is limited consultation time that leads to obtaining incomplete information from patients and, thus, reduced opportunity for deprescribing. Patient and family meetings about life expectancy, number needed to treat (NNT), and time-to-benefit of therapies are difficult for providers to undertake, especially with limited clinic hours (Hilmer et al. 2012). The mentality of "don't-rock-the-boat" is common and convenient for providers, especially if their patient is currently displaying clinical stability (Cullinan et al. 2017). Likewise, patients interested in reducing their medication load may fear these conversations as well. They may have a general fear of poor provider response, concern for being denied other helpful therapies in the future, and distress regarding "wasting time" talking about medications (Cassels 2017).

Patients and providers may not want to stop specific therapies due to concerns of worsening their underlying condition or feelings of physical dependence. There are also concerns about medication withdrawal, especially when providers feel uncomfortable designing tapering regimens. Many providers have fears about stopping preventative medications and find it more difficult than stopping medications for acute conditions (Todd et al. 2016a). Patients may intentionally and unintentionally withhold information about adverse drug events that could help guide deprescribing. This may be due to beliefs that side effects are occurring as a result of natural aging or due to poor communication with care providers. Demands and influences of family members regarding continuing medications is another barrier.

It is also important to consider steps to overcome barriers to deprescribing. Determining who has the explicit responsibility to manage patients' medications and make decisions about deprescribing needs to occur (Barnett and Jabraj 2017; Cullinan et al. 2017). It is also vital to include deprescribing recommendations in chronic disease state guidelines and to encourage providers to discuss more detailed medication expectations during initiation of therapy (i.e., situations when therapies can be stopped in the future) (Rossello et al. 2015). Finally, a culture shift needs to occur where adopting the "less-is-more" mind state surpasses the notion of "taking any medication is better than doing nothing at all" (Frank and Weir 2014). Patients and caregivers should also be encouraged to ask the following questions (Scott et al. 2015):

1. What are the treatment options (including nondrug therapies) for my condition?
2. What are the possible benefits and harms of each treatment (drug)?
3. What might be reasonable grounds for discontinuing use of a drug?

Outcomes Associated with Deprescribing

There is limited information regarding outcomes as a result of deprescribing in the older cancer population. The best evidence comes from a 2010 Garfinkel study as previously discussed. This study found improvements in quality of life, improvements in cognition, and a reduction in mortality. A study evaluating over 10,000 patients undergoing a PP assessment and reduction in PIM found no significant change in mortality but a statistically significant decrease in 90-day readmissions and hospital length of stay. In a summary of drug withdrawal trials, it was found that antihypertensives, psychotropic drugs, and benzodiazepines were appropriately discontinued and about 20–100% of patients presented with no harm (Johansson et al. 2016). Also, a study evaluating inpatient medication reviews by pharmacists or physicians found that reduction in PIM through deprescribing resulted in a 36% reduction in emergency department visits from 30 days to 1 year, reduced hospital length of stay, and global improvement in health. In contrast, a study in older frail people living in residential aged care facilities found no beneficial effects of deprescribing for reducing falls, fractures, hospital admissions, cognitive, physical, and bowel function, quality of life, or sleep (Potter et al. 2016). Eliminating unnecessary drugs through deprescribing may result in improved adherence to other essential

therapies (Scott et al. 2015). A study evaluating discontinuation of statins in patients with a limited life expectancy of 1 month to 1 year found a statistically significant improvement in patient quality of life without an increased risk of mortality (Kutner et al. 2015). This is the first randomized controlled trial evaluating deprescribing a preventative medication; this study is particularly relevant to the older cancer patient, who often presents in the later stages of the disease.

In contrast, negative outcome associated with stopping medications includes return of symptoms, drug withdrawal effects, or unexpected rebound symptoms (e.g., acid hypersecretion about cessation of a PPI or an inflammatory insult after stopping a statin). Likewise, worsening of patients' preexisting diseases can occur (i.e., return of high blood pressure). Therefore, tapering necessary medications and monitoring patients closely should be practiced (Van Nordennen et al. 2014).

The safest and most effective method to stop medications is unknown. Some evidence supports the simultaneous cessation of as many medications as possible, the "all-at-once" approach. Other studies support discontinuing one medication at time in order to determine cause-and-effect of any adverse outcomes (Garfinkel and Mangin 2010). Regardless of method, medications such as benzodiazepines, antihypertensives, opioids, and other psychotropic medications should be slowly tapered. Many resources currently exist to help guide clinicians in appropriately tapering medications (Cassels 2017).

The Future of Deprescribing in Geriatric Oncology

Additional well-designed studies may be necessary to provide sufficient evidence that deprescribing is an effective modality in this population. The study examining statin discontinuation in patients with limited life expectancy is a landmark study supporting deprescribing. It does, however, provoke the issue of what level of evidence will be sufficient enough for providers to make safe, meaningful deprescribing decisions (Holmes and Todd 2015). Whether or not randomized studies evaluating deprescribing will alleviate anxiety and fears for both patients and providers is yet to be seen.

Of particular interest is the use of clinician decision support tools and online platforms for PP assessment and deprescribing. A Canadian-based research group has developed and tested the MedStopper/database tool. This tool is a list of drug-indication pairs that, when entered into the online tool, rank medications from potentially most stoppable to least stoppable. Potentially inappropriate medications are identified through explicit screening tools such as the Beers Criteria and STOPP. Guidance is provided on tapering therapies and possible withdrawal symptoms. Medication classes, such as statins, are accompanied by risk calculators and information on NNT and NNH (Cassels 2017). In addition to this online tool, the Canadian Deprescribing Network has developed evidence-based deprescribing guidelines for PPIs, benzodiazepine receptor agonists, antipsychotic drugs, and antihyperglycemic agents (Bjerre et al. 2015; Farrell et al. 2015a, 2016; Pottie et al. 2016). These tools are concise algorithms that can be applied to a number of patient populations, including older cancer patients.

Conclusion

Older patients with cancer are at an increased risk for PP, PIM use, frailty, and many other poor outcomes. Polypharmacy should be seen as a "disease" that can interact unpredictably with other chronic disease states, anticancer therapies, and age-related physiologic changes. Pharmacokinetics and PD of drug therapies are important considerations and should be taken into account in the context of anticancer treatments as well as general pharmacotherapy. PP is common in the older cancer population, occurring in about 60% of patients. Deprescribing has been described as an effective "antidote" to PP; though, it has several barriers and there are limited studies in the older cancer population. A culture shift regarding overuse and inappropriate use of medications may be necessary to help drive policy changes related to

PP and deprescribing. Nevertheless, reducing inappropriate medication use has been considered, by several authors, as a leading global issue of the highest priority (Garfinkel and Mangin 2010).

Cross-References

- Aging and Cancer Biology
- Comorbidity in Aging and Cancer
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Drug Interactions in Aging and Cancer
- Frailty in Cancer Patients
- Geriatric Interventions in Oncology
- Normal and Abnormal Aging (General Perspective for the Oncologist)
- Pain Management in Older Cancer Patients
- Principles of Cancer Targeted Therapy in Older Adults
- Principles of Chemotherapy in Older Adults
- Research Methods: Outcomes and Survivorship Research in Geriatric Oncology
- Research Methods: Quality of Life and Patient-Reported Outcome Research in Geriatric Oncology

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Drug Interactions in Aging and Cancer 21

Ronald J. Maggiore

Contents

Abstract

Potential drug interactions (PDIs) can lead to adverse drug events (ADEs), which can be a source of potential morbidity, disability, and mortality among older adults. Older adults with cancer may be more susceptible to the negative impact of PDIs due to increased medications warranted as part of their cancer treatment (including symptom management and supportive care for the treatment plan). Polypharmacy is a geriatric syndrome that has led to increased complications among older adults with and without cancer and increases the risk of both PDIs and ADEs. Although several PDIs can be of unclear clinical significance when encountered, they may be more of an issue with competing medications used for comorbidities that face older adults with cancer. Moreover, this risk may be further augmented when the cancer treatment regimen is orally administered. The consequences of these types of PDIs may have more significant "downstream" effects on treatment adherence and persistence. However, as more anticancer drugs become available and adopted into clinical practice (particularly oral agents), additional studies will need to address PDIs within the dynamic landscape of cancer therapeutics and their impact on older adults with cancer who are at increased risk of toxicities.

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Drug interactions · Polypharmacy · Elderly · Cancer · Medication

Introduction

Medication-related issues pose potential risks for older adults in general. First, aging in of itself leads to physiologic changes that impact the pharmacokinetics and pharmacodynamics of many drugs, including anticancer agents (Gerard et al. 2016; Korc-Grodzicki et al. 2014). Second, commensurate with increasing age, there is an increase in number of comorbidities leading to a potentially legitimate need for increased number of medications (Turner et al. 2016a). In those older adults impacted by cancer in addition to these other health issues, the cancer treatment drugs and those used to support the treatment regimen ("supportive care" medications) and/or cancer-related symptoms increase the number of agents an older adult is taking concurrently at any given time (Turner et al. 2016a; Sharma et al. 2016). These observations have led to why polypharmacy can pose a potentially more significant problem for older adults with cancer, who are disproportionately affected by functional impairments and other geriatric syndromes compared to those older adults without cancer (Maggiore et al. 2010; Mohile et al. 2011).

PDIs Among Older Adults with Cancer: Insights from Polypharmacy

Exploring polypharmacy-related issues in advance lays the groundwork for addressing the complex issue of potential drug-drug interactions (PDIs) in older adults with cancer. Defining polypharmacy has been challenging since there is no universally accepted definition for it nor how best to operationalize it and its associated outcomes within a clinical research context (Beuscart et al. 2016; Maggiore et al. 2010; Sharma et al. 2016). However, several experts would agree that the number of medications, whether prescription or over-the-counter, should not be the sole aspect of polypharmacy examined or measured (Hajjar et al. 2007; Sharma et al. 2016). Appropriateness of medication use as defined by a lack of a given drug's indication, therapeutic duplicity with another agent, or agents belonging to drug classes generally is deemed unsafe for older adults in general or those with particular medical conditions. However, some older adults with particular health conditions such as certain cardiac issues may derive benefit from specific drugs or drug classes; therefore, a given patient's not being on a specific agent due to oversight may also be a manifestation of medication inappropriateness. These prescribing quality issues surrounding potentially inappropriate medication (PIM) use have led to the development of more novel criteria to measure these aspects of polypharmacy (American Geriatrics Society 2015 Beers Criteria Update Expert Panel 2015; O'Mahony et al. 2015; Schmader and Hanlon 2013). Prior studies have demonstrated that the presence of polypharmacy among older adults or patients with cancer, regardless of setting or definition, can increase the risk of adverse drug events (ADEs) and significant morbidity as a result (Budnitz et al. 2011; Hajjar et al. 2003; Hanlon et al. 2006; Maher et al. 2014). Therefore, evaluating polypharmacy in broad terms yet specifically within a geriatric oncology context is quintessential for appraising PDIs and ADEs in this population. Key findings from several geriatric oncology polypharmacy studies have been highlighted below (Table 1).

Risk for PDIs: How Many Medications Are Too Many?

We know that the risk for PDIs increases proportionally to the number of meds concurrently taken in both geriatrics and geriatric oncology studies (Hajjar et al. 2003; Hanlon et al. 2006; Nightingale et al. 2015). As a result, the degree of "pill burden" may be the most consistently reported risk factor for PDIs. There is no absolute cutoff for "too many" medications since some older adults with certain comorbid conditions may require increasing numbers of appropriately

Table 1 Select polypharmacy studies in geriatric oncology

Study	Type of study	N	Age	Number of meds per patient	Polypharmacy definition used	Polypharmacy prevalence	Outcomes	Other findings
Outpatient								
Nightingale et al. (2015)	Retrospective (~2 years, 1 site)	248	Mean=80 (range, 61–98)	Mean = 9.23 (1–30) Mean rx = 6.1 (0–20) 2.76 OTC (0–10) HCAM 0.38 (0–10)	Number of meds (Rx and OTC); PIM: HEDIS DAE Beers (2012) STOPP	≥5 meds =84%; ≥10 meds =43%; PIM of any criteria: =51%	None reported	RFs for PIM use: number of meds, number of comorbidities; pharmacist-based intervention study planned
Maggiore et al. (2014)	Retrospective (~1 year)	500			Number of meds (Rx and OTC); PIM: Zhan* Beers (2003) Beers (2012) HEDIS DAE	Mean=7 (0–25): rx: 4 (0–20) Beers 2003: 17% 2012: 29%	Not associated with any chemotoxicity or hospitalization during chemo	Common beers meds: benzodiazepines, zolpidem
Prithviraj et al. (2012)	Retrospective (approx. 1.5 years)	117	Mean =74.6 42% ≥75 years	Mean 7.3 (0–18) Rx: 5.6 (0–14) OTC: 1.7 (0–6)	Number of meds (Rx and OTC); PIM: Beers (2003)	≥5 meds: 80% Beers: 41%	None reported	≥5 meds vs. <5 meds: more likely to encounter PIM; other RFs for PIM use: ≥5 comorbidities, presence of IADL impairment, VES-13 score ≥ 3
Sokol et al. (2007)	Retrospective (unknown time period, 1 center)	100	Median =78 (range, 70–90)	Mean =9.1 (range, unknown)	Number of meds (Rx and OTC)	Not delineated	None reported	46% taking HCAM

(*continued*)

Table 1 (continued)

Study	Type of study	N	Age	Number of meds per patient	Polypharmacy definition used	Polypharmacy prevalence	Outcomes	Other findings
Inpatient								
Deliens et al. (2016)	Prospective (9 months, 1 site, geri onc unit)	91	Mean =79 (SD, +/−6)	Mean=6.73 (range, 0–17)	Number of meds (Rx and OTC); PIM: START STOPP	32–34% (START vs. STOPP at time of admission)	Pharmacist reduced prevalence to 7–16% by time of discharge (START vs. STOPP)	
Flood et al. (2009)	Prospective (~1 year, 1 site, geri onc unit)	45	Mean =73.5 years	Mean=10.9 (SD, +/−5.5)	Number of meds (Rx and OTC); PIM: Beers (2003)	21% at admission	None reported	Most common beers med encountered: promethazine

Geri onc geriatric oncology, *HCAM* herbal/complementary/alternative medications, *HEDIS DAE* Healthcare effectiveness data and information set drugs to avoid in the elderly, *IADL* instrumental activities of daily living, *OTC* over-the-counter, *PIM* potentially inappropriate medication, *RF* risk factor, *Rx* prescription, *SD* standard deviation, *VES-13* Vulnerable elders survey-13

prescribed medications to manage these conditions optimally; furthermore, the optimal threshold may be contingent upon the outcome being studied (Turner et al. 2016b). Based on a focused literature review, older adults with advanced cancer typically are taking anywhere from three to nine concurrently prescribed meds (LeBlanc et al. 2015). Several experts have used a cutoff of five or more concurrent medications (prescription vs. non-prescription notwithstanding) as exceeding this threshold appears to significantly raise the risk of PDI and risk for toxicity.

On the other hand, PIM use can range from 17% to 51% among older adults with cancer depending on the definitions utilized (Flood et al. 2009; Maggiore et al. 2014; Nightingale et al. 2015; Prithviraj et al. 2012). Increased medication use is associated with an increasing number of comorbidities in the geriatric oncology population (Nightingale et al. 2015) and, in some cancer types such as AML, may be associated with worse survival (Elliot et al. 2014). Moreover, "pill burden," which also must also take into account medication financing, dosing, side effect, and administration challenges facing the patient and his or her caregiver(s), can also serve as a major risk factor for poorer adherence to oral anticancer regimens and thus potentially worse cancer outcomes (Efficace et al. 2012; Millic et al. 2016; Ruddy et al. 2009).

PDIs: Methods for Identification

The prevalence of PDIs is also largely dependent on the definitions and methods utilized beyond just inherent issues with accuracy and reliability with patient self-report, medical record reviews, and the accounting for multiple prescribing providers and/or dispensing pharmacies. Regardless of how a given patient's medication list is obtained, significant methodological and data interpretation issues stem from the type of software or compendium that is utilized to review and analyze for PDIs and their respective severity. A review by Riechelmann and De Giglio (2009) reported that up to one-third (13–61% overall prevalence) of outpatients with cancer are affected by PDI across eight studies (years 2005–2009). Only 19% of these PDIs were categorized as high severity, with only about half of these being supported by Level 1–3 evidence. That being said, very few of the identified PDIs involved chemotherapy agents directly. Although some experts advocate for more routine involvement for electronic "built-in" alerts for PDIs in oncology practice (Riechelmann and Girardi 2016), there remains much variability among electronic drug information databases. Among different prescribing decision support tools, the evidence base each utilizes to assign a PDI's level of risk and its clinical relevance for a given patient scenario can be very heterogeneous, with some of these resources missing more common PDIs identified by a pharmacist (Clauson et al. 2007; Hoody et al. 2011; Saverno et al. 2011). Therefore, it may be prudent for oncologists to review "clinically significant" PDIs initially identified such electronic resources or tools with oncology pharmacist input where available prior to prescribing a new anticancer agent or regimen.

PDIs: Illustrative Examples

Several studies have evaluated the prevalence or incidence of PDIs (27–75%) among adults with cancer across settings, with a trend toward a higher prevalence in those studies focusing on older adults with cancer (Table 2). In addition to differences in the drug software or resources utilized, the study population varied significantly across studies that could explain some of the differences in results, especially with inherent differences in cancer types and cancer treatments encountered. Several unifying themes emerge when examining these studies as a whole. First, most studies included patients receiving or about to receive cancer treatment, the majority of which involved intravenous chemotherapy agents. Among the studies that evaluated the types of PDIs involving chemotherapy agents versus other medications, those involving chemotherapy agents tended to represent a minority of the PDIs identified (<25%). More frequent and/or more clinically significant PDIs may be encountered

Table 2 Select PDI studies in oncology and geriatric oncology

Study	Type of study	N	Age	Number of meds per patient	PDI software or resource used	PDI prevalence/ incidence	PDI level of evidence	PDI severity	PDI types
Outpatient									
Girre et al. (2011)	Prospective (1 year, single site)	105	Median = 79 (range, 70–97)	Mean=4.7 (range, 0–14); 47% taking ≥5 meds	French drug thesaurus	33% of patients; 45 PDIs (only in patients ≥2 meds: $N = 97$)	Not reported	24% of PDIs moderate-severe level	Not delineated
Popa et al. (2014)	Retrospective (10 years, single site)	244	Median = 71 (range, 70–91)	Mean =11.7 (range, 3–41)	Drug interaction facts (DIF)	75%	Level 1–3 (=high) =21% of PDIs	Not delineated	21% level 1–3 PDIs involved chemo agents
Puts et al. (2010)	Prospective (1 year, single site)	112	Mean =74.2 (range, 65–92)	Median = 5; increased to 6 @ 12 months after cancer tx initiation	Vigilance Sante software	Not reported	247 PDIs @ baseline; 273 @3 months; 229 @6 months 188; @12 months	Moderate or higher severity: 46 PDIs @ 3 months; 39 PDIs @ 6 months; 37 @ 12 months	Only up to 12% of PDIs involved a chemo agent at any given time
Riechelmann et al. (2007)	Prospective (~8 months, single site)	409	Median = 58 (range, 21–88)	Median = 5 (range, 0–23)* (Rx meds only)	DIF	27%; 276 PDIs	Level 1–3 = 53% of PDIs	77% of PDIs = moderate severity; 9% = major severity	PK: 55% PD: 25% 36 distinct PDI types (15 = warfarin + chemo) RFs for PDI: number of meds; cancer type (CNS); and use of meds for comorbid conditions (vs. supportive care)
Van Leeuwen et al. (2013)	Retrospective (1 year, 3 site, only oral	898	Median = 61 (range, 18–95)	Median = 5 (range, 1–24)	DIF + pharmacist review	46%; 1359 PDIs	Level 1–3 = 86% of PDIs 16% patient had 1+ PDI "Major	Moderate severity: 84% of PDIs; Major severity:	PD = 86% (CNS, GI, QT); chemo PDIs mostly involved

	anticancer agents)						severity" of PDIS 14$ major 83% moderate 14% involved cancer tx meds	14% 16% of patients had ≥1 had major PDI	capecitabine (warfarin); tamoxifen; temozolomide; bicalutamide; Anastrozole; methotrexate; RFs for PDI: number of meds, non-GU cancer type
Van Leeuwen et al. (2015)	Prospective (~1 year, 1 site)	302	Mean=61 years (range, 22–84)	Median = 10- (range, 1–25)	Micromedex + drugs.com website	27%; 603 PDIs	Not reported	120 PDIs (20%) deemed "clinically significant"	PK: 21%, PD: 67.5%; PD subclassification: 31% CNS interactions; 18% QT interval interactions; 13.5% GI interactions; RFs for PDIs: number of comorbid conditions; number of OTC meds
Inpatient									
Riechelmann et al. (2005)	Retrospective (6 months)	100	Median = 67 (range, 20–94)	Median = 8 (range 1–20) @ admission	DIF	63%; 180 PDIs	Level 1–3: 25% of PDIs	75% of PDIS = moderate-severe	Commonly involved drugs: Benzodiazepines; SSRIs, opioids, NSAIDs, steroids, furosemide, phenothiazines, levothyroxine, LMWH, PPIs; RFs for PDI: number of meds; length of stay

CNS central nervous system, *GI* gastrointestinal, *GU* genitourinary, *LMWH* low-molecular-weight heparin, *NSAID* nonsteroid anti-inflammatory drug, *OTC* over-the-counter, *PD* pharmacodynamic, *PDI* potential drug interactions, *PPI* proton pump inhibitor, *PK* pharmacokinetic, *RF* risk factor, *Rx* prescription, *SSRI* selective serotonin reuptake inhibitor, *Tx* therapy

when oral anticancer agents are evaluated exclusively.

Overall, the PDIs encountered by an electronic drug database could be of unclear clinical significance: how concerned should the provider be? Of the few PDIs involving anticancer and supportive care drugs identified in the studies in Table 1, interactions involving warfarin, CYP3A4-mediated agents, and concurrent use of medications that might prolong the QT interval are commonly encountered (Table 3). Finally, it is important to point out the potentially deleterious impact of acid-suppressing drugs such as proton pump inhibitors (PPIs) on the potential efficacy of oral tyrosine kinase inhibitors (TKIs) used to treat several types of cancer. For those who cannot discontinue the acid suppressant, this interaction may be circumvented with the concurrent ingestion of cola beverages with the TKI, for example (Gay et al. 2016; van Leeuwen et al. 2016).

PDIs and Outcomes: What Do We Know?

The outcome most directly attributable to PDIs is adverse drug events (ADEs), which can lead to morbidity, hospitalization, and potential death even among patients with cancer although the

Table 3 Select common PDIs encountered in oncology/geriatric oncology studies

Drug/drug class A	Drug/drug class B	Mechanism	Potential toxicity
Warfarin	Capecitabine 5-fluorouracil Tamoxifen Other drugs	Several interactions including CYP2C9	Increased serum concentrations of warfarin = increased risk of bleeding
Some SSRIs (e.g., fluoxetine) other CYP2D6 inhibitors	Tamoxifen	CYP2D6 interactions	Decreased serum concentrations of tamoxifen
NSAIDs Furosemide Sulfa drugs	Methotrexate	Decreased metabolism and/or excretion of methotrexate	Increased serum concentrations of methotrexate
Itraconazole, fluconazole, other CYP3A4 inhibitors	Vincristine Other anticancer agents that are CYP3A4 substrates	CYP3A4 interactions	Increased serum concentrations of the anticancer agent
NSAIDs	Antiplatelet agents Anticoagulants Corticosteroids SSRIs	Overlapping toxicity profiles	Increased risk of bleeding
Fentanyl	Fluconazole (CYP3A4 inhibitor)/ ondansetron	CYP3A4 interactions/ concurrent use of drugs that prolong the QT interval	Increased (inhibitor) or decreased (inducer) serum concentrations fentanyl/ increased risk of QT prolongation
Acid suppressants (e.g., PPIs)	Certain oral TKIs, such as: Axitinib Crizotinib Dabrafenib Dasatinib Erlotinib Gefitinib Nilotinib Pazopanib	May decrease absorption of the TKI	Decreased serum concentrations of the TKI

NSAID nonsteroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TKI* tyrosine kinase inhibitor

incidence may be lower than that compared to those with non-cancer chronic illnesses (Buajordet et al. 2001; Budnitz et al. 2011). The likelihood of a medication or PDI precipitating an ADE is often measured by validated algorithms (Michel and Knodel 1986). A study by Del Giglio et al. (2009) evaluated the likelihood of ADEs as the cause of admissions to an oncology ward over the course of a year. Of 458 admissions evaluated, 13% were deemed to be medication-related, with 11% of these being ADE-related due to chemotherapy (i.e., neutropenic fever mostly in patients with hematologic cancers) and 2% involving other drugs (PDIs with warfarin, NSAIDs, ACE inhibitors). Popa et al. (2014) found an association between a number of higher-evidence PDIs with an increased risk for non-hematologic chemotherapy toxicity but not hematologic toxicity. We do know that pharmacist-led interventions can decrease polypharmacy (including PIM use) and thus mitigate the prevalence of PDIs in older patients with cancer and can lead to better outcomes such as oral anticancer therapy adherence and persistence (Flood et al. 2009; Wong et al. 2016). Some online resources have been developed to aid oncology providers in evaluating PDIs with the use of some of the oral anticancer agents (http://oncologypro.esmo.org/Guidelines-Practice/Drug-Drug-Interactions-with-Kinase-Inhibitors/Types-of-Drug-Drug-Interactions).

PDIs in Geriatric Oncology: Future Directions

As noted above, several limitations impact our interpretation of the current data on PDIs (and polypharmacy) in geriatric oncology. Many studies have heretofore been retrospective, with heterogeneous methodologies and operational definitions and with very few being outcome-based. We generally know that oral anticancer therapies pose the greatest risk for clinically significant PDIs than intravenous agents. Since the conduct of many of these studies, newer oral anticancer agents have since been approved and introduced into clinical oncology practice, including agents that carry labeled QT prolongation risks (e.g., vandetanib, crizotinib, osimertinib) or those that can significantly increase the risk for severe bleeding events (e.g., ibrutinib, ponatinib).

With the advent of novel oral anticoagulants (e.g., apixaban, rivaroxaban) or use of low-molecular-weight heparins in patients with cancer instead of warfarin and less use of phenytoin as a preferred initial anticonvulsant in this population (e.g., as compared to levetiracetam), some of the more common PDIs previously studied may not be as clinically important or germane in the current era of cancer therapy. Since January 2010, at least 35 either brand-new oral anticancer agents or those with a new disease indication were approved by the US Food and Drug Administration (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm). Furthermore, some oral anticancer agents are rapidly supplanting older (and usually intravenous) cytotoxic therapy options, particularly for patients with chronic lymphocytic leukemia (i.e., ibrutinib, idelalisib) and prostate cancer (e.g., enzalutamide, abiraterone). It is important to highlight that even these drugs are metabolized extensively by the hepatic cytochrome P-450 system and thus can be heavily influenced by concurrent use of CYP3A4 inducers/inhibitors (Benoist et al. 2016; De Zwart et al. 2016; Lambert Kuhn et al. 2016).

Therefore, it will be important to reexamine in a prospective fashion how these newer oral anticancer therapies impact older adults or those with other comorbidities that may be more vulnerable to medication-related issues: polypharmacy (including PIM use), PDIs, and "pill burden." Potential outcomes of interest would warrant more rigorous evaluation of their impact on older adults with cancer: ADEs (including chemotherapy toxicity), financial toxicity, functional outcomes, and morbidity such as unplanned emergency room visits and hospitalizations. Certainly, the development of more innovative interventions will be key to address these issues and successfully mitigate such risks. Given the increasing complexity of both geriatric and cancer care in general, a multidisciplinary approach will likely need to be incorporated in future studies and in clinical practice.

Cross-References

- Comorbidity in Aging and Cancer
- Decision Making and Safety Issues in Older Cancer Patients
- Pharmacology of Aging and Cancer
- Principles of Chemotherapy in Older Adults

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Comorbidity in Aging and Cancer

22

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Contents

Abstract

Comorbidity, the presence of coexisting diseases, is common in older adults with cancer. However, measurement of comorbidity is challenging due to its manifold presentation; numerous measures have been developed and validated, but there is no "gold standard" for comorbidity measurement in patients with cancer. However, a few tools have been developed specifically for quantification of comorbidity in older adults and/or patients with cancer. Comorbidity has complex interactions with cancer risk, prognosis, cancer treatment decisions, and tolerability of cancer treatment. For older adults in particular, comorbidity can imply "competing risks" for mortality and therefore a projected lack of benefit for

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anticancer therapies; on the other hand, comorbidity is not always associated with worse outcomes from these therapies. Comprehensive geriatric assessment (CGA) along with assessment of patients' goals and overall life expectancy can assist with decision-making in older adults with cancer and comorbidity.

Keywords
Comorbidity · Cancer

Introduction

Cancer is a disease of aging. By 2030, it is estimated that 70% of incident cancers will be diagnosed in persons ≥65 years (Smith et al. 2009). As the population ages, and as cancer detection and treatments improve, rapidly increasing numbers of older adults will be either cancer survivors or living with cancer as a chronic condition. Many other chronic diseases also increase in incidence with increasing age, including cardiovascular disease, kidney disease, lung disease, metabolic syndromes, and degenerative musculoskeletal diseases. The interplay between age, cancer, and other chronic diseases is extraordinarily complex and affects the care of the older patient with cancer in a number of ways. Older patients, and especially those with significant chronic conditions, are typically excluded from cancer clinical trials, thus limiting the evidence base available to their providers (Lewis et al. 2003); moreover, clinical guidelines for cancer treatment do not often consider the potential interactions between chronic diseases and cancer or cancer treatments (Boyd et al. 2005). Co-management of cancer and other chronic diseases may be very challenging in the setting of increasing fragmentation of healthcare, particularly for the older patient, who may have more difficulty coordinating and attending multiple specialist appointments. A cancer diagnosis often dominates discussions of clinical decision-making, but many older adults (especially those with indolent malignancies) are more likely to die of other causes, leading to overtreatment of cancer. On the other hand, older adults with chronic diseases may be denied treatment for cancer based on concern for toxicity, and undertreatment is also possible. This chapter further explores the relationship between cancer and comorbidity in older patients.

The objectives of this chapter are:

1. To define comorbidity, discuss its prevalence in older patients with cancer, and review the available measures of comorbidity in patients with cancer
2. To review what is known about the association between comorbidity and cancer risk, cancer detection, and survival
3. To present a general approach to decision-making in older adults with cancer and comorbidity
4. To examine the effect of comorbidity on cancer treatment choice and tolerance
5. To discuss the potential impact of cancer treatment on comorbidities, in particular geriatric syndromes

Definition of Comorbidity

Comorbidity is the presence of any additional coexisting ailment in a patient with a particular index disease, such as cancer (Feinstein 1970). Typically, these coexisting ailments are chronic diseases or health conditions which have long-term consequences for health and quality of life; comorbidities can influence the approach to management of the index disease. Comorbidity is associated with adverse outcomes in older adults with cancer, including decreased survival (Sogaard et al. 2013; Piccirillo et al. 2004; Lee et al. 2011), reduced quality of life, increased hospitalizations and healthcare costs, and increased toxicity from anticancer therapies (Lee et al. 2011). Some comorbidities can increase the risk of developing cancer (Extermann 2007; Giovannucci et al. 2010; Vigneri 2009).

Comorbidities are typically classified into specific disease categories, often grouped by organ system; examples include diabetes, coronary artery disease, or chronic renal insufficiency. However, another type of comorbidity prevalent in older adults, particularly frail older adults, is the

"geriatric syndrome." Geriatric syndromes are multifactorial conditions not limited to a particular organ system and include cognitive impairment, delirium, fatigue, incontinence, malnutrition, pressure ulcers, gait disorders, falls, sleep disorders, and sensory deficits. Some of these syndromes may be the result of a specific disease, but they may also result from low physiologic reserve, or "the loss of compensatory ability through the accumulated effects of multiple impairments," thus relating them to frailty, itself a complex geriatric syndrome (Tinetti et al. 1995; Fried et al. 2001). Some geriatric syndromes, unlike chronic diseases, may be intermittent. Like chronic diseases, however, they can impact a patient's functionality, vulnerability to adverse outcomes, and survival (Naeim and Reuben 2001).

Prevalence of Comorbidity

The prevalence of comorbidity in patients with cancer varies widely, depending upon how it is defined and measured (see below); in one review of the literature, prevalence estimates ranged from 0.4% to 90% (Lee et al. 2011). Comorbidity prevalence can also vary by cancer primary site: patients with lung and colorectal cancers have a higher prevalence and burden of comorbidity compared to patients with breast or prostate cancers, whose prevalence is similar to that of non-cancer cohorts (Cho et al. 2013; Edwards et al. 2014). This difference may be at least partially attributable to risk factors (such as smoking or dietary intake) which contribute both to cancer and to other chronic conditions. Among patients with cancer, those from racial/ethnic minority groups (Putt et al. 2009; Tammemagi et al. 2005) and those with a low socioeconomic status (SES) have a higher prevalence of comorbidity (Tammemagi et al. 2005; Louwman et al. 2010; Cook et al. 2013). Patients with low SES have a higher incidence of certain cancers that have a tendency to co-occur with chronic conditions (such as lung cancer).

Geriatric syndromes may be more prevalent in patients with cancer: in a study of Medicare beneficiaries (n = 12,480), 18% (n = 2349) reported a history of cancer; of those with cancer, 60.3% had at least one geriatric syndrome, compared with 53.2% of non-cancer patients ($p < 0.001$) (Mohile et al. 2011).

Measures of Comorbidity for Older Patients with Cancer

Given the breadth of the concept of comorbidity, it is challenging to determine how best to quantify comorbidity as well as how to incorporate this measure into treatment decision-making for older adults with cancer. One recent review assessed 21 distinct published measures of comorbidity in adults with cancer using six qualitative criteria: experience with cancer patients, content/face validity, concurrent validity, predictive validity, reliability, and feasibility (Sarfati 2012). The authors concluded that no gold standard approach exists to measure comorbidity in the context of cancer. However, 8 of the 21 indices analyzed (Charlson Comorbidity Index [CCI] (Charlson et al. 1987), Satariano Index (Satariano and Ragland 1994), Elixhauser (Elixhauser et al. 1998) and Tammemagi (Tammemagi et al. 2005) approaches, Fleming's Comprehensive Prognostic Index (Fleming et al. 1999), National Cancer Institute [NCI] Combined Comorbidity Index (Klabunde et al. 2007), Alcohol-Tobacco-Related Comorbidities Index (Reid et al. 2002), and Washington University Head and Neck Comorbidity Index (Piccirillo et al. 2002)) scored at least moderately well on all criteria. Of these, three (CCI, Elixhauser approach, and NCI Combined Comorbidity Index) were developed for use in all cancer subtypes; the remainder are cancer site specific. Several measures, such as the Cumulative Illness Rating Scale (CIRS) (Linn et al. 1968), Index of Coexistent Disease (ICED) (Greenfield et al. 1993), and Adult Comorbidity Evaluation-27 (ACE-27) (Piccirillo et al. 2004), scored highly on all criteria except for feasibility due to the amount and detail of data capture required. Some included measures which were developed for other specific purposes, lacking generalizability to the cancer population. One of the authors

has subsequently developed cancer-specific measures of comorbidity, using administrative hospitalization and pharmaceutical data (Sarfati et al. 2014a, b).

Another review narrowed focus to four validated comorbidity measures incorporated into clinical trials of older adults with cancer: the CCI, CIRS, ICED, and the Kaplan-Feinstein Index (Kaplan and Feinstein 1974). All were found to be relatively easy to use, did not require much time to be completed (<10 min), and had a generally good inter-rater and test-retest reliability (Extermann 2000). More recently, the Cancer and Aging Research Group (CARG, http://www.mycarg.org) in collaboration with the National Cancer Institute (NCI) and the National Institute on Aging (NIA) held a discussion focusing on comorbidity measurement in the older adult, generating a summary of comorbidity measurement scales (Williams et al. 2016a). The authors concluded that ultimately, it is not as important as exactly how comorbidity is measured, but rather that comorbidity is being considered in older adults with cancer. However, a standardized measure of comorbidity would facilitate research and cross-trial comparisons.

For older adults with cancer, there are no specific screening or measurement tools for geriatric syndromes. Often, the presence of these syndromes is uncovered during the course of a comprehensive geriatric assessment (CGA), a multidisciplinary assessment of an older adult's health and functioning. Comorbidity is one domain included within the assessment, incorporating one or more of the tools discussed above as well as, typically, attention to geriatric syndromes. The CGA is resource-intensive to perform, and who to assess with this method remains unclear (Mohile et al. 2015). The use of CGA in the care of older adults with cancer is discussed later in the chapter.

In summary, there is no standard tool for the quantification of comorbidity burden in older adults with cancer. Some measures have been studied head to head in specific populations of patients with cancer (Sarfati 2012). A majority of the studies included the CCI given its usefulness in non-site-specific cancer. Ultimately, the appropriate tool depends on the population, setting, and the specific clinical or research question. No one tool is optimal for all situations, but measurement of comorbidity is critical in older adults with cancer given its impact on prognosis, treatment tolerability, and survival outcomes. Table 1 summarizes the comorbidity measures available.

Comorbidity and Cancer Risk

Cancer is a disease of aging; advanced age is one of the biggest risk factors for development of cancer. At 50 years of age, the risk for developing cancer is approximately 1/1000, but by age 80, the risk has increased to about 1% per year (Extermann 2007). The interaction between comorbidity and cancer risk is complex. Increasing prevalence of comorbidities with age may contribute to the increased risk of cancer. In addition, many of the risk factors associated with developing cancer (lifestyle, diet, obesity, smoking, and alcohol abuse) are also risk factors for the development of many common chronic conditions. Certain chronic conditions themselves are also independent risk factors for cancer, perhaps due to shared pathophysiologic mechanisms; for example, the inflammatory pathways activated in diseases such as diabetes, obesity, and autoimmune disorders are known to promote tumorigenesis and tumor progression (Extermann 2007; Giovannucci et al. 2010; Vigneri et al. 2009). Less commonly, some medications used to treat chronic conditions have been associated with increased cancer risk (Extermann 2007).

Diabetes is increasing in prevalence, due both to lifestyle risk factors and advancing age of the population. More than 25% of adults ≥65 years have diabetes (Centers for Disease Control and Prevention 2017). Diabetic patients have an increased risk of breast, pancreatic, liver, colorectal, and endometrial cancers. Compared to non-diabetics, diabetics have a relative risk (RR) >2 for cancers of the liver, pancreas, and endometrium; RR of 1.2–1.5 is seen for cancers of the colon and rectum (Vigneri et al. 2009). The mechanisms which link diabetes and cancer risk may include hyperinsulinemia (endogenous due to

Table 1 Comorbidity measures

Index	Items	Data source	Population	Reason/purpose	Inclusion of older adults in development	Studies using index in cancer patients
Summative						
Satariano (Satariano and Ragland 1994)	7 selected conditions	Clinical notes data, administrative data	1,011 breast cancer patients	Assess effect of comorbidity on 3-year survival	46% ≥65 years; 26% age 75–84	Breast (Satariano and Ragland 1994; Newschaffer et al. 1997), head and neck (Reid et al. 2002)
National Institute on Aging/National Cancer Institute Collaborative Study (Yancik et al. 1996)	6 selected conditions	Clinical notes data	7,631 patients with cancer	Investigate comorbidity burden	3 cohorts of equal numbers: age 55–64, age 65–74, and age ≥ 75 years	Various cancers (Yancik et al. 1996)
Elixhauser (Elixhauser et al. 1998)	30 dichotomous conditions	Administrative data	1,779,167 adult acute care hospital patients	Measure comorbidity and effect on length of stay, total charges, and in-hospital mortality	Included all age ≥ 18 years; mean age of cohort 57 years	Cervical (Brewer et al. 2011), colorectal (Lieffers et al. 2011), head and neck (Lee et al. 2016)
Alcohol-Tobacco-Related Comorbidities Index (Reid et al. 2002)	11 conditions associated with alcohol or tobacco	Administrative data	9,386 head and neck cancer patients	Assess comorbidity and association with survival	All age ≥ 65: 61.9% 65–74 years, 31.6% 75–84 years, 6.5% ≥85 years	Head and neck (Reid et al. 2002; Castro et al. 2007)
Tammemagi (Tammemagi et al. 2005, 2003)	259 comorbidities in 56 comorbidity categories (lung) 268 comorbidities in 16 comorbidity categories (breast)	Administrative data	1,155 lung and 906 breast cancer patients	Assess comorbidity and association with 1-year mortality	Lung: age ranges not reported Breast: 54% >60 years, 9% >80 years	Breast (Tammemagi et al. 2005), lung (Tammemagi et al. 2003)
Multipurpose Australian Comorbidity Scoring System (Holman et al. 2005)	102 conditions	Administrative data	1,069,770 hospital patients	Develop generalized measure of comorbidity, effect on 1-year mortality, 30-day readmission, and LOS	Age data not reported	Development cohort included 615 breast cancer patients (Holman et al. 2005)
Systems based						
Cumulative Illness Rating Scale (Linn et al. 1968)	13 or 14 organ system categories, each rated 0–4	Clinical notes data	Unclear	Measure of physical impairment	Modified CIRS-G (Miller et al. 1992) was developed from	Various cancers (used CIRS-G) (Extermann et al. 1998), colorectal

(*continued*)

Table 1 (continued)

Index	Items	Data source	Population	Reason/purpose	Inclusion of older adults in development	Studies using index in cancer patients
					141 patients ≥60 years (mean age 67 years)	(Munro and Bentley 2004), hand neck (Castro et al. 2007; Hall et al. 2002), prostate (Boulos et al. 2006)
Kaplan-Feinstein Index (Kaplan and Feinstein 1974)	12 conditions, each rated 0–3	Clinical notes data	188 men with diabetes	Measure of comorbidity and impact on survival	Half of cohort ≥55 years; not otherwise described	Breast (Charlson et al. 1987; Newschaffer et al. 1997; Silliman and Lash 1999), head and neck (Piccirillo et al. 2002; Castro et al. 2007; Hall et al. 2002), prostate (Boulos et al. 2006; Albertsen et al. 1996)
Index of Coexistent Disease (Greenfield et al. 1993)	Disease severity subindex: 14 organ systems, each rated 0–4 Functional severity subindex: 12	Clinical notes data	356 patients undergoing total hip replacement	Measure impact of comorbidity and physical functioning	Mean age 64 years; ~25% >73 years	Breast (Mandelblatt et al. 2001; Lash et al. 2003), head, and neck (Castro et al. 2007; Hall et al. 2002), prostate (Boulos et al. 2006; Albertsen et al. 1996)
Total Illness Burden Index (Greenfield et al. 1995)/Total Illness Burden Index-CaP (Litwin et al. 2007)	84 items included in 11 subdimensions with severity rated and subdimensions weighted on clinical impact	Patient symptom report	1,738 general patients and 2,894 prostate cancer patients	Measure total burden of disease	General: mean age 66; prostate cancer: mean age 69, 75% between 60 and 80 years	Breast (Silliman and Lash 1999; Mandelblatt et al. 2001), prostate (Litwin et al. 2007)
Adult Comorbidity Evaluation-27 (Piccirillo et al. 2003)	27 conditions, each rated into 3 grades of severity	Clinical notes data, administrative data	11,906 cancer patients	Assess comorbidity among cancer patients	Unclear; in updated cohort of 17,712 patients, 29% 65–74 years, 17% ≥75 years	Various cancers (Piccirillo et al. 2004, 2003), Various cancers in ICU (Soares et al. 2005), colorectal (Hines et al. 2009), head and heck (Castro et al. 2007; Sanabria et al. 2008)

Weighted						
Charlson Comorbidity Index (Charlson et al. 1987)	19 conditions weighted 1–6	Clinical notes data, administrative data, patient questionnaire	559 general medical patients	Develop a method to classify comorbidity and estimate risk of death	Unclear in development cohorts Studies in older patients: breast (Newschaffer et al. 1997, 1998; Ahern et al. 2009), head and neck (Reid et al. 2002, 2001), lung cancer (Blanco et al. 2008), colorectal cancer (Lemmens et al. 2005)	Various cancers (Klabunde et al. 2007; Extermann et al. 1998), breast (Newschaffer et al. 1997; Holman et al. 2005; Silliman and Lash 1999; Mandelblatt et al. 2001; Lash et al. 2003), cancer in ICU (Soares et al. 2005), cervical (Brewer et al. 2011), colorectal (Lieffers et al. 2011; Munro and Bentley 2004; Hines et al. 2009; Sarfati et al. 2009; Dobbins et al. 2015), head and neck (Reid et al. 2002, 2001; Castro et al. 2007; Hall et al. 2002; Chang et al. 2016), lung (Colinet et al. 2005; Jacot et al. 2008), prostate (Boulos et al. 2006; Albertsen et al. 1996; Froehner et al. 2003, 2014)
Chronic Disease Score (Von Korff et al. 1992)/ RxRisk (Clark et al. 1995)	Sum of scores assigned for each class of medication used by a patient over a 1-year period	Administrative data	122,911 enrollees in an HMO	Predict resource use in HMOs	Included age $\geq$ 18 years; descriptive statistics not reported	Head and neck (Hall et al. 2002), prostate (Boulos et al. 2006)
Comprehensive Prognostic Index (Fleming et al. 1999)	Comorbidity included in multivariable model, including interaction terms	Administrative data	848 breast cancer patients	Develop site-specific measures of comorbidity for breast and prostate cancers	All patients $\geq$67 years	Breast (Fleming et al. 1999)
National Cancer Institute Comorbidity	16 conditions weighted by	Administrative data	28,868 prostate and 14,943	Measure comorbidity and association with	All patients $\geq$66 years (Medicare-SEER data)	Various cancers (Klabunde et al. 2007), breast (Klabunde et al.

(*continued*)

Table 1 (continued)

Index	Items	Data source	Population	Reason/purpose	Inclusion of older adults in development	Studies using index in cancer patients
Index (Klabunde et al. 2007, 2000)	empirically derived weights		breast cancer patients	2-year non-cancer mortality		2000), colorectal (Hines et al. 2009; Baldwin et al. 2006), head and neck (Sanabria et al. 2008), prostate (Klabunde et al. 2000)
Elixhauser Index (van Walraven et al. 2009)	30 conditions weighted by empirically derived weights	Administrative data	228,565 adult acute care hospital patients	Combine Elixhauser conditions into index discriminative for death in hospital	Mean age 59 years	Colorectal (Baldwin et al. 2006), head and neck (Chang et al. 2016)
Cancer-specific						
Washington University Head and Neck Comorbidity Index (Piccirillo et al. 2002)	7 conditions, each rated 0–4	Clinical notes data, Administrative data	1,094 head and neck cancer patients	Assess comorbidity ability to predict survival	39% >65 years	Head and neck (Piccirillo et al. 2002; Castro et al. 2007; Sanabria et al. 2008)
Simplified Comorbidity Index (Colinet et al. 2005)	7 conditions weighted between 1 and 7	Clinical notes data	735 patients with lung cancer	Assess comorbidity and ability to predict survival	Median age 62.5 years	Lung (Colinet et al. 2005; Jacot et al. 2008)
Hematopoietic Cell Transplantation-Comorbidity Index (Sorror et al. 2005)	17 conditions, each rated 0–3	Clinical notes data	1,055 patients undergoing hematopoietic cell transplantation (HCT)	Develop a comorbidity score for HCT that predicts non-relapse mortality and survival	Median age 45 years; included patients up to 73 years	HCT (Sorror et al. 2005)
C3 Index (Sarfati et al. 2014a)	Cancer site-specific: 50 weighted conditions; non-site-specific: 42 weighted conditions	Administrative data	14,096 patients in New Zealand cancer registry	Develop cancer-specific index and assess ability to predict survival	25% age 65–74 years; 30% ≥75 years	Colorectal, breast, gynecologic, upper GI, urologic (Sarfati et al. 2014a)

Pharmacy-based comorbidity index (PBCI) (Sarfati et al. 2014b)	19 weighted conditions	Pharmacy-based data	14,096 patients in New Zealand cancer registry	Develop cancer-specific index and assess ability to predict survival	25% age 65–74 years; 30% ≥75 years	Colorectal, breast, gynecologic, upper GI, urologic (Sarfati et al. 2014b)
Case-mix approaches						
Diagnostic Cost Group (Ash et al. 1989)	800 diagnostic classifications by ICD-9 into 78 diagnostic subgroups aggregated into 9 diagnostic cost groups	Administrative data	38,705 Medicare beneficiaries	Predict resource use in HMOs	All patients ≥65 years	Colorectal (Baldwin et al. 2006)
Adjusted Clinical Groups (Weiner et al. 1991)	5000 ICD-9 diagnosis codes assigned to 34 ambulatory diagnostic groups	Administrative data	16,000 HMO enrollees and Maryland Medicaid beneficiaries	Predict resource use in HMOs	Unclear, included all ages from birth	Colorectal (Baldwin et al. 2006)
Overall health						
American Society of Anesthesiologists (Reid et al. 2001)	Score from 1 (healthy) to 6 (brain dead) based on severity of systemic disease	Clinical notes data may be obtained from administrative	388 head and neck cancer surgical patients	Originally to assess acute operative risk but evaluated as measure of comorbidity and prognostic ability for mortality in head and neck cancer	All patients ≥65 years: 66.5% 65–74 years, 28.6% 75–84 years, 4.9% ≥85 years	Breast (Lash et al. 2003), colorectal (Dobbins et al. 2015), head and neck (Reid et al. 2001), prostate (Froehner et al. 2003, 2014)
Older Americans Resources and Services (OARS) Questionnaire Physical Health subscale (Fillenbaum and Smyer 1981)	14 specific comorbid conditions rated on 3-point scale	Patient questionnaire	997 community-dwelling older adults (age ≥ 65 years)	Measure degree that comorbidity interferes with patients activities	All patients ≥65 years	Used as part of geriatric assessment for breast, colorectal, lung, and lymphoma patients (Hurria et al. 2005)

Adapted from Sarfati 2012, with permission

insulin resistance or exogenous), hyperglycemia, or chronic inflammation, but these mechanisms are not completely understood (Giovannucci et al. 2010). The effect of hyperinsulinemia on insulin-like growth factor-1 (IGF-1) and insulin receptors has been postulated to have an impact on cellular signaling pathways including proliferation, protection from apoptotic stimuli, invasion, and metastasis. Moreover, the chronic pro-inflammatory state caused by metabolic abnormalities seen in diabetes reduces intracellular antioxidant capacity, predisposing susceptible cells to malignant transformation (Vigneri et al. 2009).

Obesity, a risk factor for many comorbidities, including diabetes, is also a risk factor for multiple cancer types, including postmenopausal breast cancer and cancers of the endometrium, esophagus, colon and rectum, prostate, pancreas, and kidneys, as well as leukemia and multiple myeloma. It is estimated that 20% of all cancers are related to excess weight, with a substantial proportion (25–50%) of these cases associated with obesity in postmenopausal women (Reeves et al. 2007). Specifically, the risk of developing breast cancer is increased in obese versus nonobese postmenopausal women, whereas obese young premenopausal women appear to be at decreased risk (Extermann 2007). In addition, women who gain significant weight during adulthood are at increased risk of breast cancer (Magnusson et al. 1998). The mechanisms by which obesity influences cancer risk are not fully understood. However, proposed mechanisms include increased levels of leptin as a growth factor for cancer, as well as involvement of interleukin-6 (IL-6) and IGF-1 which both increase with increasing weight (Extermann 2007; Vigneri et al. 2009). However, risk seems to decrease to baseline levels with weight loss (Parker and Folsom 2003).

However, aging itself is associated with an increase in inflammatory cytokines (including IL-6) and a state of chronic inflammation, and the term "inflammaging" was coined to describe this phenomenon (Franceschi and Campisi 2014). It has long been recognized that inflammation and cancer are related, and inflammation is increasingly recognized as a contributor to the development of most or all age-related chronic conditions, including arthritis, cardiovascular disease, and metabolic syndromes. Therefore, the association between certain chronic conditions and the risk of cancer may reflect these underlying shared etiologic pathways. More research is needed to elucidate the interactions between increasing age, comorbidities, and cancer risk, including determination of whether "inflammaging" can be prevented or mitigated and whether this affects risk and outcomes of cancer and chronic illness.

Comorbidity and Prognosis

Cancer Screening and Early Diagnosis

The early detection of cancer improves outcomes including mortality and quality of life. However, in older adults decisions regarding screening are not always straightforward. Guidelines have been created by multiple groups to help with early detection of certain cancers, but most lack evidence supporting use in older or frail adults or those with significant comorbidities that pose competing risks for morbidity and mortality.

Several large studies of screening for breast, colorectal, and prostate cancers have not shown an interaction between comorbidity burden (typically assessed using the CCI) and likelihood of screening (Terret et al. 2009). However, other studies have shown that the presence of comorbidity can increase or decrease receipt of cancer screening, via separate mechanisms. Certain conditions such as diabetes, cognitive decline, psychiatric disorders, and hip fracture have been associated with a trend toward lower use of screening for breast, cervical, and colorectal cancers (Heflin et al. 2002; McBean and Yu 2007; Kiefe et al. 1998). It is postulated that these comorbidities may dominate the use of clinical resources (the "competing demands" hypothesis), leaving little time to address screening, and/or clinicians may believe that cancer screening is unlikely to offer benefit in the setting of these

comorbidities. Functional loss due to chronic conditions influences providers to recommend against screening in an older adult (Blustein and Weiss 1998). Conversely, the presence of comorbidities has been associated with an increase in receipt of cancer screening in some studies (the "surveillance effect"), thought to be due to more frequent contact with healthcare providers (Heflin et al. 2002). In some cases, the effects of a particular comorbidity are mixed: end-stage renal disease (ESRD), for example, is associated with increased screening for colorectal cancer (likely secondary to the association between ESRD and anemia) and decreased screening for prostate cancer (perhaps attributable to anuria and resultant lack of urinary symptoms) (Taneja et al. 2007).

Cancer screening guidelines do not take comorbidity into account but increasingly incorporate language regarding life expectancy (Table 2). Severe or chronic comorbidities can significantly impact life expectancy and thus can indirectly impact calculation of risk/benefit of cancer screening. Estimates of life expectancy can be performed using population data (Walter and Covinsky 2001), or by using validated indices such as the Lee-Schonberg index (Lee et al. 2006; Schonberg et al. 2009), which incorporate questions about comorbidity (e.g., diagnoses of diabetes, chronic lung disease, and congestive heart failure) and estimate 4- and 10-year likelihood of mortality. Both of these methods for calculation of life expectancy are available at http://eprognosis.ucsf.edu. Decision-making modules for breast and colorectal cancer screening, also available at this website, calculate number needed to harm, number needed to screen to prevent one death, and ratio of patients who would die in 10 years regardless of screening decision based upon entered age, BMI, functional measures, and selected comorbidities.

Comorbidities may also influence stage of cancer at diagnosis, although the relationship is again complex. A review evaluating the impact of comorbidity on cancer diagnosis and survival highlighted multiple studies indicating an association between comorbidity (generally measured by the CCI) and an earlier stage at diagnosis for cancers of the lung, breast cancer, and colon/rectum, again perhaps due to the surveillance effect (Sogaard et al. 2013). One study, however, suggested a more complicated relationship between comorbidity and stage of breast cancer at diagnosis: women with cardiovascular disease, osteoarthritis, and genitourinary disease had a 7–24% lower risk of being diagnosed with advanced breast cancer, while women with diabetes, renal disease and other endocrine disorders, psychiatric disease, osteoporosis, hematologic disease, obesity, and AIDS had an 11–20% higher risk of being diagnosed with advanced disease (Fleming et al. 2005). A study of 149,045 Medicare beneficiaries $\geq$67 years indicated likelihood of advanced-stage breast cancer was highest in patients with "unstable" comorbidities (defined as comorbidities that are life-threatening and/or difficult to control such as severe heart failure and end-stage liver disease) compared to those with "stable" or no comorbidities, even when controlling for mammographic screening use and time-to-diagnosis after mammography (Yasmeen et al. 2012). A study of 14,096 patients with breast, colon, rectal, liver, stomach, ovarian, uterine, bladder, or kidney cancer showed an association between comorbidity burden (measured by the C3 Index (Sarfati et al. 2014a)) and odds of being diagnosed with distant metastases as well as the odds of remaining unstaged after diagnosis (Gurney et al. 2015). Dementia had the strongest individual impact on advanced or unknown stage at diagnosis.

Clearly, the interactions between comorbidity, cancer screening, and stage of the cancer at diagnosis in older adults are complicated. Comorbidities appear to independently influence patients and providers decisions about cancer screening, though how they influence the decision varies based on severity and type of comorbidity as well as the patient's and provider's preferences, estimation of life expectancy, and assessment of risk/benefit of screening. Both the surveillance effect and the competing demands hypothesis are likely to play roles in these relationships.

Table 2 Selected screening guidelines

	Last update	Recommendation (average-risk patients 65 and older)	Consid. of life expectancy?	Age cutoff
Breast cancer				
USPSTF (Siu and U.S. Preventive Services Task Force 2016)	2016	Age 65–74: Screen with mammography every 2 years	No	75
		Age 75 and older: No recommendation for screening (evidence of benefit is lacking)		
ACS (Oeffinger et al. 2015)	2015	Age 65 and older: Mammograms every 2 years or can continue yearly screening for 55 and older; screening should continue as long as a woman is in good health and is expected to live 10 more years or longer	Yes	No
NCCN	2017	Age 65 and older: Recommend annual screening with mammogram; no upper age limit, consider severe comorbid conditions limiting life expectancy (e.g., less than 10 years), and no further intervention would occur based on screening findings	Yes	No
ACOG (American College of O-G 2011)	2011	Age 65–74: Screening with mammography and clinical breast exam annually	Yes	No
		Age 75 or older: Woman should in consultation with their physicians, decide whether to continue mammographic screening		
ACR (Lee et al. 2010)	2010	Age 65–74: Screening with mammography annually	Yes	No
		Age 75 and older: Screening with mammography should stop when life expectancy is less than 5–7 years on the basis of age or comorbid conditions		

Cervical cancer				
USPSTF (Moyer and U.S. Preventive Services Task Force 2012a)	2012	Age 66 or older: If adequate prior screening and are not high risk, then recommend against further screening	No	Yes
ACS (Saslow et al. 2012), NCCN, ACOG	2012	Women ages 66+ who have had ≥3 consecutive negative Pap tests or ≥ 2 consecutive negative HPV and Pap tests within the last 10 years, with the most recent test occurring in the last 5 years, should stop cervical cancer screening	No	Yes
Colorectal cancer				
USPSTF (U.S. Preventive Services Task Force et al. 2016)	2016	Age 65–75: Screen with high-sensitivity fecal occult blood testing, sigmoidoscopy, or colonoscopy	Yes	86
		Age 76–85: Individual decision, taking into account the patient's overall health and prior screening history		
ACS (Levin et al. 2008)	2008	Age 65 and older: Screen; no upper age limit provided	No	No
NCCN	2017	Age 65–75: Screen with colonoscopy, stool-based testing, flexible sigmoidoscopy, or CT colonography	Yes	86
		Age 76–85: Individualized based on discussion of risks and benefits based on comorbidity status and estimated life expectancy		
MSTF (Rex et al. 2017)	2017	Age 65–75: Screen with first-tier test which includes colonoscopy and fecal immunochemical test (FIT) (second-tier tests include CT colonography, FIT-fecal DNA test every 3 years, and flexible sigmoidoscopy)	Yes	No
		Age 76 and older: Consider discontinuation of screening when persons up to date with screening, who have prior negative screening (particularly colonoscopy), reach age 75 or when life expectancy is less than 10 years Persons without prior screening should be considered for screening up to age 85, depending on age and comorbidities		

(*continued*)

Table 2 (continued)

	Last update	Recommendation (average-risk patients 65 and older)	Consid. of life expectancy?	Age cutoff
Lung cancer				
USPSTF (Moyer and U.S. Preventive Services Task Force 2014)	2014	Age 65–80: If 30-pack-year smoking hx and currently smoking or quit <15 years ago, screen annually for lung cancer with low-dose CT. Discontinue screening when the patient has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the willingness to have curative lung surgery	Yes	81
ACS (Wender et al. 2013)	2013	Age 65–74: Screen with low-dose CT if in good health, have at least a 30-pack-year smoking history, and are currently smoking or quit <15 years ago	Yes	75
NCCN	2017	Age 65–74: If ≥30 pack-year smoking history and smoking cessation <15 years ago, screen them annually until they are no longer a candidate for definitive treatment	Yes	75
Prostate cancer				
USPSTF (Moyer and U.S. Preventive Services Task Force 2012b; Draft Recommendation Statement 2017)	2012	All ages: Recommend again prostate-specific antigen (PSA)-based screening	N/A	N/A
	2017 (draft)	Age 65–69: Recommend that clinicians inform men about the potential benefits and harms of PSA-based screening for prostate cancer. Recommend individualized decision-making about screening after discussion	Yes	70
		Age 70 and older: Recommend against PSA-based screening		

ACS (Wolf et al. 2010)	2010	Age 65 or older: Men who have at least a 10-year life expectancy should have an opportunity to make an informed decision with their healthcare provider about whether to be screened for prostate cancer after receiving information about the potential benefits, risks, and uncertainties associated with prostate cancer screening; prostate cancer screening should not occur without an informed decision-making process	Yes	No
NCCN	2017	Age 65–75: Panel supports continued use of PSA for early detection of prostate cancer in informed, healthy men	Yes	No
		Age 76 or older: Testing above the age of 75 should be done with caution and only in very healthy men with little or no comorbidity. Very few men in this age group benefit from PSA testing		
AUA (Carter et al. 2013)	2013 Reviewed 2015	Age 65–69: Strongly recommend shared decision-making for men age 55–69 years that are considering PSA screening and proceeding based on a man's values and preferences Does not recommend routine PSA screening in any man with less than a 10- to 15-year life expectancy	Yes	70
		Age 70 or older: Does not recommend routine PSA screening in men age 70+ years or any man with less than a 10- to 15-year life expectancy		

Abbreviations: *USPSTF* US Preventative Services Task Force, *ACS* American Cancer Society, *NCCN* National Comprehensive Cancer Network, *ACOG* American College of Obstetricians and Gynecologists, *ACR* American College of Radiology, *MSTF* US Multi-Society Task Force of Colorectal Cancer (represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy), *AUA* American Urological Association

Comorbidity and Survival Outcomes

Comorbidity has been associated with poorer overall survival in patients with cancer (Sogaard et al. 2013). Comorbidity may impact survival in several ways, including delays in cancer diagnosis (see above discussion), selection of less aggressive treatment regimens (Lee et al. 2011), potentiation of treatment-related toxicities (Asmis et al. 2008; Hurria et al. 2011a), association with increased cancer recurrence,(Piccirillo et al. 2004; Meyerhardt et al. 2003) or as a competing cause of death (Lee et al. 2011). The relationship between comorbidity, cancer, and survival is not straightforward, but some general trends can be surmised from the available literature. Most observational studies in patients with cancer show a 1.1–5.8-fold higher 5-year mortality for patients with comorbidity (inconsistently but most often measured using the CCI) (Sogaard et al. 2013). The more lethal the cancer type, the less impact comorbidities had on overall survival: the relative impact of comorbidity on survival is much higher in patients with breast cancer than those with lung cancer, for example (Read et al. 2004; Janssen-Heijnen et al. 2007). Increasing severity of comorbidity is correlated with decreasing overall survival: in a study of 62,591 Danish women with early-stage breast cancer, the adjusted hazard ratios (HR) for overall (all-cause) survival were 1.45 for patients with low comorbidity (95% confidence interval [CI] 1.4–1.51), 1.52 (1.45–1.6) for patients with moderate comorbidity, and 2.21 (2.08–2.35) for patients with high comorbidity as measured by the CCI (Land et al. 2012a). A US study including 32,074 patients (most $\geq$65 years) with melanoma and colorectal, breast, and prostate cancers reported that comorbidity was associated with later stage at diagnosis and poorer survival but that the poorer overall survival was attributable to the comorbid (non-cancer) causes (Gonzalez et al. 2001). Other large studies have shown similar findings (Edwards et al. 2014; Piccirillo and Costas 2004).

It is less clear that comorbidity impacts cancer-specific survival. A study of 6325 Danish patients $\geq$70 years confirmed that comorbidity was associated with an increased overall mortality for all cancer subtypes examined but was associated with increased cancer-specific mortality only for lung cancer (Land et al. 2012b). An inverse association between comorbidity burden and cancer-specific survival has been shown in a few studies of patients with colorectal (Sarfati et al. 2009; van de Poll-Franse et al. 2012) and breast (Land et al. 2012a) cancer; however, other studies have not upheld this association (Braithwaite et al. 2012; Janssen-Heijnen et al. 2005). The validity of cause-of-death data has been questioned, as it is possible that a considerable number of deaths are incorrectly assigned as due to cancer, when in fact they were due to non-cancer comorbidity (Sarfati et al. 2010). Other potentially confounding factors, including age, functional status, and differing measures for comorbidity used across studies, make it very difficult to tease out correlations.

There is some evidence that comorbidities impact progression-free survival of cancer in addition to overall survival. Diabetes, in particular, has been shown to increase the recurrence risk of colorectal cancer (Meyerhardt et al. 2003); the association of hyperinsulinemia with cancer risk has been discussed previously in this chapter. However, in retrospective cohort studies, metformin (commonly used to treat diabetes) has been associated with reduced recurrence risk in cancers of the breast, liver, ovaries, uterus, colorectum, and pancreas (Morales and Morris 2015). In a prospective cohort study of 17,712 patients with cancer treated at a single site, the adjusted odds ratios (OR) for recurrence compared to patients with no comorbidity were 1.18 (95% CI, 1.07–1.3), 1.37 (1.22–1.53), and 1.54 (1.31–1.8) for patients with mild, moderate, and severe comorbidity, respectively (Piccirillo et al. 2004).

Comorbidity and Cancer Treatment

Approach to Decision-Making in Older Adults with Cancer and Comorbidities

The impact of comorbidity contributes to the considerable complexity involved in treatment decisions for older patients with cancer. Older patients

and patients with significant comorbidity are underrepresented in randomized clinical trials for cancer treatments (Lewis et al. 2003; Scher and Hurria 2012; Chao et al. 2010), limiting the applicability of results to these patients (Fortin et al. 2006). Oncologists cannot simply rely upon clinical "gestalt" and the assessment of physical fitness, as measures of comorbidity have been shown to be poorly correlated with measures of functional status in older adults with cancer (Extermann et al. 1998). On the other hand, some studies have shown a synergistic, rather than additive, effect of comorbidity and physical frailty on mortality outcomes (Chen et al. 2014). Comorbidity is associated with both polypharmacy and potentially inappropriate medications in older adults with cancer (Nightingale et al. 2015), increasing the risk of drug-drug interactions and adverse drug events (ADEs) (Riechelmann et al. 2005, 2007). The comorbidities themselves may introduce drug-disease interactions with chemotherapy or increase toxicity of therapy through other mechanisms. Oncologists, older patients, and caregivers face a daunting task in the selection of treatment approach.

Perhaps the first appropriate step (predicated on the congruence of treatment with the patient's wishes) is to obtain as much information as is feasible about the interlocking domains contributing to the health and functioning of an older patient with cancer, including an evaluation and measure of comorbidity burden. The comprehensive geriatric assessment (CGA) is an interdisciplinary evaluation of an older person across multiple domains (physical fitness, social and emotional functioning, cognition, comorbidities, medication use, and nutrition), using a set of validated instruments (Extermann and Hurria 2007). It is recommended for all older adults with cancer by the American Society of Clinical Oncology (ASCO) (Mohile et al. 2018), International Society of Geriatric Oncolohy (SIOG) (Extermann et al. 2005) and National Comprehensive Cancer Network (NCCN) (Hurria et al. 2012) guidelines. The CGA has been shown to predict adverse outcomes including mortality (Ramjaun et al. 2013; Maione et al. 2005; Klepin et al. 2013) and treatment toxicity (Hurria et al. 2011a; Ramjaun et al. 2013; Extermann et al. 2012) in older adults with cancer. Its major limitation is the time and clinical resources required to perform it, but the use of screening tools (Augschoell et al. 2014; Bellera et al. 2012) and/or abbreviated CGA (Overcash et al. 2005; Shahrokni et al. 2017) may mitigate this limitation. CGA has been shown to be feasible to perform in clinical trials (Hurria et al. 2011b).

The next step in decision-making is to determine the patient's overall life expectancy. This may be estimated from population data (Walter and Covinsky 2001), validated indices (Lee et al. 2006; Schonberg et al. 2017) (available at https://eprognosis.ucsf.edu), or CGA-based prediction tools (Brunello et al. 2016; Kanesvaran et al. 2011). Patients with very limited life expectancy from non-cancer causes ("competing risks") may not have sufficient time to benefit from antineoplastic therapy, even if they could potentially tolerate it. This determination may be especially crucial for curative-intent therapies such as adjuvant chemotherapy; patients with severe comorbidities or other competing risk for mortality may not live long enough for the projected benefit (reduced risk of recurrence) to outweigh the immediate risk of toxicity (Ramsdale et al. 2013). Indeed, estimation and comparison of the risk of death from cancer versus death from non-cancer causes is an important step in determination of appropriate treatment strategy for older adults.

Cancer-specific prognosis and prediction tools have emerged to help guide treatment decisions, particularly for adjuvant therapy. Adjuvant! Online is an online risk assessment tool to predict benefit of adjuvant therapy in patients with early-stage breast cancer. It includes an estimate of comorbidity burden, but the categories are not well-defined, and the model output is very sensitive to variation in comorbidity; provider interpretation of comorbidity burden can therefore significantly skew the risk/benefit ratio of adjuvant treatment (Ozanne et al. 2009). Moreover, this tool was developed in a cohort of women $\leq$69 years of age and does not accurately predict outcomes in older patients (de Glas et al. 2014).

The PREDICT tool for benefit of adjuvant therapy in early-stage breast cancer, on the other hand, predicts 5-year overall survival in older adults with breast cancer and slightly overestimates 10-year overall survival, except in the patients >85 years (de Glas et al. 2016). However, PREDICT does not incorporate comorbidity burden in its assessment (Wishart et al. 2010). Multiple other cancer site-specific prediction tools exist for recurrence or survival (Rabin et al. 2013); most include age but not comorbidity.

Once the decision to pursue treatment is made, based upon patient preference and life expectancy estimates, subsequent refinement of the treatment plan should incorporate consideration of patient comorbidities. Comorbidities can introduce significant drug-disease and/or drug-drug interactions into the treatment plan, and some treatment options should be avoided for patients with certain comorbidities (e.g., doxorubicin for patients with severe cardiac disease, cisplatin for patients with renal insufficiency). General associations of toxicity of antineoplastic therapy (surgery, chemotherapy, and radiotherapy) in patients with comorbidities will be explored, but a full discussion of drug-disease interactions with chemotherapy is beyond the scope of this chapter; this information is widely available in cancer and chemotherapeutics textbooks. The impact of cancer treatment on geriatric syndromes will be discussed later in the chapter.

Comorbidities and Cancer Treatment Choice

Vignette studies indicate that clinicians are less likely to offer cancer treatment to older patients and patients with comorbidity (Keating et al. 2008; Krzyzanowska et al. 2009; van der Poel et al. 2015; Ring 2010). One review examined the impact of comorbidity on treatment recommendations by multidisciplinary teams (i.e., in tumor boards or cancer team meetings), where decisions are increasingly made for patients with cancer. It noted that comorbidity was not often considered in these decisions, but when they were, they were associated with failure to reach a treatment recommendation as well as guideline-discordant treatment. Furthermore, multidisciplinary team decisions were less likely to be implemented for patients with comorbidity (Stairmand et al. 2015). A review of chemotherapy use in patients with solid tumors (Lee et al. 2011) reported that comorbidity is associated with decreased chemotherapy receipt in 11 of 16 examined studies (with reported ORs ranging from 0.25 to 0.99), with no association reported in 4 studies. Two of four studies examining referral patterns showed that patients with comorbidity were less likely to even be referred to an oncologist. Most of these studies did not report survival outcomes, so it is unclear how decreased treatment affected survival. Moreover, it is unclear whether decreased use of chemotherapy resulted from physician decision to offer treatment, patient preferences, or other factors.

The benefit/risk ratio of cancer treatment is often most compelling in patients with curable malignancies. Patients with comorbidities are less likely to be offered and to receive curative-intent treatment for their cancer. Curative-intent treatments for solid tumor subtypes typically involve surgery and may additionally involve chemotherapy and radiotherapy; curative-intent therapies for hematologic malignancies typically involve chemotherapy and may require autologous or allogeneic stem cell transplant. Some illustrative examples of the impact of comorbidity on treatment selection and receipt are reviewed below; the available data are limited by variability in the definitions of comorbidity and the tools used to measure it. In general, comorbidity affects curative-intent treatment decisions independent of age but to a lesser extent than age itself.

Breast. In an analysis of the SEER-Medicare dataset, patients with early breast cancer and severe ("unstable") comorbidities are less likely to receive breast-conserving surgery (BCS) plus radiotherapy (RT) versus BCS alone or mastectomy, and this finding is independent of age; interestingly, patients with less severe ("stable") comorbidities were more likely to receive BCS + RT than those women with no

comorbidities (Yasmeen et al. 2013). The findings of CALGB 9343 (Hughes et al. 2013), indicating that adjuvant RT may be omitted in patients ≥70 years with early favorable-risk tumors, have not significantly changed overall practice patterns for these patients, and comorbidity continues to be associated with decreased receipt of adjuvant RT. (Chu et al. 2017) However, though age is associated with decreased receipt of adjuvant systemic therapy (chemotherapy and hormonal therapy) (Bouchardy et al. 2003), comorbidities do not seem to affect these decisions in most studies (Lash et al. 2003; Houterman et al. 2004).

Colorectal. Studies of curative-intent surgery for patients with colorectal cancer either show no association (Lemmens et al. 2005; Janssen-Heijnen et al. 2005) or an inverse association (Zhang et al. 2007) between increasing comorbidity and receipt of surgery. For rectal cancer, receipt of adjuvant RT is lower among patients with comorbidity (Janssen-Heijnen et al. 2005). Numerous studies confirm that receipt of adjuvant chemotherapy is lower for patients with comorbidity, independent of age (Etzioni et al. 2008; Khrizman et al. 2013). In SEER-Medicare data, the OR for receipt of chemotherapy is 0.38 for patients with the most comorbidity (CCI ≥2), compared to no comorbidity (CCI 0) (Schrag et al. 2001).

Lung. The presence of comorbidity is associated with lower resection rates in patients aged 60–79 with localized non-small cell lung cancer (NSCLC) (Janssen-Heijnen et al. 2005). However, age appears to be much more predictive of treatment receipt than comorbidity: in a study of >20,000 veterans ≥65 years, comorbidity was only weakly negatively associated with treatment receipt, and a fit patient aged 75–84 with no comorbidities was significantly less likely to receive surgery than a patient aged 65–74 with severe comorbidity (Wang et al. 2012). For limited small cell lung cancer, patients ≥70 with comorbidities are more likely to receive chemotherapy alone versus definitive chemoradiation, independent of age (Janssen-Heijnen et al. 2005).

Other solid tumors. In patients >75 years with localized prostate cancer, patients with comorbidities were less likely to receive radical prostatectomy and more likely to receive RT or hormonal therapies (Hall et al. 2005). In patients >70 years with ovarian cancer, increasing severity of comorbidity was associated with less use of surgery and standard chemotherapy (Jorgensen et al. 2012).

Hematologic malignancies. In studies of older adults with aggressive non-Hodgkin lymphoma (NHL), comorbidity was either not associated with receipt of curative-intent therapy (Lin et al. 2012) or inversely associated (although with less effect than increasing age) (Janssen-Heijnen et al. 2005). For patients with leukemia or being considered for hematopoietic stem cell transplant, a comorbidity index has been developed and validated (Hematopoietic Cell Transplantation-Comorbidity Index, HCT-CI) (ElSawy et al. 2015), with strong prognostic significance. It has been used to select intensity of leukemia treatment for older adults (Djunic et al. 2012) and is suggested to evaluate eligibility for transplant in addition to age (Sorror et al. 2014).

Comorbidities and Cancer Treatment Toxicity

A description of treatment tolerance and toxicity is difficult to distill from discussion of individual interactions between treatment and specific chronic conditions; for example, patients with renal insufficiency are likely to be at high risk from nephrotoxic chemotherapy, but are not necessarily at higher risk of toxicity from other therapies. However, a number of studies have examined the relationship between general measures of comorbidity and cancer treatment tolerance. In the abovementioned review of comorbidity and chemotherapy use in patients with solid tumors (Lee et al. 2011), five of seven studies examining chemotherapy toxicity demonstrated increased rates of grade 3–4 toxicity in patients with comorbidities; in three other studies, there were no differences in hospitalization rates or complications at 1 year between patients with and without comorbidities. Multiple other studies have indicated that comorbidity is associated with

increased toxicity from chemotherapy (Hall et al. 2005; Gronberg et al. 2010) or RT (Hamstra et al. 2013) or increased surgical complications (Dehal et al. 2013; van Gestel et al. 2013; Tomaszewski et al. 2014). However, other studies have found no increase in chemotherapy toxicity (Jehn et al. 2014; Gross et al. 2007; LoConte et al. 2010; Vickers et al. 2012) or adverse surgical (Peters et al. 2011; Lemmens et al. 2007) or RT (Peters et al. 2011; Cardia et al. 2011) outcomes. Moreover, patients with comorbidity benefit from treatment for their cancer in many of these studies, with further confirmation of benefit in propensity-matched cohorts (Gross et al. 2007; Bradley et al. 2014). Patients with more lethal cancers and comorbidities may gain more benefit than risk from aggressive antineoplastic therapy, even if elderly; on the other hand, patients may be over-treated if they have less aggressive malignancies, such as low-risk prostate cancer, and are more likely to die from non-cancer causes (Bradley et al. 2014).

For older patients with cancer, tools have been developed and validated to predict chemotherapy toxicity (Hurria et al. 2011a; Extermann et al. 2012). In the development cohort for the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score, 518 patients $\geq$70 years with hematologic and solid tumor malignancies were assessed at baseline with CGA, including comorbidity assessment with the CIRS-G, and then followed up to 6 months to measure incidence of grade 3–4 toxicity during chemotherapy (Extermann et al. 2012). CIRS-G was not associated with chemotherapy toxicity in this cohort and is not included in the final scoring tool. In the development of the Cancer and Aging Research Group (CARG) tool (Hurria et al. 2011a), 500 patients $\geq$65 years with solid tumor malignancies were assessed at baseline, including comorbidity evaluation with the OARS Physical Health survey; this was not associated with grade 3–5 toxicity from chemotherapy, but several items related to comorbidity are included in the final model: anemia, renal insufficiency, and poor hearing were all associated with increased toxicity in this cohort.

Impact of Cancer Treatment on Comorbidities

The impact of cancer treatment on comorbidities is obviously highly dependent on the individual comorbidities as well as the particular treatment regimen chosen. It is important to remember that for chemotherapy regimens in particular, the treatment encompasses not only the chemotherapeutic agents but a number of supportive care medications, increasing the risk of drug-drug and drug-disease interactions. Please refer to ▶ Chap. 20, "Pharmacology of Aging and Cancer" for additional discussion of these risks. For older adults, the impact of cancer treatment on the development or trajectory of geriatric syndromes (including dementia/cognitive impairment, frailty/functional impairment, and incontinence) is of particular interest.

Cognitive impairment. Postoperative delirium is common after cancer surgery; incidence in studies ranges from 11% to 50% (Zhu et al. 2017; Raats et al. 2015; Gallagher et al. 2014; Takeuchi et al. 2012). Although approximately 30–40% of cases are preventable, high-risk patients are often not identified and managed preoperatively, and delirium is often not recognized early, if at all (Korc-Grodzicki et al. 2015). Delirium has long-term consequences for the older patient, including persistent cognitive impairment and even progression to dementia, as well as significantly increased mortality (Inouye et al. 2014).

The subjective phenomenon of "chemo brain" has long been recognized by patients young and old, but the extent of objective impairment varies across studies (Ahles et al. 2012); patient-reported measures in patients with breast cancer who received adjuvant chemotherapy demonstrate significant impairment persisting to at least 6 months post-chemotherapy (Janelsins et al. 2016), and studies of childhood survivors of cancer indicate that cognitive issues can persist years after completion of treatment (Williams et al. 2016b). Hormone therapy, in particular androgen deprivation therapy (ADT) for prostate cancer, has also been associated with cognitive decline, particularly for visuomotor tasks (McGinty et al. 2014), and evidence suggests the risk of impairment increases

with increasing length of treatment (Gonzalez et al. 2015). However, not all studies have confirmed an association between ADT and cognitive decline (Alibhai et al. 2010).

It has long been recognized that RT to the brain, particularly whole-brain RT (WBRT), can cause significant cognitive impairment. Although modern RT techniques prevent most cases of acute brain injury and early-delayed impairment (1–6 months posttreatment), up to 90% of patients develop cognitive impairment >6 months post-treatment ("late-delayed brain injury") (Greene-Schloesser et al. 2012). This impairment, which includes progression to overt dementia, has significant interactions with and effects on quality of life (QoL) and functional status (Greene-Schloesser and Robbins 2012).

Functional impairment and frailty. Data on the effects of cancer treatment on functional status and emergence of frailty are very limited. Obviously, older patients may become functionally impaired after cancer surgery due to immobility, pain, delirium, or a combination of factors; increased age, pre-existing severe comorbidities, and frailty/sarcopenia increase the risk of postoperative functional decline and disability (Billmeier et al. 2013; Shen et al. 2017). The effects of chemotherapy on functional status and development of frailty are less clear; the implementation of longitudinal CGA measures over time throughout the treatment course in multiple ongoing studies will hopefully address this question. The use of ADT in older men with prostate cancer has been associated with falls and frailty (Bylow et al. 2011; Winters-Stone et al. 2017), presumably due to the decline in testosterone and subsequent changes in body composition such as muscle loss and gain of fat. These functional impairments can persist even after discontinuation of ADT (Moe et al. 2016).

Incontinence. Urinary incontinence impairs QoL and social functioning in older adults. Both prostatectomy and prostate irradiation cause high rates of urinary incontinence (Wallis et al. 2017). Urinary incontinence a year post-surgery is most prevalent in men who were obese and inactive (59%) compared to nonobese and physically active (16%) (Wolin et al. 2010). Incontinence can also result from treatment of rectal, gynecologic, or bladder cancers, particularly after pelvic surgery or irradiation, metastatic cancer to the spine causing spinal cord compression, or use of neurotoxic chemotherapies such as taxanes (Denlinger and Engstrom 2011; Shah-Khan and Shah 2008).

Conclusion

The interrelationships between age, comorbidity, cancer, and cancer treatment are complex and heterogeneous and not easily distilled for use in algorithmic approaches to the treatment of the older patient. However, this chapter has attempted to review what is known about these relationships and provide a general approach to the older patient with cancer and comorbidity. Patient preferences play a strong role in treatment decisions, and life expectancy should be estimated for every patient to assist in calculation of the risk/benefit ratio of treatment options, particularly for curative-intent therapies. Online tools such as the CARG and CRASH scores for chemotherapy toxicity can help further refine estimation of risk. In addition to considering the impact of treatment on the trajectory of chronic diseases in older patients, providers should also consider the potential impact on a subset of comorbid conditions particularly associated with aging: the geriatric syndromes, including frailty, cognitive impairment, and incontinence.

Many gaps in knowledge still exist regarding the impact of comorbidity in older adults with cancer. Measures of comorbidity vary widely across studies, and the best method for measuring it is unclear (Sarfati 2012). Many studies do not incorporate measures of comorbidity at all, leading to calls for standardized inclusion of estimation of comorbidity burden in clinical trials (Williams et al. 2016a). Common eligibility criteria in clinical trials limit enrollment of older adults with comorbidities, severely limiting the evidence base available for clinical decision-making. Inclusion of a more representative population in clinical trials, via relaxed eligibility criteria, and use of "practical" clinical trial design are two approaches to provide more generalizable

data (Kim et al. 2016). Ultimately, bridging these knowledge gaps is crucial to providing high-quality care for older patients with cancer.

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Biomarkers of Aging (With a Clinical Potential in Oncology)

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Joleen M. Hubbard

Contents

Abstract

Frailty is a result of underlying physiologic processes associated with aging that lead to poor functional reserve. With increasing degrees of frailty, the ability to recover from major stresses on the body such as cancer treatment becomes more difficult. Varying degrees of frailty can be subtle, which explains the difficulty of distinguishing which older adults will have excess toxicity from cancer therapy and ones will tolerate it well. Thus, a biomarker of aging would be a very useful tool to predict toxicity and functional decline with cancer treatment and guide treatment decisions for older patients.

Based on the large body of work in the field of aging research, several processes have emerged as hallmarks of the aging process. There is a decline of the lymphocyte component of the total leukocyte count. Systemic inflammation increases and likely contributes to age-related diseases. Telomere length decreases with cellular replication over time. Finally, repeated exposure to environmental stress results in cellular senescence. Researchers are now exploring biomarkers of these processes and their potential application in geriatric oncology. While they may not be pure aging biomarkers, they may be characterized as biomarkers of frailty that have the

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potential to identify patients at increased risk for adverse events, functional decline, and poorer survival related to cancer treatment. This chapter will discuss the characteristics of an aging biomarker, the various markers that have been investigated, and the evidence for the use of these biomarkers in older adults with cancer.

Keywords
Biological marker · Frailty · Inflammatory markers · Telomere length · Immunosenescence

Introduction

Frailty exists on a continuum from pre-frail to frail, eventually leading to disability. As a person progresses on this continuum, their functional reserve decreases, placing the patient at increased risk for poor outcomes after major physiologic stresses on the body such as injury, surgery, and cancer therapy. While older age is a risk factor for frailty, the development of frailty is not dependent on chronologic age. Frailty is a result of underlying physiologic processes leading to poor functional reserve, and measurement of these processes can give more of a sense of a person's biologic age.

Understanding a patient's biologic age is a large need in the field of oncology. Varying degrees of functional reserve among older cancer patients result in great heterogeneity in the ability of older adults to tolerate cancer treatment. Some older patients tolerate treatment well and derive as much benefit from treatment as younger patients, while others have increased rates of toxicity resulting in treatment reductions and/or cessation of treatment. This variation in treatment tolerance is likely a reflection of varying degrees of frailty among older patients, which is a known risk factor for poor tolerance of cancer treatment. A number of studies have shown that pre-frail and frail patients, identified by a geriatric assessment, are at increased risk of toxicity to cancer therapy (Extermann et al. 2012; Hurria et al. 2011; Cohen et al. 2016).

Currently, pre-frail and frail patients are identified by administering a geriatric assessment tool. There is international consensus emphasizing the importance of geriatric assessment in older adults, although there is a lack of consensus on which scale to use (Wildiers et al. 2014). Geriatric assessment tools have a moderate ability to predict toxicity; however, the lack of financial resources and expertise has limited the routine use of these tools in routine clinical practice in the United States. As the cancer incidence rises with the rapidly aging population, this will become an increasing problem.

Although useful for identifying frail patients, geriatric assessments do not give us a measure of the underlying physiologic mechanisms that contribute to frailty. There is a known phenotype associated with both aging and frailty, which includes cellular and systemic inflammation, shortened and/or dysfunctional telomeres, and a decrease in muscle mass. These factors are likely interconnected as part of an "inflammaging" process and may be candidates for easily measuring a patient's degree of frailty and, therefore, biologic age.

The Ideal Aging Biomarker

The American Federation for Aging provided guidelines on four characteristics of an ideal aging biomarker (Simm et al. 2008; Baker and Sprott 1988; Johnson 2006). The biomarker of aging should be associated with the following abilities:

1. Predict the rate of aging.
2. Monitor the process of aging, not the biology of a disease.
3. Be tested repeatedly without harming the individual.
4. Be able to be tested in both human and animal models.

The difficulty with identifying biomarkers of frailty in the oncology population is that there is a large interplay between the potential biomarkers, disease, and treatment. Patients may be frail

related to the disease itself. For instance, patients with widely metastatic disease have a high degree of systemic inflammation leading to anorexia, cachexia, and poor physical performance. In chemosensitive disease, treatment of these patients with systemic therapy can result in improvement of these processes. In addition, the treatment of the disease may contribute to frailty (Demaria et al. 2017; Bailur et al. 2017).

Since many processes related to aging and frailty contribute to diseases associated with aging, it is unlikely that we will find a pure biomarker of aging that is not affected by the underlying disease. However, these markers may be very useful as predictive markers of toxicity and/or functional decline from cancer therapy. These biomarkers could be used to predict adverse outcomes prior to initiating therapy and may be a useful guide during the treatment of the disease.

The Ideal Frailty Biomarker for Oncology

Given the interplay of biomarkers of frailty between the patient, the disease, and the treatment, it will be important to assess these markers over time to determine their ability to predict which patients are at risk. Biomarkers of frailty need to be tested in prospective clinical trials to determine the following:

1. Feasibility of rapid, repeated measurement before, during, and after treatment.
2. Correlation with toxicity (development of adverse events).
3. Correlation with adjustments in doses, withholding doses, or discontinuation of treatment.
4. Correlation with physical performance and functional decline.

Identifying frailty among cancer patients is extremely important for multiple reasons. First, it is important to recognize upfront which patients are at increased risk for toxicity and decreased functional decline with cancer treatment. This information helps guide the clinician and patient to make informed choices regarding the type and aggressiveness of cancer treatment that patient should pursue. Second, while on cancer treatment, it is important to recognize if frailty is developing and/or worsening, so that adjustments in doses and interventions such as physical therapy and nutritional support can be offered to prevent the transition into disability. Third, investigating the underlying biology is the identification of targets for the development of therapeutic and/or pharmacologic interventions.

Classes of Biomarkers of Aging

Cellular Markers of Inflammation

Increased age is associated with decreased cell-mediated immunity termed immunosenescence. In the peripheral blood, this manifests as an increase in myeloid cells and a decrease in lymphoid cells (Sieburg et al. 2006). In the general geriatric population, lymphopenia is considered to be a marker of frailty. In the general geriatric population, higher neutrophil and lower lymphocyte counts are associated with lower physical activity and poor muscular strength (Fernandez-Garrido et al. 2014).

Numerous studies have evaluated lymphopenia as a marker for outcomes in oncology patients. Lymphopenia is independently associated with both progression-free and overall survival in a variety of cancers (Ray-Coquard et al. 2009). Low lymphocyte counts may also be a predictor for hematologic toxicity. When measured prior to treatment, lymphopenia has been shown to be associated with higher levels of chemotherapy-induced neutropenia and febrile neutropenia (Blay et al. 1996; Ray-Coquard et al. 2003).

The exact mechanism is unknown, but there is a suggestion that early lymphoid precursors are the most sensitive to induction of differentiation in response to DNA damage (Wang et al. 2012). Regardless of the cause, lymphopenia is considered a marker of immunosenescence (Falandry et al. 2013; Pawelec and Solana 1997). Multiple studies have evaluated the

lymphocyte count in relation to other leukocytes and platelets as a marker of aging and/or frailty as well as a prognostic factor. The neutrophil-lymphocyte ratio (NLR), the lymphocyte-monocyte ratio (LMR), and the platelet-lymphocyte ratio (PLR) all have robust data showing an association with oncologic outcomes. Because these ratios can be derived from a complete blood count test routinely measured prior to treatment, they may be a readily accessible, easily measured biomarker.

Neutrophil-Lymphocyte Ratio (NLR)

A recent meta-analysis of 100 studies including 40,559 patients with solid tumors reported by Templeton et al. (2014a) evaluated the effect of the neutrophil-lymphocyte ratio (NLR) on cancer-specific and overall survival outcomes. The hazard ratio for overall survival among all tumor types and stages showed poorer outcomes for patients with a high NLR (cutoff 4.0) in terms of cancer-specific survival (HR 1.61, 95% CI = 1.36–1.91; $P < 0.001$), progression-free survival (HR 1.63, 95% CI = 1.39–1.91; $P < 0.001$), and overall survival (HR 1.81, 95% CI = 1.67–1.97; $P < 0.001$). These effects were consistent regardless of the disease subtype, site of disease, and stage of disease.

More recently, the relationship between frailty and ratios of leukocyte counts was evaluated in older adults with cancer (Nishijima et al. 2017). Using the Carolina Frailty Index (CFI), 133 patients who had a geriatric assessment were characterized as robust (54%), pre-frail (22%), and frail (24%). The CFI was positively correlated with the NLR ($r = 0.22$, $p = 0.025$). On multivariate analysis, those with an elevated NLR were more likely to be frail or pre-frail (OR 3.8, 95% CI = 1.1–12.8). Higher NLR was also significantly associated with instrumental activity of daily living (IADL) scores ($p = 0.040$) and a prolonged timed up and go (TUG) test ($p = 0.016$).

The relationship between the NLR both frailty and survival outcomes in these studies warrants further investigation to determine how best to utilize this information to guide cancer treatment for older adults.

Lymphocyte-Monocyte Ratio (LMR)

The aforementioned study reported by Nishijima et al. (2017) also evaluated the relationship between the LMR and frailty. The LMR was positively correlated with the IADL score ($r = 0.197$, $p = 0.046$). Patients with prolonged TUG tests also had a lower LMR ($p = 0.013$).

The LMR has also been shown to correlate with oncologic survival outcomes in multiple different malignancies. A meta-analysis involving 4260 patients with head and neck cancer demonstrated a significant associated with elevated LMR and improved DFS (HR 0.70; 95% CI 0.62–0.80) as well as improved OS (HR 0.5; 95% CI 0.44–0.57) (Tham et al. 2018). Another meta-analysis of 1795 patients with various stages of pancreatic cancer also demonstrated improved disease control DFS/RFS/TTP (HR =0.38, 95% CI: 0.15–0.95, $P = 0.04$) and OS (HR = 0.56, 95% CI: 0.38–0.83, $P = 0.004$) for those with an elevated LMR. These results were independent of ethnicity, surgical treatment, and cancer stage (Li et al. 2017).

The largest meta-analysis evaluating the relationship between LMR and non-hematologic solid tumors was reported by Nishijima et al. (2015). This analysis included 11,197 patients from 29 studies. Patients that had a LMR <3.0 had poorer cancer-specific survival (HR, 1.73; 95% CI: 1.55–1.93; $P < 0.001$), disease-free survival (HR, 1.56; 95% CI: 1.31–1.86; $P < 0.001$), and overall survival (HR, 1.56; 95% CI: 1.27–1.91; $P < 0.001$). The LMR was prognostic for survival for multiple tumor types and stages of disease.

Platelet-Lymphocyte Ratio (PLR)

Templeton et al. (2014b) also performed a large meta-analysis investigating the prognostic role of the PLR in 12,574 patients with solid tumor malignancies. Among the 12 studies with a dichotomous definition for elevated PLR (median cutoff 185), the hazard ratio for PLR on overall survival was stronger for patients with metastatic disease (HR 2.0; 95% CI: 1.6–2.7) than patients with nonmetastatic disease (HR 1.5; 95% CI: 1.0–2.2). Within the eight studies that categorized PLR into three groups (<150/150–300/>300),

the association with poorer overall survival was significant for metastatic disease (HR 1.6; 95% CI: 1.1–2.4) but nonsignificant for early-stage disease (HR 1.0; 95% CI: 0.8–1.3). The negative prognostic association for PLR was significant for colorectal, hepatocellular, gastroesophageal, ovarian, and pancreatic carcinomas in the dichotomous group and for colorectal cancers among the studies that categorized PLR into three groups. Based on these results, PLR may also provide prognostic information for older adults with cancer, especially for those with metastatic disease.

Circulating Markers of Systemic Inflammation

Levels of circulating pro-inflammatory mediators such as IL-6 and TNF-alpha D-dimer, and plasminogen activator inhibitor (PAI)-1, increase with age (Ershler et al. 1993; Fagiolo et al. 1993; Sindermann et al. 1993). These markers are thought to accelerate the aging process and exacerbate multiple age-related diseases (Bruunsgaard et al. 2001; Franceschi et al. 2007; Vasto et al. 2007). There is a co-stimulatory affect between markers of inflammation and pro-thrombotic factors. Cytokines such as TNF-α and IL-6 stimulate production of pro-thrombotic factors such as PAI-1 and fibrinogen (Kanapuru and Ershler 2009). In turn, D-dimer, a marker of the clotting process, has been shown to induce synthesis and release cytokines IL-1B, IL-6, and PAI-1 (Robson et al. 1994). Likewise, when vascular cell adhesion molecule (VCAM) is exposed to inflammatory markers TNF-α and IL-1B, it is cleaved to soluble (s)-VCAM, which is elevated in patients with age-related diseases (Carter and Wicks 2001).

Several studies have shown that inflammatory mediators correlate with measures of physical function and are elevated to a greater degree in frail patients than in age-matched, non-frail controls (Cesari et al. 2004; Ferrucci et al. 2002a; Hubbard et al. 2009; Leng et al. 2007; Pieper et al. 2000; Walston et al. 2002; Yao et al. 2011; Collerton et al. 2012). A study of 110 patients >75 years demonstrated that a combination of inflammatory markers (TNF-α, IL-6, CRP) and low albumin correlated with lower physical function scores, independent of age, sex, body mass index (BMI), smoking status, number of comorbidities, and number of medications (Hubbard et al. 2009).

In the general geriatric population, elevated chronic inflammatory and pro-coagulant markers predict functional decline (Cohen et al. 2003; De Martinis et al. 2006; de Saint-Hubert et al. 2011; Ferrucci et al. 1999, 2002b; Huffman et al. 2011; Puts et al. 2005; Reuben et al. 2002). An analysis of disabled women ≥65 years showed higher IL-6 levels at baseline were associated with higher levels of functional decline including decreased mobility, activities of daily living deficits, increased walking limitations, and decreased walking speed, compared to women with low IL-6 levels (Ferrucci et al. 2002a). These markers also correlate with functional decline after hospitalization and postoperative complications from oncologic surgery (de Saint-Hubert et al. 2011; Ronning et al. 2010).

Markers of chronic inflammation and coagulation are also associated with all-cause mortality risk in the elderly. In a population of community-dwelling adults (mean age 78), soluble (s)-VCAM was independently correlated with poorer functional status at baseline (HR 1.2, $p = 0.002$) (Huffman et al. 2011). After adjusting for functional status, demographic factors, and comorbidities, higher plasma s-VCAM, D-dimer, and IL-6 concentrations were independently related to mortality within 4 years. Inflammatory mediators can have greater predictive ability among patients without baseline functional impairments, suggesting they may identify pre-frail patients that may not otherwise have been identified without extensive geriatric assessment testing (Pieper et al. 2000; Cohen et al. 2003; Reuben et al. 2002).

Circulating Inflammatory Markers in Oncologic Studies

Markers of systemic inflammation correlate with physical function, functional decline, and mortality in the general geriatric population. These circulating inflammatory markers are felt to reflect

underlying biologic aging and frailty. Multiple studies have evaluated these biomarkers' association with frailty, toxicity, and survival outcomes for cancer patients.

Systemic inflammatory markers have been shown to correlate with frailty in cancer patients. Browers et al. (2015) measured systemic markers of inflammation felt to be related to aging and frailty including telomere length, interleukin-6 (IL-6), regulated upon activation normal T cell expressed and secreted (RANTES), monocyte chemotactic protein 1 (MCP-1), and insulin-like growth factor 1 (IGF-1) among young ($n = 42$) and older ($n = 162$) patients with nonmetastatic breast cancer. The biomarker levels were then correlated with patients' Leuven Oncogeriatric Frailty Score (LOFS). The investigators found that IL-6 levels correlated with frailty among older patients. IL-6, telomere length, IGF-1, and MCP-1 correlated with age.

Multiple studies have shown elevated inflammatory markers are associated with a poorer prognosis among oncology patients. For example, higher circulating IL-6 levels have been shown to correlate with poorer survival in patients with hormone-refractory metastatic breast cancer (Bachelot et al. 2003). Likewise, elevated C-reactive protein (CRP) is associated with worse survival in multiple urologic cancers, including renal, bladder, and prostate cancers as well as colorectal and gastroesophageal cancers (Saito and Kihara 2011; Roxburgh and McMillan 2010).

Investigators have shown that systemic inflammation plays a major role in the decline of cancer patients, especially in terms of nutrition and physical function. The systemic inflammation-based Glasgow Prognostic Score (GPS), based on levels of CRP and hypoalbuminemia, was derived as a surrogate of systemic inflammatory status. Data from 8333 patients from 28 studies in patients with operable cancer demonstrate the GPS was a predictor of survival independent of stage, pathological features, and comorbidity (HR range 1.5–5.1) (McMillan 2013). Similar prognostic ability of the GPS was seen in 11 studies involving 1504 patients with metastatic cancer. In a study of 56 patients with advanced-stage colorectal cancer, the GPS not only predicted survival, but it also predicted toxicity to chemotherapy (Sharma et al. 2008). A higher GPS score correlated with higher grade 2/3 diarrhea and higher incidence of grade 2/3 toxicity compared to those with lower scores ($p = 0.023$ and 0.015, respectively).

One argument against using inflammatory mediators has been that they may reflect other underlying processes such as the response to surgical intervention and the underlying cancer itself. If used in the adjuvant setting, circulating acute phase reactants from the surgery itself should be resolved 6–8 weeks postoperatively (Baigrie et al. 1992; Wirtz et al. 2000). In addition, multiple studies have associated inflammatory markers with poorer prognosis and toxicity, independent of tumor stage (Bachelot et al. 2003; Laird et al. 2013).

Although chronic inflammatory mediators have not been established as true aging biomarkers, the fact that they correlate with measures of physical status, functional decline, and mortality in the older adult population suggests they may reflect underlying biologic processes that could predict a patient's risk of toxicity from cancer treatment and, therefore, their ability to tolerate it. The levels of inflammatory mediators can be measured with ELISA assays on plasma samples collected during blood draws routinely done for cancer management. Therefore, the measurement of these levels could become an efficient way of providing the oncologist insight into potential tolerance of cancer therapy as well as prognosis and provide guidance as to the most appropriate regimens and doses for the older cancer patient.

Telomere Shortening

Telomeres are DNA protein complexes capping the end of chromosomes that provide chromosomal stability and prevent DNA degradation and recombination. Telomeres shorten with each cell division, eventually leading to cellular senescence and apoptosis (de Lange 2002). Cawthon et al. (2003) reported a pivotal study of 143 patients >60 years of age which showed that shorter telomere length correlated with both

age and higher mortality. Subsequent studies have not shown a consistent correlation with telomere length and mortality, but several have shown positive association with telomere length and better health in older age (Atzmon et al. 2010; Bekaert et al. 2005; Njajou et al. 2009; Pallis 2013). Various lifestyle factors, including obesity, smoking, and marital status, also affect telomere length (Mishra et al. 2012).

Because there appears to be associations with telomere length and health status, investigators have studied telomere length as a potential biomarker among cancer patients. Willeit et al. (2010) evaluated telomere length of 787 individuals. Shorter telomere length was associated with developing cancer over the course of 10 years (HR 1.60; 95% CI: 1.30–1.98; $P < 0.001$). The shortest telomere length also correlated with higher cancer mortality (HR 2.13; 95% CI: 1.58–2.86; $P < 0.001$). There have been reports of shortened telomere length and poorer prognosis in a number of different cancers including colorectal, breast, lung, and sarcoma (Pallis et al. 2014). However, not all studies consistently show a correlation between telomere length and cancer incidence and/or mortality (Pooley et al. 2010; Prescott et al. 2012).

It does not appear that telomere length is associated with frailty as measured by geriatric assessment. A study reported by Falci et al. (2013) evaluated telomerase activity and telomere length of cancer patients $\geq$70 years of age ($n = 52$) compared with 39 age-matched controls that underwent a geriatric assessment. Telomere length was significantly shorter in cancer patients, but only correlated with age in non-cancer patients. They did not find that telomere length was associated with geriatric assessment scores. Several other studies have not found a correlation between measures of frailty and telomere length in the general population (Lorenzi et al. 2018; Saum et al. 2014).

Telomere length does not appear to be associated with frailty, which would potentially predict an increased risk for toxicity. There are a few studies on telomere length and toxicity. One study in colorectal cancer did find an association of telomere length with hematologic toxicity and mucositis in patients receiving 5-fluorouracil (Garg et al. 2012). Among breast cancer patients receiving paclitaxel, those with a higher percentage of critically shortened telomeres had higher toxicity, but there was no correlation with toxicity and average telomere length (Quintela-Fandino et al. 2017).

While telomere length plays a role in the aging process, the conflicting results in studies related to cancer incidence and mortality make the role of this biomarker in geriatric oncology unclear. In addition, there is not universal agreement on the method of measuring of telomere length, which can be complex (shortest telomere length by fluorescent in situ hybridization, quantitative real-time polymerase chain reaction [qPCR], measuring cleaved fragments). Further studies are needed to determine if telomere length can consistently predict outcomes for cancer patients.

Cellular Senescence Markers

Senescent cells accumulate with age as a reaction to lifelong cellular stress (Ressler et al. 2006; Liu et al. 2009). Although senescent cells are not mitotically active, they acquire a senescence-associated secretory phenotype (SASP), with increased production of proteins involved in chronic inflammation and coagulation, very similar to the markers associated with poorer physical function and mortality in the elderly (Campisi 2005; Coppe et al. 2008). p16INK4a is considered a marker of cellular senescence and is felt to be a potential biomarker for aging.

The p16INK4a gene is a cell cycle regulator that inhibits downstream activation of cyclin-dependent kinases 4/6 leading to permanent cell cycle arrest, otherwise known as cellular senescence (Romagosa et al. 2011). p16INK4a is activated during cellular stress responses and considered a tumor suppressor gene. Circulating levels of p16INK4a can be measured in T lymphocytes by qPCR.

p16INK4a age levels increase with age and age-related diseases (Lawrence et al. 2018; Tsygankov et al. 2009). Higher levels of p16INK4a expression in T lymphocytes are seen

with lifestyle factors such as inactivity and tobacco use (Song et al. 2010). p16INK4a levels appear to be associated with frailty in the general geriatric population. In a small study of older women ($n = 11$) in a resistance training program, higher levels of p16INK4a-positive cells in adipose tissue were associated with poorer grip strength, 400-meter walk time, gait speed, and their perception of mobility (Justice et al. 2017). Waaijer et al. (2017) found a stronger association of p16INK4a levels with functional measures than with age.

Transgenic mouse models allow researchers to track and eliminate senescent cells. After exposure to a cellular senescence-inducing agent such as chemotherapy, Demaria et al. (2017) showed senescent cells in mice contribute to local and systemic inflammation leading to worsening side effects, and clearing these cells reduces those effects. They also found that humans with increased senescent marker expression in T cells prior to receiving chemotherapy had a greater degree of chemotherapy-induced fatigue. These results suggest that markers of senescence may be able to predict greater toxicity to cancer treatment.

Importantly, chemotherapy may also affect p16INK4a expression in patients exposed to chemotherapy. In a study of breast cancer patients undergoing adjuvant anthracycline-based chemotherapy, chemotherapy exposures were associated with an increase in p16INK4a expression that would be found with 10.4 years of aging (Sanoff et al. 2014). Therefore, this biomarker may also predict accelerated aging in cancer survivors.

Discussion

It is likely that all of the aforementioned potential markers of aging and/or frailty are interrelated. For instance, telomere shortening and the resultant dysfunction lead to cellular senescence (Wang et al. 2012). Cellular senescence is felt to be an underlying process contributing to the increase in inflammation associated with functional decline and mortality in the elderly (Franceschi et al. 2007; De Martinis et al. 2006; Freund et al. 2010). Inflammation can lead to impaired lymphopoiesis (Wang et al. 2012). Systemic inflammation is also associated with sarcopenia, which can result in a more sedentary lifestyle that is also associated with shortened telomeres (Mishra et al. 2012).

Regardless of the underlying process that set off the interrelated processes associated with biologic aging, further study is needed to determine which markers are the most easily measured, low burden to patient and the financial system, and the most reliable at identifying frail patients vulnerable to the toxicities from cancer treatment. This research will also provide valuable information on the underlying biologic mechanisms contributing to increased toxicity and poorer survival outcomes. Ultimately, identifying the underlying mechanisms of frailty leaves the potential for pharmacologic interventions that may improve the tolerability of cancer treatment for frail patients.

Cross-References

- Aging and Cancer Biology
- Cellular Senescence and Tumor Promotion
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Frailty in Cancer Patients
- Geriatric Screening in Cancer Patients
- Immunosenescence and Cancer Immunotherapy at Old Age: Basics

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Part IV

Geriatric Assessment and Management in Oncology

William Dale

Geriatric Screening in Cancer Patients 24

Lore Decoster and Cindy Kenis

Contents

Abstract

Cancer is primarily a disease of older persons. This older population with cancer is heterogeneous with respect to overall health status due to differences in the aging process. The performance of a multidimensional geriatric assessment is recommended in older patients with cancer to inventory health problems and tailor geriatric interventions and treatment decisions accordingly. This strategy however requires

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resources and may not be necessary in all older patients with cancer. Therefore the use of geriatric screening tools is proposed in order to identify those patients who would benefit from further evaluation by geriatric assessment and subsequent multidisciplinary approach. Several screening tools have been studied in geriatric oncology with different performance for various parameters such as sensitivity and specificity for detecting an impaired geriatric assessment and prognostic and predictive value for various outcome measures, depending on the setting. In clinical practice, the preferred screening tool may depend on the clinical situation. If the result is abnormal, a screening tool should always be followed by a geriatric assessment and subsequent multidisciplinary approach.

Keywords
Screening tools · Geriatric assessment · Elderly · Cancer

Introduction

Treatment decisions for older patients with cancer are complex. Because of variations in the aging process, the overall health status of this older population with cancer is very heterogeneous with differences in comorbidities, functional status, geriatric syndromes, and socioeconomic aspects resulting in decreased physical reserve. In addition, cancer and its treatment may further decrease this physical reserve. Chronological age is a poor descriptor of this process, and the gold standard for its evaluation is a geriatric assessment (GA) (Puts et al. 2012; Wildiers et al. 2014). A GA is a multidimensional, interdisciplinary diagnostic process to determine an older person's psychosocial, functional, cognitive, and nutritional health status in order to develop a coordinated and integrated plan for treatment and follow-up. The performance of GA in older patients with cancer has shown to identify previously unknown health problems, predict treatment-related toxicity and oncological outcomes including overall survival, and influence cancer treatment decisions. In addition GA can be followed by GA-based recommendations and interventions in order to possibly improve outcome parameters. Implementing the performance of a GA in all older patients with cancer is however resource-intensive, which ultimately limits its widespread use, and not necessary in all patients. Therefore the use of geriatric screening tools has been proposed to identify patients in need of GA and multidisciplinary approach (Decoster et al. 2015; Hamaker et al. 2012).

Definition of a Screening Tool

A screening tool in older patients with cancer is a brief assessment, conducted to help the clinician to identify those patients in need of further evaluation by GA and subsequent GA-based recommendations and interventions and follow-up. A GA assesses multiple geriatric domains such as social support, functional status (FS), falls, cognition, mood, nutrition, comorbidities, and polypharmacy. A screening tool typically assesses only a few domains from the GA or each of the domains superficially.

Screening tools might also have prognostic/predictive value for important outcome measures such as treatment-related toxicity, functional decline, and overall survival (OS).

Screening tools should be simple and take a few minutes, while GA takes much longer. High sensitivity and negative predictive value (NPV) are the most important characteristics for screening tools in order to identify all patients at risk for adverse outcomes. In addition, a high specificity is of interest in order to limit the number of fit patients who unnecessarily undergo GA.

Screening Tools in Older Patients with Cancer

The International Society of Geriatric Oncology (SIOG) provided a consensus statement to recommend the use of screening tools for older patients with cancer who should be further assessed by GA (Decoster et al. 2015).

A variety of screening tools have been investigated in older patients with cancer with the G8 and Vulnerable Elders Survey-13 (VES-13) as the most widely studied. Screening tools are available at www.siog.org.

Most screening tools were compared to geriatric assessment (GA) for sensitivity and specificity, although the geriatric domains and tools used in the GA as well as the cutoff for abnormal GA varied between different trials making comparison difficult. In addition many screening tools were also compared to different outcome measures including FS, treatment-related toxicity, and OS. There are a variety of benefits and challenges with each screening tool, which must be weighed against one another.

G8

The G8 is an eight-item screening tool, specifically developed for older patients with cancer (Bellera et al. 2012). The G8 covers a number of domains from the GA including functional capacity, health, nutritional status, and cognitive impairment as well as self-rated health. The maximum total score for the G8 is 17, and a score of 14 or lower is considered abnormal. The G8 can be administered by any health-care professional and takes about 5 min to complete.

The G8 is one of the most sensitive screening tools (sensitivity ranging from 65% to 92%); however, it has only modest specificity (range 3–75%) (Decoster et al. 2015). The G8 has also been validated in a population of older patients with hematological malignancies where a cutoff of $\leq$14 resulted in a sensitivity of 89% and a specificity of 100% (Velghe et al. 2014).

Attempts to improve the G8 have been made. An IADL-modified G8 with replacement of the G8 neuropsychological item by the four-item IADL score leads to a more specific test than the original G8 (specificity of 67% vs. 65%, $p < 0.05$), while sensitivity was maintained (77% vs. 76%, $p = 0.53$) (Petit-Monéger et al. 2016). In a second study, a modified G8 was developed including six independent predictors for abnormal G8: weight loss, cognition/mood, performance status, health status, polypharmacy ($\geq$6 medications per day), and history of heart failure/coronary heart disease. This modified G8 demonstrated a sensitivity of 89% and a specificity of 79% at the optimized cutoff of $\geq$6/35, and its performance was homogeneous across tumor subtypes (Martinez-Tapia et al. 2016). Both modified G8 tools should be further evaluated within the older population with cancer.

G8 was also compared to different outcome measures. The tool showed high sensitivity and NPV for functional decline within 3 months of cancer treatment decision but low specificity (Kenis et al. 2014). In various cancers, G8 was predictive for chemotherapy-related toxicity, but this was not observed in hematological malignancies (Dubruille et al. 2013; Stokoe et al. 2012). Finally G8 was prognostic for OS in two studies in various cancer types but not in hematological malignancies (Dubruille et al. 2013; Kenis et al. 2014; Liuu et al. 2012).

Vulnerable Elders Survey (VES)-13

The VES-13 is a 13-item self-administered tool developed for identifying older people in the community at an increased risk of functional decline or death over 2 years (Saliba et al. 2001). The VES-13 includes functional capacity, self-reported health, and age. The maximum total score is 10 with a score of $\geq$3 considered abnormal, and it takes approximately 5 min to complete. Patients 85 or older score three points based on their age and are therefore at the cutoff value only because of age. In older persons in the community, abnormal VES-13 was associated with functional decline, OS, and health outcomes (Min et al. 2009; Saliba et al. 2001).

Although self-completion may be an asset because the patient can perform the screening before his/her appointment, this may also be a disadvantage. Patients may over- or underestimate their own health status, and self-completion may sometimes be troublesome because of a low level of education, cognitive impairment, or language barrier. In a study in older patients with breast cancer, more than one third was unable to

complete VES-13 autonomously (Monfardini et al. 2010).

In older patients with cancer, sensitivity of VES-13 ranged from 39% to 88% and specificity from 62% to 100% (Decoster et al. 2015). When compared with subparts of GA, VES-13 showed a high sensitivity for FS but not for comorbidity.

In two studies comparing G8 with VES-13, the G8 was significantly more sensitive (Pottel et al. 2012; Soubeyran et al. 2014).

In various cancers, VES-13 was predictive for the occurrence of severe chemotherapy-related toxicity (Stokoe et al. 2012), and in a study in gastrointestinal cancers treated with chemotherapy, VES-13 was significantly correlated with OS (Kitamura et al. 2013).

Flemish Version of the Triage Risk Screening Tool (fTRST)

The triage risk screening tool (TRST) was developed to identify older patients at risk for failed discharge home from the emergency department (Meldon et al. 2003). The fTRST is a modified version of the TRST developed for older persons on non-geriatric hospital departments. The tool is composed of five yes/no questions, and a score of $\geq$2 is considered as at risk. The fTRST is a very short tool, which takes only 2 min to complete.

In older patients with cancer, the fTRST demonstrated a sensitivity of 64–67% with a specificity of 80–100% when using the validated cutoff of $\geq$2. When lowering the cutoff to $\geq$1, the sensitivity was increased to 91% but at the cost of lower specificity (42–50%) (Decoster et al. 2015).

In two direct comparisons with the G8, the fTRST was equally sensitive (Kenis et al. 2009, 2014).

fTRST was predictive for functional decline and prognostic for OS for both cutoff scores (Kenis et al. 2014).

Groningen Frailty Indicator (GFI)

The GFI is a 15-item questionnaire addressing various domains. It was developed in people aged 65 years and over including hospital inpatients, nursing home residents, and community-dwelling elderly (Steverink et al. 2001). A score of $\geq$4 indicates a risk for physical, social, and/or psychological impairment. In community-dwelling elderly, an abnormal GFI correlated more strongly with a decline in self-management abilities than chronological age (Schuurmans et al. 2004).

In older patients with cancer, the sensitivity to detect abnormal GA ranged from 39% to 66% and specificity from 86% to 87% (Decoster et al. 2015). In direct comparisons, both the G8 and the VES-13 were more sensitive than the GFI (Baitar et al. 2013; Kellen et al. 2010; Kenis et al. 2009).

In two studies in patients treated with chemotherapy, the GFI correlated with OS (Aaldriks et al. 2011, 2013).

Study of Osteoporotic Fractures (SOF) Index

The SOF index is a three-item tool designed to measure pre-frailty and frailty. Patients presenting one of the items were considered to be in a pre-frailty status, and patients with more than one item were considered frail.

In older men and women without cancer, a score of two or more was associated with higher risk of recurrent falls, disability, fractures, and death (Ensrud et al. 2008, 2009).

In various cancer patients, the SOF index demonstrated a sensitivity of 89% and a specificity of 81% when compared to GA (Decoster et al. 2015).

Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

KPS and ECOG-PS are tools frequently used by oncologists to classify the performance status of their patients (Karnofsky and Burchenal 1949; Oken et al. 1982).

When compared to the GA, the KPS resulted in a sensitivity and a specificity of, respectively, 29% and 44% for a cutoff value of $<$80 and 78% and 91% for a cutoff value of $\leq$80 (Decoster et al. 2015).

The ECOG-PS on the other hand resulted in a sensitivity of 94% and a specificity of 55% at a cutoff of 1 (Decoster et al. 2015).

Fried Frailty Criteria of Physical Frailty Phenotype

The Fried frailty criteria include five items: weight loss, handgrip strength, gait speed, exhaustion, and physical performance. A score of ≥ 3 indicates "frailty."

In the general population, the physical frailty phenotype predicts the risk of falls, disability, fracture, and death (Ensrud et al. 2008, 2009).

When compared to the GA, the Fried frailty criteria resulted in sensitivity and specificity ranging, respectively, from 37% to 87% and from 49% to 86% (Decoster et al. 2015). In subgroup analysis, wide variations in specificity were observed in different tumor types: for example, 60% in early breast cancer versus 19% in early gastrointestinal cancer (Kellen et al. 2010).

Barber Questionnaire

The Barber questionnaire was developed to identify older persons at risk for dependency in the community (Barber et al. 1980). It consists of nine yes/no questions, and patients with a score of ≥ 1 are considered candidates for further evaluation through GA.

In various cancers, the Barber questionnaire presented a sensitivity of 74% and a specificity of 30% to detect an abnormal GA (Decoster et al. 2015). In a breast cancer population, the sensitivity was lower at 59%, but the specificity was higher at 79% (Molina-Garrido and Guillen-Ponce 2011).

Identification of Seniors at Risk (ISAR)

The ISAR is a six-item, self-administered tool developed for the emergency department (McCusker et al. 1998). A score of two or more categorizes patients as at risk for adverse outcome.

For older patients presenting at the emergency department, ISAR correlates with baseline functional impairment and with functional decline at 6 months (McCusker et al. 1998).

In older patients with cancer, sensitivity and specificity were 70% and 10%, respectively, to detect abnormal GA (Decoster et al. 2015).

Oncogeriatric Screen (OGS)

The OGS is a screening tool developed for oncology patients aged 75 years or over (Valéro et al. 2011). It consists of ten yes/no questions exploring five items (autonomy, malnutrition, depression, cognition, and comorbidity). Patients are considered in need of further evaluation through GA if at least one response for an item is positive. The OGS is a tool to be filled in by the treating physician.

In a study in various cancers, patients presented with one to three risks out of the five items were considered "vulnerable," and patients with four or five risks were considered "frail" using the Balducci classification ("fit," "vulnerable," and "frail") (Balducci and Extermann 2000). In this trial the OGS demonstrated a sensitivity of 88% and a specificity of 44% (Valéro et al. 2011).

Abbreviated Comprehensive Geriatric Assessment (aCGA)

The aCGA is a screening tool developed in older patients with cancer and consists of the 15 items of the full GA that correlated the most with the findings of the GA (Overcash et al. 2005, 2006). It takes approximately 5 min to complete the aCGA.

The aCGA has a sensitivity of 51% and a specificity of 97% when compared to the full GA (Decoster et al. 2015). The sensitivity was high for functional impairment (97% for activities of daily living (ADL) and 92% for instrumental activities of daily living (IADL)) but low for cognitive impairment (23%) (Kellen et al. 2010).

Gerhematolim

Gerhematolim is a screening tool developed for older patients with hematological malignancies (Fargeas et al. 2009a). It is composed of 27 questions and biological data.

In a study in hematological malignancies, it resulted in a sensitivity of 95% and a specificity of 87% compared with GA (Fargeas et al. 2009b).

Senior Adult Oncology Program 2 (SAOP2)

The SAOP2 screening tool was developed for older patients with cancer to determine when a multidisciplinary approach was indicated (Extermann et al. 2009).

In a small group of patients with various cancers, the tool demonstrated a very high sensitivity of 100% but a low specificity of 40%. Of note, specificity in this trial was defined as impairment in the same domain as the screening question.

Functional Tests as Screening Tool

Different functional tests have also been investigated as screening tools to identify patients at risk of adverse outcome who might benefit from GA.

The first is the physical performance test (PPT), which was designed in older outpatients (Reuben and Siu 1990). It is an objective measure of physical function based on seven timed items. Each item was scored on a five-point Likert scale (0–4) with the best score being 28. Patients were classified in three classes: no health impairment (PPR $>$ 20), moderate impairment (10 $<$ PPT $<$ 21), and severe impairment (PPT $<$ 11). The PPT takes approximately 5 min. When compared to the KPS, the PPT seemed to be a more accurate measure of impairment in older cancer patients with 83% of patients with a KPS between 60% and 80% demonstrating no health impairment according to the PPT (Terret et al. 2003).

The handgrip test measures the maximal strength of the dominant hand using a hydraulic hand dynamometer. In the general older population, handgrip strength is predictive for functional decline (Garcia-Pena et al. 2013). The result of this test in older patients with cancer was significantly higher in fit patients and lower in frail patients according to both the impression of the oncologist and the VES-13 (Servent et al. 2012). In older patients with cancer, the handgrip test was significantly associated with OS (Kanesvaran et al. 2011).

The timed up and go (TUG) is a test of balance and requires a person to stand up, walk 3 m, turn, walk back, and sit down. The time to complete the test is correlated with functional mobility in hospitalized older persons (Podsiadlo and Richardson 1991). In a cohort of older patients undergoing surgery for solid tumors, the TUG was as predictive as the GA in identifying patients at high risk of complications (Huisman et al. 2014).

Use of Screening Tools in Daily Practice

In a busy oncology practice, SIOG recommended to incorporate a geriatric screening tool in the routine assessment of all older patients with cancer in order to identify patients in need of further evaluation by GA (Decoster et al. 2015). No particular screening tool was recommended but rather left to the discretion of the professional health-care provider to choose the tool that fits best with their practice model and patient population. The choice of the tool may therefore depend on different factors such as ease of use, local experience and preferences, available time, personnel to perform the test, and accuracy of the test in the setting. However it was clearly stated that screening tools should not replace GA and an abnormal result on the screening tool should always be followed by GA in order to set up a multidisciplinary care plan for tailored geriatric interventions and follow-up.

Discussion

The management of older patients with cancer is a major public health challenge due to the heterogeneity of this population with regard to social

status, functional capacities, mental status, nutrition, comorbidities, and polypharmacy. Chronological age and clinical judgment are not effective to identify fit from unfit patients.

The gold standard to obtain a complete image of the global health of the older patient remains the performance of GA, which may lead to GA-based recommendations and interventions and treatment adaptations (Wildiers et al. 2014). However although the performance of such a lengthy GA should be considered as time well spent, it is not necessary in all older patients with cancer.

For this reason a two-step approach has been proposed by the recommendation guideline of SIOG in which patients are first screened by means of a geriatric screening tool and, if the result is abnormal, are evaluated by GA (Decoster et al. 2015). It is important to realize that although we have a large amount of screening performance data, screening tools should never replace GA because such an assessment will give more information on the global health status of the patient, will correctly identify the problems present, and allow tailored interventions.

The use of screening tools in geriatric oncology does have some limitations such as the following: (1) the minimum age (65 or 70) at which to start applying these tools is unclear with both age cutoffs used in clinical studies, (2) screening tools do not identify the precise geriatric problem in contrary to GA and as a consequence cannot trigger tailored recommendations and interventions and follow-up, and (3) for centers that do not have access to geriatric expertise, an abnormal result on the screening tool should be followed by a referral to a geriatric team outside the center and may thus cause delays in treatment decision-making and planning, but on the other hand, a normal result on the screening tool may reassure the treating physician that the patient will likely not have an abnormal GA.

Many different screening tools have been studied in older patients with cancer, and some of them were specifically developed for the older population with cancer (G8, OGS, aCGA, SAOP2, Gerhematolim). The two most studied screening tools in older patients with cancer are G8 and VES-13, of which the G8 data are the most robust (extensively studied, high sensitivity with acceptable specificity, and prognostic/predictive for important outcome measures). However, the performance of different screening tools may depend on the setting, and the preferred screening tool may depend on the clinical situation. For that reason, SIOG did not recommend or discourage a specific screening tool (Decoster et al. 2015). The choice of screening tools is thus left to the treating geriatric oncology team based on the local expertise and situation; however preference should go to tools, which are extensively studied and demonstrated high sensitivity.

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Comprehensive Geriatric Assessment (CGA) for Cancer Patients

25

Koshy Alexander and Beatriz Korc-Grodzicki

Contents

Abstract

Chronologic age alone is a poor descriptor of heterogeneity in the aging process and is an inadequate indicator to determine responses among older patients to cancer treatment. Geriatric conditions such as functional and cognitive impairments are frequently unrecognized or inadequately addressed in older adults. Identifying geriatric conditions by performing a geriatric assessment can help clinicians manage these conditions and prevent or delay their complications. A comprehensive geriatric assessment (CGA) includes evaluation of an older individual's functional status, comorbid medical conditions, cognition, nutritional status, psychological state, and social support, as well as a review of the patient's medications. Multiple studies have shown the benefits of utilization of CGA in older cancer patients.

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Administering a CGA may not be practical in all clinical settings. Screening tools may be considered initially keeping in mind that they do not replace CGA. If abnormal, screening should be followed by CGA and guided multidisciplinary interventions. This chapter will describe the CGA domains, the most commonly used assessment tools, as well as the benefits of performing such assessments in the older cancer patients.

Keywords
Geriatric assessment · Physiologic age

Introduction

Geriatric conditions such as functional and cognitive impairments are frequently unrecognized or inadequately addressed in older adults. Identifying geriatric conditions by performing a proper assessment can help clinicians manage these conditions and prevent or delay their complications. Comprehensive geriatric assessment (CGA) involves the evaluation of the physical, psychosocial, and environmental factors that impact the well-being of older individuals (Devons 2002). CGA is a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological, and functional capabilities of a frail elderly person in order to develop a coordinated and integrated plan for treatment and long-term follow-up (Ellis et al. 2011).

Chronologic age alone is a poor descriptor of heterogeneity in the aging process and is an inadequate indicator to determine responses among older patients to cancer treatment. There is wide variation in the ability of patients of the same age to tolerate cancer therapy. A systematic and evidence-based way of describing this heterogeneity is needed to guide oncology treatment decisions. Rather than chronologic age, patients' physiologic age or fitness level based on a "fit to frail" spectrum is more meaningful. Frailty is an important geriatric syndrome that is characterized by multisystem dysregulation, leading to decreased physiological reserve and increased vulnerability for adverse health outcomes (Li et al. 2011). Frail older adults have multiple chronic conditions and difficulties maintaining independence. They may be more vulnerable to therapy toxicities and may not have substantial lasting benefits from therapy. CGA may be used as a tool to determine reversible deficits and devise treatment strategies to mitigate such deficits. The CGA represents the future of geriatric oncology to reduce toxicities and treatment-related hospitalization of the elderly (Della Pepa et al. 2017).

Which patients would benefit from CGA is an area of controversy. Many oncologic studies have used age $\geq$70 years as the age for implementing geriatric assessment, but other age cutoffs have been proposed (Wildiers et al. 2014). The International Society of Geriatric Oncology (SIOG) in 2005 created a task force to review the evidence on the use of CGA in older cancer patients. SIOG recommends that a CGA, with or without screening and with follow-up, should be used in older cancer patients (age $\geq$65) in order to detect unaddressed problems and improve their functional status and possibly their survival (Extermann et al. 2005). Administering a CGA can be time consuming and may not be practical in all clinical settings. Hence screening tools can be considered initially. Screening tools (detailed in ► Chap. 24, "Geriatric Screening in Cancer Patients") should not replace CGA but could be used in a busy practice in order to identify those patients in need of full CGA. If abnormal, screening should be followed by CGA and guided multidisciplinary interventions (Decoster et al. 2015). The National Comprehensive Cancer Network (NCCN) guidelines for senior adult oncology addresses specific issues related to the management of cancer in older adults including the role of CGA in proper selection of patients for cancer treatment (Hurria et al. 2012). In 2015, an expert panel using the Delphi technique met consensus that "all patients aged 75 years or older and those who are younger with age-related health concerns" should undergo CGA and that all domains (function, physical performance, comorbidity/polypharmacy, cognition, nutrition, psychological status, and social support) should be included (Mohile et al. 2015).

Domains

CGA in older cancer patients includes evaluation of functional status, comorbid medical conditions, cognition, nutritional status, psychological state, and social support as well as a review of the patient's medications (Extermann and Hurria 2007). When providers and investigators evaluate only some, but not all of the above domains, it is called Geriatric Assessment (GA), as opposed to evaluation of the full spectrum which constitutes a CGA. There are no specific tools that are set as the "gold standard" for the assessment of each domain. The choice of tools is usually provider and resources driven (Table 1).

Cognition

One in three seniors dies with a form of dementia in the United States today. Of the estimated 5.5 million Americans living with Alzheimer's dementia in 2017, an estimated 5.3 million are age 65 and older (Alzheimer's Association 2017). The incidence of dementia doubles every 5 years after the age of 65 years (Corrada et al. 2010). Since over 50% of new cancers are diagnosed in those over the age of 65, the overlap of cognitive dysfunction and cancer is a real problem. Preexisting dementia affects the diagnosis and treatment of cancer. Patients with a precancer diagnosis of dementia are less likely to receive invasive diagnostic testing as well as standard or curative intent treatments (Gupta and Lamont 2004; Gorin et al. 2005).

Impaired cognition can result in significant difficulties in understanding treatments and procedures, which is important in the process of obtaining informed consent, remembering and following treatment instructions, delaying diagnosis of complications, and decreasing adherence to prescribed primary and supportive treatments. At the same time, both cancer and cancer therapies can negatively affect cognition, and older adults with preexisting cognitive impairment may be more susceptible to cognitive decline with therapy than younger patients (Magnuson et al. 2016). Hence, it is imperative to evaluate and continue to monitor cognitive function in older cancer patients through the treatment trajectory.

Tools for the Assessment of Cognition

The *MiniCog*® (Shephard and Kosslyn 2005) is a fast and simple screening test that requires minimal training to administer. It combines an uncued 3-item recall test with a clock-drawing test (CDT) and assesses executive function and memory. Scoring is not affected by education levels or language abilities.

The *Folstein Mini-Mental State Examination (MMSE)* (Folstein et al. 1975) is a widely used 30-point screening tool that assesses multiple cognitive domains. Education levels, language, and culture can be barriers.

The *Montreal Cognitive Assessment (MoCA)* (Nasreddine et al. 2005) was designed as a rapid screening instrument for mild cognitive dysfunction. It takes a little longer to administer, 10–12 min, but is more sensitive in detecting mild changes. It is also a 30-point tool that assesses multiple cognitive domains including attention and concentration, executive function, conceptual thinking, etc.

The *Blessed Orientation-Memory-Concentration (BOMC) Test* and a 6-item Orientation-Concentration-Memory test based on it are available (Katzman et al. 1983). A positive correlation has been shown between scores on the 6-item test and neuropathology (plaque counts obtained from the cerebral cortex of 38 subjects at autopsy). This test is easily administered by a nonphysician and can discriminate among mild, moderate, and severe cognitive deficits. This test is used in the Cancer and Aging Research Group toxicity tool (Hurria et al. 2011).

Cognitive screening tests may not be sensitive enough to detect subtle disorders. Hence more detailed neuropsychological tests administered by trained neuropsychologists may be considered when necessary.

Function

Performance Status

Functional disability is common in older cancer patients and its prevalence increases with age

Table 1 Domains and frequently used assessment tools

Domain	Tool	Type of tool	Scoring, comments
Cognition	MiniCog (Shephard and Kosslyn 2005)	Performance based	Not influenced by education level or language abilities
	Mini-Mental State Examination (Folstein et al. 1975)	Performance based	Score may be influenced by educational level, age, language, and motor, visual, or hearing impairments
	Montreal Cognitive Assessment (Nasreddine et al. 2005)	Performance based	Greater sensitivity to detect mild levels of cognitive impairment
	The Blessed Orientation-Memory-Concentration Test (Katzman et al. 1983)	Performance based	A 6-item shorter version based on this tool is also validated. Each score is multiplied by a constant, yielding a weighted score
Function and performance	Performance status scales: Karnofsky Performance Status (Schag et al. 1984)	Self-report	Scored 100 (normal without complaints) to 0 (dead), at 10 point decrements
	Eastern Cooperative Oncology Group (Oken et al. 1982)	Self-report	Scored 0 (fully active without restrictions) to 5 (dead)
	Activities of Daily Living (Katz 1983)	Self-report	Skills needed to live independently in the home
	Instrumental Activities of Daily Living (Lawton and Brody 1969)	Self-report	Tasks needed to live independently in the community
	Timed Up and Go (Podsiadlo and Richardson 1991)	Performance based	Quick, requires no special equipment or training
	Gait Speed (Studenski et al. 2011)	Performance based	Speed is of walk at a "comfortable pace"
	Grip Strength (Mathiowetz et al. 1985)	Performance based	Requires a hand-held dynamometer
	Tinetti Gait and Balance Scale (Tinetti 1986)	Performance based	Balance-sitting, standing, turning in diff circumstances. Gait-stance, initiation, stepping, trunk sway
Comorbidity	Charlson Comorbidity Index (Charlson et al. 1987)	Calculated	Mortality predictor
	Cumulative Illness Rating Scale – Geriatrics (Salvi et al. 2008)	Calculated	Diseases of physiological systems are assigned points (1–5) based on their severity to get a total score
Nutrition	Body Mass Index	Calculated	Based on height and weight
	Mini Nutritional Assessment (Oster et al. 1999)	Self-report	Identifies those "at risk" of malnutrition
Psychosocial status and quality of life	Medical Outcomes Study- Social Support Survey (Sherbourne and Stewart 1991)	Self-report	Measures emotional, tangible, affectionate support, and positive social interaction
	UCLA Loneliness Scale (Russell 1996)	Self-report	Options for each question ranges from "Often" to "Never"
	Geriatric Depression Scale (Yesavage et al. 1982)	Self-report	Distinguishes mild and severe depression from normal
	Patient Health Questionnaire-9 (Kroenke et al. 2001)	Self-report	Scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day)
	Distress Thermometer (Roth et al. 1998)	Self-report	Single item tool. Scored 0 (none) to 10 (extreme)

(*continued*)

Table 1 (continued)

Domain	Tool	Type of tool	Scoring, comments
Medication appropriateness and polypharmacy	Brown Bag Review	Medication review	Reduces costs and improves patient welfare
	Use of inappropriate medications in the elderly; e.g., Beer's criteria (Fick et al. 2015) Screening Tool of Older People's Prescriptions and the Screening Tool to Alert to Right Treatment (O'Mahony et al. 2015)	Medication review	Identifies inappropriate medications and prescribing omissions
	Number of medications	Medication review	Identifies polypharmacy
	Fit fOR The Aged score (Wehling et al. 2016)	Medication review	Classifies medications into A (indispensable) through D (avoid)

(Serraino et al. 2001). Performance status scores such as the Eastern Cooperative Oncology Group (ECOG) (Oken et al. 1982) and Karnofsky Performance Status (KPS) (Schag et al. 1984) are scores often used in oncology to estimate a patient's functional status. However, they tend to under-represent the degree of functional impairment in older patients (Repetto et al. 2002).

A better understanding of the older patient's functional status can be obtained by assessing the patient's ability to perform his/her activities of daily living (ADL) independently. The basic ADLs are self-care skills needed in order to live independently in the home, which include bathing, dressing, grooming, toileting, transferring, feeding, and continence (Katz 1983). In patients with dementia, caregiver rated ADL tools are also available (Bucks et al. 1996; Hindmarch et al. 1998). The instrumental activities of daily living (IADLs) refer to tasks that are needed to live independently in the community and include shopping, transportation, using the telephone, managing finances, medication management, cooking, cleaning, and laundry (Lawton and Brody 1969).

In a study on older lung cancer patients receiving chemotherapy, independence in performing IADLs and higher quality of life scores were associated with better prognosis (Maione et al. 2005). Impaired functional status is associated with a higher risk of toxicity from chemotherapy. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score (Extermann et al. 2012) and the scoring system developed by the Cancer and Aging Research Group (CARG) (Hurria et al. 2011) detailed in ▶ Chap. 38, "Early-Stage Breast Cancer in Older Adults" include assessment of patient's function.

Falls

A fall is as "an unexpected event in which the participant comes to rest on the ground, floor, or lower level" (Lamb et al. 2005). Approximately 30% of people over 65 years of age living in the community fall each year (Campbell et al. 1990). The rate of fall-related injuries increases with age (Peel et al. 2002). Older people fall more often for a variety of reasons including problems with balance, poor vision, and dementia. Falls tend to have a multifactorial etiology including intrinsic (person-related) and extrinsic (environment-related) factors. Hence the assessment (Smith et al. 2017) and interventions (Gillespie et al. 2012) to prevent them should be multidisciplinary (physical therapy, occupational therapy, home safety, medication evaluation, evaluation for cataracts, etc.) with the goal to minimize the risks without compromising functional independence. The Tinetti Gait and Balance Scale is a rapid,

reproducible assessment tool for the evaluation of fall risks, gait, and balance (Tinetti 1986). The test is scored on the patient's ability to perform specific tasks and takes 10–15 min to complete.

Physical Function

Physical function can also be assessed by other objective and sensitive measures of performance, including gait speed, grip strength, balance, and lower extremity strength. Decreases in these measures are associated with worse clinical outcomes (Cesari et al. 2009). A commonly used test for functional mobility is the *Timed Up and Go (TUG)*, which is brief and simple to implement in clinical settings. It measures the time it takes for a patient to stand up from an armchair, walk 10 ft. to a marker on the floor, turn, walk back to the chair and sit down (Podsiadlo and Richardson 1991). It can predict the patient's ability to go outside alone safely. Those with compromised performance in the TUG commonly have difficulties in ADLs. *Gait Speed* is an important indicator in older persons, as it has been shown to be an independent predictor of mortality across numerous population-based studies (Studenski et al. 2011). Average gait speeds for community-dwelling older adults range from 0.60 to 1.45 m/s with a desired gait speed often cited as 1.2 m/s, the speed required to cross most intersections (Hornyak et al. 2012). Patients are instructed to "walk at a comfortable pace" when measuring the speed. Grip strength measured by a hand-held dynamometer is important to assess cancer patients and is relatively quick and easy to do. *Grip strength* correlates with sarcopenia and has been shown to be associated with adverse outcomes in patients with cancer (Kilgour et al. 2013; Chen et al. 2011).

Comorbidity

Comorbidity in cancer patients represents the sum of the medical conditions, other than the cancer, the individual suffers from. As an individual ages, the life expectancy decreases (Walter and Covinsky 2001) and the number of comorbid medical conditions increases (Yancik 1997). Consequently, an older patient may have multiple competing risks for death. In the elderly, the combination of a high burden of competing risks and high rates of treatment-related complications conspires to reduce the net benefit of numerous interventions (Welch et al. 1996). Hence the impact of these comorbid medical conditions should be taken into consideration when charting out treatment plans and estimating the risks and benefits of treatments. Frequent comorbidities in the elderly such as cardiovascular disease, hypertension, diabetes, or dementia influence the management of cancer. Comorbidities may increase the risk of complications, modify cancer behavior, or mask symptoms. On the other hand, cancer treatment may decompensate or worsen previously stable comorbid conditions.

Measurement of Comorbidity

Comorbidity burden is often measured using standardized indices such as the Charlson Comorbidity Index (CCI) (Charlson et al. 1987) and the Cumulative Illness Rating Scale – Geriatrics (CIRS-G) (Salvi et al. 2008). The CCI is the most extensively studied comorbidity index for predicting mortality. It is based on the 1-year mortality of patients admitted to a medical hospital service. It is a simple instrument validated in older cancer patients with well-defined rating criteria. The CCI however, may under-detect non-lethal endpoints. The Cumulative Illness Rating Scale (CIRS) addresses all relevant body systems without using specific diagnoses. Its geriatric version, the CIRS-G, was designed for use in elderly populations. While it details several geriatric concerns, the scale may over-detect minor problems and it is quite complicated to rate. Other valid comorbidity indices such as the Index of Coexisting Disease (ICED) and the Kaplan Index have been less utilized in the Geriatric Oncology literature (de Groot et al. 2003).

Nutrition

Nutritional status should be assessed as part of CGA, as malnutrition and weight have significant roles in older cancer patients. With the growing

global obesity epidemic, there is consistent evidence that higher amounts of body fat are associated with increased risks of a number of cancers (Lauby-Secretan et al. 2016). On the other hand, weight loss in patients with cancer is an independent adverse prognostic factor and is associated with a lower performance status (Dewys et al. 1980). Malnutrition is prevalent up to 83% in older patients with cancer scheduled to receive chemotherapy and weight loss has been observed in 40–91.6% of patients during the course of chemotherapy, depending on cancer location (Cailleta et al. 2016). Malnutrition is associated with treatment complications and increasing mortality in patients receiving chemotherapy, radiation therapy, or surgery (van der Schaaf et al. 2014; Gourin et al. 2014; Fiorelli et al. 2014; Langius et al. 2013; Ehrsson et al. 2012; Buskermolen et al. 2012). Assessment tools include Body Mass Index (BMI), unintentional weight loss, as well as longer, validated tool such as the Mini Nutritional Assessment (MNA) (Oster et al. 1999). The MNA correlates highly with clinical assessment and objective indicators of nutritional status.

Psychosocial Status

Social Isolation

Social isolation, the lack of social ties, is an independent predictor of mortality in the older population in general (Seeman et al. 1993). In a study on breast cancer survivors, patients with inadequate social support experienced greater distress (Kornblith et al. 2003). Social isolation and low levels of social support have been associated with an increased incidence of cancer as well as higher mortality risk in patients with cancer (Ikeda et al. 2013; Kroenke et al. 2006). Increased social isolation is a risk factor for poor tolerance of adverse effects of cancer treatment (Penedo et al. 2012). The *Medical Outcomes Study (MOS) Social Support Survey* provides a multidimensional tool to evaluate emotional/informational, tangible, and affectionate support as well as positive social interactions. Adequacy of the MOS Social Support Survey correlates with improved functioning and wellbeing, whereas low scores indicate the need for support services to improve health outcomes (Sherbourne and Stewart 1991). The *UCLA Loneliness Scale* measures the adequacy of an individual's interpersonal relationships and loneliness (Russell 1996).

Depression

In older cancer patients, the prevalence of clinically significant depression ranges from 3% to 25%. Though the psychological impact of cancer on the elderly is less adverse or similar compared with younger patients, organic mental disorders are more prevalent in the older group (Kua 2005). Patients with cancer and depression are less likely to receive definitive treatment, and hence, experience worse survival compared to those without depression (Goodwin et al. 2004). The *Geriatric Depression Scale* (in its variants with 2, 4, 15, or 30 items) is a widely used tool to assess depressive symptoms. It is a multiquestion, self-rating instrument, validated in the aged, and capable of distinguishing the mildly and severely depressed from normal (Yesavage et al. 1982). In various studies utilizing CGA in patients with solid tumors, it identified depression in 10–65% of patients (Caillet et al. 2014). The *PHQ-9 questionnaire* scores each of the nine DSM-IV criteria for depressive disorders as "0" (not at all) to "3" (nearly every day) making a criteria-based diagnosis. It is additionally, a reliable and valid measure of depression severity. These characteristics plus its brevity make the PHQ-9 a useful clinical and research tool (Kroenke et al. 2001).

Distress

Receiving a diagnosis of breast cancer, contemplating the uncertainty of the future, and anticipating the daunting process of choosing and undergoing treatments can induce significant distress. The *Distress Thermometer (DT)* is a single item tool that asks patients to rate their distress in the past week on a scale of 0 ("no distress") to 10 ("extreme distress") (Roth et al. 1998). It is used in psycho-oncology and validated for patients and cancer patients' families (Nelson et al. 2010). It offers an efficient means

of identifying cancer patients with psychological distress.

Medications and Polypharmacy

Pharmacotherapy in older patients is a complex issue. Regular, comprehensive medication reviews are necessary to address potentially inappropriate medications (PIM) and to identify potential drug-drug and drug-disease interactions. The review should include prescription and over-the-counter medications as well as all alternative/homeopathic supplements. Pharmacist-led comprehensive medication assessments in geriatric oncology patients have demonstrated a high prevalence of polypharmacy (5–9 medications), excessive polypharmacy (10 or more medications), and PIM use (Nightingale et al. 2015).

Polypharmacy is common among the elderly, and although it can be therapeutic in nature, it is linked to adverse events (Hammond and Wilson 2013). The medical comorbidity burden in older patients increases the number of drugs prescribed increasing the potential for side effects from individual drugs as well as those resulting from drug-drug interactions. There is substantial overlap between use of prescription medications and herbals/supplements. A study showed that among prescription drug users, 16% also took an herbal/supplement for nonspecific reasons such as "health." This raises the concern further for unintended interactions (Kaufman et al. 2002). In cancer patients, the drug burden includes not only those used in the treatment of the cancer but also those used for supportive care and the management of symptoms related to therapy-induced toxicity (Lichtman and Boparai 2008).

Older adults are prone to medication errors and discrepancies due to complex regimens, formulary changes, particularly at changes in care settings such as discharge from the hospital. Patients with medication discrepancies also have higher rehospitalization rates (Coleman et al. 2005). Increased pill burden and regimen complexity can also result in nonadherence.

Tools such as *Beers criteria* (Fick et al. 2015) and *Screening Tool of Older People's Prescriptions (STOPP)* and the *Screening Tool to Alert to Right Treatment (START)* (O'Mahony et al. 2015) can help identify PIMs and potential prescribing omissions (PPO). PIM and PPO exposure are associated with increased rates of hospital visits (Moriarty et al. 2014). Efficient software systems can be incorporated into the electronic prescription algorithm to easily identify PIMs and PPOs.

The *Medication Appropriateness Index Criteria* measures the appropriateness of prescribing.

It uses 10 criteria for *each* medication to determine whether it is appropriate, marginally appropriate, or inappropriate (Samsa et al. 1994).

Fit fOR The Aged (FORTA) is the first positive/negative listing approach labeling medications used to treat chronic illnesses in older patients from A (indispensable), B (beneficial), C (questionable) to D (avoid). Applying FORTA to hospitalized geriatric patients leads to improvement of medication quality (Wehling et al. 2016).

A "*brown bag check up*" (i.e., asking the patient to bring all medications to the visit) is the single most efficient medication review and should be included in the CGA. It is an effective means of helping patients to derive maximum benefit from their medicines, of identifying medication-related problems, and of reducing wastage of medicines (Nathan et al. 1999). Review all medication bottles. Throw away expired medications. Provide patients with a pill box and a large font typed medication list with clear directions and indications.

Benefits of CGA

The CGA has been demonstrated to be superior to clinical judgment, even by experienced clinicians, when used to evaluate older cancer patients for fitness status (Tucci et al. 2009). Multiple studies have suggested a spectrum of benefits that arise from the utilization of CGA in older cancer patients (Table 2). A prospective multicentric study on the large-scale feasibility and usefulness of CGA in clinical oncology showed that CGA

Table 2 Benefits of the CGA in older cancer patients

Detection of unknown geriatric syndromes
Help in treatment decision making
Help in the risk stratification of patients prior to potentially high-risk therapy
Prediction of complication and side effects from cancer treatment
Identification of new deficits during the treatment trajectory
Devise treatment strategies to mitigate geriatric syndromes
Estimation of mortality risk
As the basis for the design of discharge planning

detected unknown geriatric problems in 51% of patients ≥70 years. When the physician was aware of the assessment results at the time of decision making, geriatric interventions were planned in 25.7%, and the treatment decision was influenced in 25.3% of the patients (Kenis et al. 2013). CGA is used in treatment decision making by clinicians, helping to risk stratify patients prior to potentially high-risk therapy. It has a role in predicting complications and side effects from cancer treatment (Hurria et al. 2011; Extermann et al. 2012; Corre et al. 2016). During the cancer treatment trajectory CGA may be used as a tool to identify new deficits such as decline in functional activity levels, and devise treatment strategies to mitigate such deficits. A number of studies have shown the use of CGA in the estimation of survival (Klepin et al. 2013; Stotter et al. 2015; Antonio et al. 2016). The online e-prognosis indices incorporate CGA elements to estimate mortality risk (Yourman et al. 2012). It may provide an effective approach to the management of pain and psychological status in the hospitalized older cancer patient (Rao et al. 2005).

Methods of Administering a CGA

CGA ideally includes an interdisciplinary team of specialized professionals to perform each assessment. Though it can take up to 2 h, most studies that measured time to administer, did it under an hour (Puts et al. 2012). An argument often used against the implementation of CGA in an oncology setting is that it is resource intensive and time consuming (Overcash et al. 2005). There are multiple ways of overcoming this problem. One way is by the use of screening tools to tease out the subset of patients that would need a full CGA, as recommended by the SIOG taskforce (Decoster et al. 2015). However, none of the published assessment tools was recommended by the task force. A review of Table 1 makes it evident that many of the tools used in CGA can be self-report tools. Having patients complete those tools on their own followed by the clinician conducting the other performance-based assessments is another way of overcoming this barrier.

Clinician Interview

A study with 30 cancer patients undergoing chemotherapy or radiotherapy was conducted in 1996. They were given a specifically structured multidimensional questionnaire (MACE) three times during 1 week by two different physicians. They collected information on demographics, socioeconomic status, cognitive status, depression, physical performance, disability, and tumor characteristics. They demonstrated that structured evaluation of functional status is feasible and reliable (Monfardini et al. 1996). A number of studies have since been done where the CGA was implemented by clinicians either in the inpatient setting (Basso et al. 2008) or in the outpatient clinic setting (Molina-Garrido and Guillen-Ponce 2011).

Self-administered

The feasibility of performing a cancer specific GA was studied in 2005. It included the following domains: functional status, comorbidity, cognition, psychological status, social functioning and support, and nutritional status. It was administered to cancer patients receiving chemotherapy at Memorial Sloan-Kettering Cancer Center (New York, NY) or the University of Chicago (Chicago, IL) (Hurria et al. 2005). KPS, TUG, and Blessed Orientation-Memory-Concentration

test were performed by a health care provider. It showed that the GA could be completed by the majority of patients without assistance.

Snail Mail Surveys

A 2002 self-reported assessment study at the Durham Veterans Affairs Medical Center included 266 male patients. They mailed out to these patients a survey that assessed 10 domains (demographics, comorbid conditions, activities of daily living, functional status, pain, financial well being, social support, emotional state, spiritual well-being, and quality of life). 76% of the patients who received their surveys and kept their appointments returned the assessment tool demonstrating that it can be conducted in an outpatient cancer community using a self-report format (Ingram et al. 2002).

Email/Electronic

The Geriatrics division at MSKCC assessed the feasibility of performing an electronic CGA, the *Electronic Rapid Fitness Assessment (eRFA)* (Shahrokni et al. 2017). The questionnaire was emailed to the patients once a geriatric appointment was scheduled. In 2015, 636 older patients with cancer (median age, 80 years) completed the eRFA during preoperative evaluation. The median time to completion was 11 min. Only 13% of patients needed someone else to complete the assessment for them. A tool to assess cognition and the TUG were performed by a clinician at the clinic appointment. This study demonstrated the feasibility of an electronic CGA. The eRFA is now used at MSKCC on a routine basis.

Another study from the City of Hope Comprehensive Cancer Center looked at computer-based GA in older cancer patients via two methods of electronic data capture compared with paper-and-pencil data capture. It too showed that delivering a computer-based GA is feasible, reliable, and valid (Hurria et al. 2016).

Conclusions

As the incidence of cancer increases with age and the geriatric population continues to expand, it is critical to develop strategies to provide optimal care for older cancer patients. It is important to distinguish functional from chronologic age and to evaluate physiologic reserves, risk of treatment complications, and probability of survival. Identifying remediable conditions and addressing them could improve therapeutic tolerability, quality of life, and overall survival. All older cancer patients should undergo CGA and the results should be analyzed relative to morbidity, mortality, and other outcomes. The availability of self-administered paper or electronic formats makes this increasingly feasible. If impediments to performing a CGA still exist, screening tests could be used. However, those found to be at risk on the screening test, should be further evaluated with a full CGA.

Cross-References

▶ Geriatric Screening in Cancer Patients

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Frailty in Cancer Patients

26

Siri Rostoft

Contents

Abstract

An older cancer patient who is frail has reduced tolerance to treatment such as chemotherapy and surgery and is at increased risk of toxicity and complications. The term *frailty* is defined as an increased vulnerability to stressors due to a multisystem reduction in reserve capacity. Frailty is linked to higher chronological age and comorbidities but is considered a distinct concept. By identifying frailty in a cancer patient, the treating physician gets a more precise estimation of individual vulnerability compared to looking at chronological age alone. Recognizing frailty has consequences for treatment decisions in the oncology setting because frailty summarizes health status. A patient who is frail has a limited life expectancy compared to a fit patient with the same chronological age. When interpreting clinical trials in older cancer patients, reporting of patient frailty in addition to age is necessary because it is relevant for evaluating generalizability to clinical practice. Unfortunately, frail patients are often excluded from clinical trials.

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Keywords
Frailty · Geriatric assessment · Functional status · Cognitive impairment · Preoperative assessment · Gait speed

Abbreviations

ADL	Activities of daily living
CI	Confidence interval
G8	Geriatric-8
GA	Geriatric assessment
VES-13	Vulnerable Elders Survey-13

Introduction

An older cancer patient who is frail has reduced tolerance to treatment such as chemotherapy and surgery and is therefore at increased risk of toxicity and complications. The term *frailty* is defined as an increased vulnerability to stressors due to a multisystem reduction in reserve capacity. Frailty is linked to higher chronological age and comorbidities but is considered a distinct concept. By identifying frailty in a cancer patient, the treating physician gets a more precise estimation of individual vulnerability compared to looking at chronological age alone. Recognizing frailty has consequences for treatment decisions in the oncology setting because frailty summarizes health status.

Case Vignette

A 69-year-old male was admitted to the cancer unit at his local hospital because of locally advanced rectal cancer. According to guidelines, the proposed treatment was preoperative radiochemotherapy followed by surgery. In his medical records, it was noted that he had hypertension and that he was overweight.

He was treated as an inpatient, and 1 week into treatment he became noncooperative and aggressive, pulled out his i.v. lines, and refused to get out of bed. The attending oncologist suspected acute delirium and called the geriatrician to get some advice.

The geriatrician was surprised that acute delirium had developed in an otherwise healthy 69-year-old male undergoing chemoradiotherapy. However, when looking more closely into the premorbid functional and cognitive status of the patient, it became evident that he fulfilled the criteria for frailty: A discussion with his daughter revealed that he was dependent in basic activities of daily living and needed home nursing four times a day. He was able to ambulate in his own house, but he never went out of the house, and he had fallen several times during the last months. He had gradually (over years) developed problems with his short-term memory and was now unable to pay his bills or engage in social activities. The information of his premorbid functional and cognitive status was highly relevant in the context of a newly diagnosed rectal cancer. The risk of delirium is increased in patients with pretreatment cognitive impairment (Fong et al. 2015). The risk of further functional decline is high (Covinsky et al. 2011). The risk of chemotherapy toxicity is higher when there is mobility reduction, falls, or need for assistance with medication (Hurria et al. 2011). The risk of complications after surgery is much higher in patients who are frail before surgery (Kristjansson et al. 2010). Furthermore, long-term survival is poor in frail individuals with rectal cancer (Ommundsen et al. 2014).

Definition and Identification of Frailty in Cancer Patients

Frailty is defined as a state of increased vulnerability toward stressors due to a multisystem reduction in reserve capacity (Morley et al. 2013). In the context of older patients with cancer, a frail patient has increased risk of toxicity of medical cancer treatment and radiation therapy and an increased risk of postoperative complications after cancer surgery (Feng et al. 2015; Handforth et al. 2015). Frailty is more prevalent with increasing age, but high chronological age does not necessarily lead to frailty. Thus, by estimating a person's level of frailty, one gets a more precise quantification of vulnerability than by looking at chronological age alone (Hubbard and Woodhouse 2010). Frailty is

associated with other negative outcomes such as institutionalization, functional decline, and mortality (Morley et al. 2013).

Even though there is an agreement in the literature about how to define frailty, there is no standardized way of identifying frailty in an individual patient. The two most commonly used methods are the physical frailty phenotype and the accumulation of deficits theory (Huisingh-Scheetz and Walston 2017). In the phenotypic frailty model, which was proposed by Fried and colleagues, the patient is assessed in five dimensions: weight loss, physical activity, exhaustion, grip strength, and walking speed (Fried et al. 2001). A person who scores poorly (below the 20 percentile of the normal population) in at least three of these five dimensions is considered frail, while a person who scores poorly in two dimensions is categorized as pre-frail. This way of assessing frailty is closely linked to sarcopenia (loss of muscle mass and function) and functional status, but does not take into account comorbidity and cognitive function. In this theory, underlying physiological decline contributes to frailty and leads to comorbidities. Rockwood and colleagues, on the other hand, have suggested to assess frailty based on counting the number of deficits across a variety of health indicators such as functional status, cognitive function, comorbidities, emotional and nutritional status, as well as social support (Mitnitski et al. 2001). The more that is wrong with the person, the frailer the person is, and in the end the system fails entirely. In this model, comorbidities and disability are deficits associated with aging that eventually leads to a physiological decline. By performing a geriatric assessment (GA), it is possible to identify the number of deficits in a patient across multiple areas.

In the oncology setting, the clinical definition of frailty suggested by Dr Balducci is still referenced. Dr Balducci outlined three treatment groups of older cancer patients that could be identified from a geriatric assessment (GA) – fit, intermediate, and frail. He suggested that the fit elderly should receive treatment similar to younger patients, while frail elderly should be offered mainly palliative care. The intermediate patients would need an individualized approach (Balducci and Extermann 2000). Balducci's criteria for defining the frail older patients were based on the criteria originally presented by Winograd et al. (1991). The Winograd frailty criteria were impairment of single activities of daily living (ADL), imbalance/dizziness, impaired mobility, chronic disability, weight loss, falls during the last 3 months, confusion, vision or hearing impairment, depression, malnutrition, mild or moderate dementia, urinary incontinence, social or family problems, polypharmacy, and prolonged bed rest. Several of these elements, such as falls, confusion/delirium, and incontinence, are considered *geriatric syndromes*. Geriatric syndromes result from shared risk factors such as high age, cognitive impairment, functional disability, and reduced mobility. Such risk factors lead to falls, delirium, and functional decline and may in turn lead to frailty (Inouye et al. 2007).

Another way of assessing frailty with a single physical performance assessment has been proposed: measuring usual gait speed (Clegg et al. 2015). This can be done by asking a patient to walk 4 m at his or her usual pace and then calculating the speed. A slow gait speed is most commonly defined as less than 0.8 m/s (Odden et al. 2012). Slower walkers or persons not able to complete a 4 m walk test are considered frail. In a recent study, slow gait speed was identified as a predictor of early death in older patients with cancer independent of cancer site and cancer extension, with a hazard ratio of 5.6 (95% confidence interval (CI) 1.6–19.7) (Pamoukdjian et al. 2017). Another example of a single indicator of frailty is multiple falls. In patients undergoing elective colorectal surgery, the incidence of postoperative complications was 100% in patients who had experienced three or more falls in the last 6 months (Jones et al. 2013).

Frailty Tools and Screening

With a variety of tools to choose from, the question of how to assess frailty in the oncology setting is frequently raised. Selecting the right tool will depend on the setting, first of all whether the

setting is clinical practice or research. In general, the screening tools based on phenotypic frailty model work well as pure risk assessment tools, while tools that evaluate various domains of a GA may identify areas that need further investigation and can be optimized or treated, such as malnutrition or depression. A GA is thus able to identify both *if* and *why* a patient is frail.

The most frequently tested screening tools for frailty in geriatric oncology are the geriatric-8 (G8) and the Vulnerable Elders Survey-13 (VES-13) (Luciani et al. 2010; Soubeyran et al. 2014). The G8 is based mainly on a tool called the Mini Nutritional Assessment, and adding ADL questions to the original screening increases its performance (Petit-Moneger et al. 2016). VES-13 is mainly a scoring of functional status. A comprehensive review of frailty screening tests in cancer patients from 2012 concluded that none demonstrate the optimal combination of high sensitivity and negative predictive value and an acceptable specificity for predicting abnormal GA to be considered for favored use (Hamaker et al. 2012). However, it should be noted that none of the tested screening tools in that review included a physical performance measure. It has been shown that screening tools that include objective physical performance measures, such as gait speed or grip strength, have better predictive ability than those without (Woo et al. 2012). Thus, it is recommended that a frailty screening tool should include a simple physical performance measure. In the clinical setting, physicians may consider adding Mini-Cog to screen for cognitive impairment in addition to the frailty screening (Tsoi et al. 2015).

A proposed flowchart for screening for frailty in cancer patients is presented in Fig. 1.

Data Regarding Frailty in Oncology

The exact prevalence of frailty in cancer patients is difficult to assess due to a variety of definitions of frailty in different studies. According to a systematic review from 2015, the prevalence of frailty in oncology varies from 6% to 86%, while the prevalence of pre-frailty is between 13% and 79% (Handforth et al. 2015). In any case, frailty was independently associated with all-cause mortality and treatment complications across different tumor and treatment types. The data linking frailty to postoperative complications across different types of surgery and cancer are solid (Huisingh-Scheetz and Walston 2017). In a prospective cohort of 178 patients over the age of 69 years who were electively operated for colorectal cancer, being frail assessed by the Balducci criteria increased the risk of postoperative complications with an odds ratio of 2.97 (95% CI 1.61–5.50) (Kristjansson et al. 2010). In the same cohort, 5-year survival was 24% in frail patients compared to 66% in non-frail patients (Ommundsen et al. 2014). Neither postoperative morbidity nor survival was related to patient age. A recent systematic review in older surgical cancer patients confirmed that frailty is an important predictor of negative outcomes across different tools and settings (Huisman et al. 2017). For chemotherapy toxicity and radiotherapy fatigue, there are fewer studies looking at frailty, although components of a GA predict toxicity and mortality from chemotherapy (Hurria et al. 2011; Extermann et al. 2012). Among patients over 65 years with cancer, neither the G8 nor the Groningen Frailty Indicator predicted serious events following the first cycle of (radio)chemotherapy (Baitar et al. 2014). However, G8 predicted 1-year survival (Soubeyran et al. 2014). In a study of older patients with stage III or IV colorectal cancer undergoing chemotherapy, VES-13 significantly predicted mortality (Ramsdale et al. 2013). Radiotherapy fatigue was associated with both phenotypic frailty and GA in well-functioning older women with breast cancer (Denkinger et al. 2015).

In conclusion, it seems that at least half of older patients with cancer have either pre-frailty or frailty, and frailty should therefore be assessed routinely. However, establishing a common definition of frailty in oncology that allows for

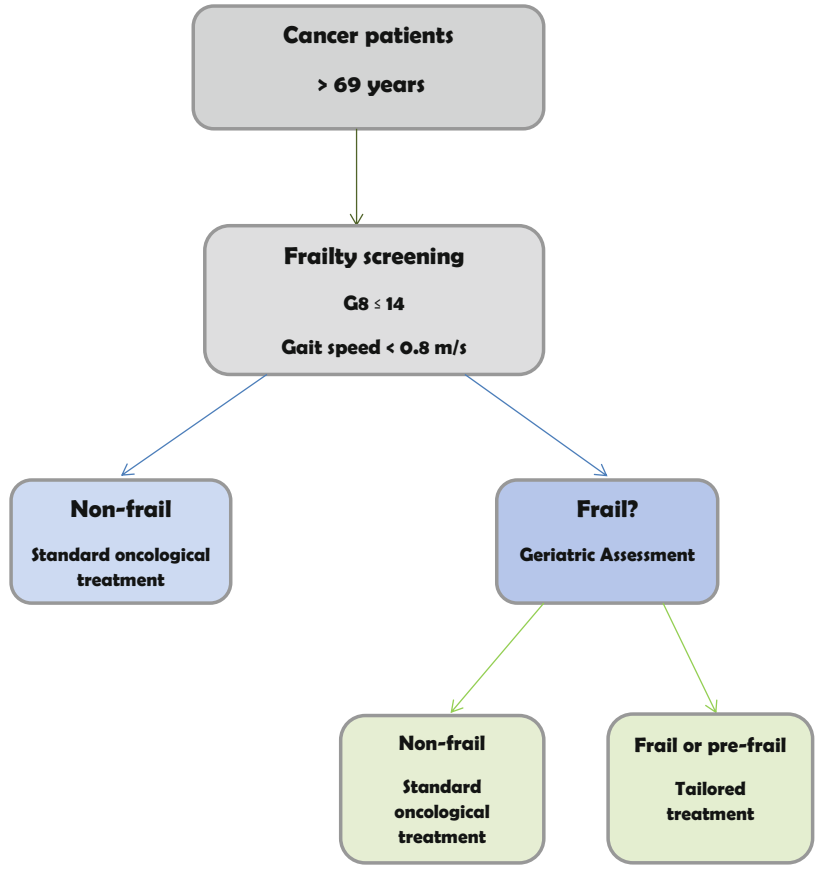

Fig. 1 Proposed flowchart for frailty screening in cancer patients

comparison of datasets is necessary in order to make further advances in this field.

Other Clinical Implications of Identifying Frailty in a Patient with Cancer

Frailty identifies vulnerability that may influence treatment decisions, but there are other clinical implications of identifying frailty in an older patient with cancer that deserves mentioning.

Cognitive impairment: Identifying cognitive impairment in cancer patients is important for several reasons. Firstly, cognitive impairment may influence decision-making capacity. If cognitive testing prior to treatment initiation reveals reduced decision-making capacity, caregivers need to be involved in the decision process.

Secondly, cognitive impairment increases the risk of acute confusional state (delirium) in relation to surgery and chemotherapy. An increased risk of delirium could be communicated to the patient and caregiver in order to reduce the stress of experiencing delirium. Delirium may also be prevented by multifactorial interventions with an odds ratio of 0.47, 95% CI 0.38–0.58, as described in a recent systematic review and meta-analysis (Hshieh et al. 2015). Establishing a baseline cognitive status before initiating cancer treatment is particularly valuable in cases where cognitive symptoms appear during the treatment trajectory. If no one assessed cognitive status before treatment, it is difficult to entangle whether the cognitive symptoms result from the cancer

treatment. Identifying cognitive impairment may also influence the treatment trajectory by identifying when it is necessary to establish services that ensure safety – such as home nursing for safe handling of medications and treatment-related toxicities.

Functional impairment: If frailty is identified as a consequence of functional impairment, the patient is at risk for further functional decline due to cancer and cancer treatment. In such cases, a physical therapist could be consulted in order to minimize further functional decline through specific exercise. Because functional decline happens gradually, establishing a baseline before treatment is essential in order to reveal changes in physical functioning. Older patients tend to prioritize maintaining their independence over survival (Fried et al. 2002; Akishita et al. 2013), and thus assessing functional status throughout the treatment trajectory is as important as assessing tumor-related factors. Furthermore, functional impairment is a consistent predictor of treatment complications and mortality – independent of tumor-related factors.

How to Manage Frailty in Older Cancer Patients

Apart from being a valuable predictor of clinical outcomes, little is known about how to specifically manage frailty in cancer patients. Frailty intervention trials are mainly studying a combination of exercise and micronutrients, macronutrients, nutritional supplement, or food regimens in order to reverse frailty, and such trials are not specific to older patients with cancer (Manal et al. 2015). Intuitively, a management plan for frail older cancer patients should be based on deficits identified through a GA and include optimization of comorbidities and polypharmacy, exercise to prevent functional decline, nutritional support to avoid weight loss, psychological support in case of emotional distress, and home care if cognitive impairment is identified in order to minimize the risk of poor compliance or treatment complications.

Summary

Frailty of pre-frailty is present in approximately half of older cancer patients. Frailty is a valuable predictor of clinical outcomes, and assessing frailty is essential in order to determine risk of treatment complications and life expectancy. Frailty is associated with higher age, but not all older patients are frail. Thus, determining a patient's level of frailty is necessary in order to avoid both over-and undertreatment of older patients with cancer.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Geriatric Interventions in Oncology
- ▶ Geriatric Screening in Cancer Patients
- ▶ Normal and Abnormal Aging (General Perspective for the Oncologist)
- ▶ Predictive Tools for Older Cancer Patient Management

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Geriatric Interventions in Oncology

27

Allison Magnuson

Contents

Abstract

Cancer care for older adults is complex. Frequently older adults have coexisting medical and social issues that complicate cancer treatment and require additional attention. A geriatric assessment (GA) can aid in detecting concurrent medical, psychological, and social issues and has been shown to be feasible in the oncology setting. Results of the GA can be used to develop goal-directed interventions for impairments that are detected. Although the development of GA-based management interventions is common practice by geriatricians in the non-cancer population, it is not yet routine practice for older adults with cancer. Emerging data in small, pilot studies suggest that it is feasible to develop GA-guided management interventions in the oncology setting, although the optimal model for care delivery and potential benefit of such interventions remains unclear. Multiple ongoing studies are evaluating the benefit of GA-guided management interventions for older adults with cancer. In this chapter, the role of GA in oncology with resultant GA-based management interventions is reviewed.

Keywords

Interventions · Geriatric assessment with management · Geriatric assessment-guided interventions

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Introduction

Cancer disproportionately affects older individuals, and with the aging of our population, there will be an increasing number of older adults

diagnosed with cancer (Siegel et al. 2015). (▶ Chap. 1, "Population Trends in Aging and Cancer") As chronologic age increases, health status becomes progressively heterogeneous (Mohile et al. 2011; Koroukian et al. 2006). Thus patients with the same chronologic age may not be similar with regard to physiologic age and tolerance to cancer therapies. A geriatric assessment (GA) is recommended to assess an older patient's fitness for cancer therapy (Hurria et al. 2012). (▶ Chap. 25, "Comprehensive Geriatric Assessment (CGA) for Cancer Patients") GA is a compilation of assessment tools to evaluate areas that commonly affect older adults. Typically, GA involves evaluation of a patient's physical function, comorbidities, cognition, psychological status, social support, nutritional status, and medication review. In the oncology setting, GA has been shown to be feasible to incorporate into routine care in both the academic and community setting; it has been shown to influence decision-making by oncologists, and elements of the GA are predictive of chemotherapy toxicity (Hurria et al. 2005, 2011, 2016; Williams et al. 2014; Hamaker et al. 2014; Extermann et al. 2011). In older adults without cancer, geriatricians utilize the GA to develop targeted management interventions to improve outcomes, although there is limited data on the benefit of such GA-guided interventions in oncology care. Within the geriatric oncology community, furthering the evidence base on interventions in oncology care is a focus of future research (Mohile et al. 2016; Magnuson et al. 2016a). A few small, pilot studies have assessed the feasibility of incorporating GA with management interventions into oncology care, and other studies have evaluated the benefit of interventions in a single GA domain in older adults with cancer. Here we provided an updated review of current evidence of GA with management interventions in oncology care.

Geriatric Assessment in the Oncology Setting

It is feasible to utilize GA in routine oncology clinical practice. Hurria and colleagues developed a cancer-specific GA (Hurria et al. 2005). This cancer-specific GA is completed independently by the patient and includes evaluation of functional status, comorbidity, cognition, psychological status, social support and functioning, and nutritional status. In the pilot study evaluating feasibility, the majority of patients were able to complete the assessment without assistance, and the mean time to completion was 27 min. The GA has been shown to be feasible to use in both academic and community oncology settings (Williams et al. 2014; Chapman et al. 2014). Elements of the GA have been shown to be predictive of chemotherapy toxicity (Hurria et al. 2011, 2016; Extermann et al. 2011) (▶ Chap. 29, "Predictive Tools for Older Cancer Patient Management"). Extermann and colleagues developed a chemotherapy toxicity risk prediction model, the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score (Extermann et al. 2011). The CRASH score was subdivided into risk factors for hematologic and non-hematologic chemotherapy toxicity. Elements of the GA that were predictive of hematologic toxicity included laboratory values (lymphocyte count, aspartate aminotransferase level, and lactate dehydrogenase level), Instrumental Activities of Daily Living (IADL) score, diastolic blood pressure, and Chemotox score (toxicity of chemotherapy regimen). Elements of the GA that were predictive of non-hematologic toxicity were laboratory values (hemoglobin, creatinine clearance, and albumin), self-rated health status, Eastern Cooperative Oncology Group (ECOG) performance status, mini-mental status score, mini-nutritional assessment score, and Chemotox score. Another study by the Cancer and Aging Research Group (CARG) also developed a chemotherapy toxicity risk prediction tool based upon GA results and other patient and treatment variables (Hurria et al. 2011). Factors that were predictive of chemotherapy toxicity included age >71, cancer type (gastrointestinal and genitourinary conferred higher risk), chemotherapy dosing (standard versus dose reduced), number of chemotherapy drugs (mono- versus polychemotherapy regimen), laboratory values (hemoglobin, creatinine clearance), hearing impairment, history of falls in the past 6 months, limited ability to ambulate one block, the need for

assistance in taking medications, and decreased social activities because of physical or emotional health. The CARG model was subsequently validated in a second cohort of patients as well (Hurria et al. 2016). Geriatric evaluation has also been shown to influence treatment decisions for older cancer patients (▶ Chap. 60, "Decision Making and Safety Issues in Older Cancer Patients"). Hamaker and colleagues performed a systematic review to summarize data on the effects of geriatric evaluation on treatment decisions for older cancer patients (Hamaker et al. 2014). Ten studies were included, with the initial treatment plan modified in a median of 39% of patients after geriatric evaluation. The majority of these treatment changes resulted in less intensive treatment. All but one study also reported on recommendations for geriatric-related interventions and found that over 70% of subjects received recommendations for interventions.

GA with Management Interventions

GA can identify areas of potential concern, or "impairments," in one or more of these domains for a particular patient. There is extensive research in older adults without cancer evaluating the utility of specific goal-directed interventions to address impairments identified on GA and the impact of such interventions on a variety of outcomes. Several studies have been performed on community-dwelling subjects without cancer. The DEED II study was a randomized, controlled trial of comprehensive GA and multidisciplinary intervention for older adults discharged from the emergency department (ED) (Caplan et al. 2004). In this study, 739 patients aged ≥75 who were discharged from an Australian ED were randomized to a comprehensive GA and home follow-up versus usual care. Investigators determined that subjects who received the intervention had a lower rate of readmissions to the hospital during the 30 days following their initial ED visit and a lower rate of ED visits during an 18-month follow-up period. Patients in the intervention group also maintained a greater degree of physical and mental function as well. Frese and colleagues performed a study of in-home preventive comprehensive geriatric assessment in Germany (Frese et al. 2012). In this study, 1620 community-living subjects aged ≥70 underwent a home visit with a GA followed by recommendations for their primary care provider. Investigators observed a 20% reduction in mortality and a 22% lower risk of nursing home admission at follow-up (average 6.2 years after randomization). Stott and colleagues also evaluated a home-based geriatric assessment and intervention program for patients aged ≥65 who were high risk for hospital readmission (Stott et al. 2006). The intervention involved a comprehensive GA and home-based nursing, occupational therapy, physiotherapy, and geriatric medical review. Investigators observed that patients randomized to the intervention had improvement in the basic and extended activities of daily living, as compared to a decline in the control group.

Other studies have focused on the evaluation of GA with management in the inpatient setting or the inpatient to outpatient transition. Nikolaus and colleagues performed a randomized trial of comprehensive GA and post-discharge home intervention in 545 older adults admitted to a geriatric hospital (Nikolaus et al. 1999). In this study, the intervention group was observed to have a decreased length of stay and lower rates of immediate nursing home placement, although there was no difference in survival or readmissions between the two groups. Cohen and colleagues evaluated the impact of an inpatient and outpatient GA in 11 Veterans Affairs medical centers (Cohen et al. 2002). Patients were randomly assigned to receive either inpatient geriatric unit care versus usual inpatient care, followed by either outpatient care at a geriatric clinic versus usual outpatient care. No significant effects were observed on overall survival; however the intervention group did have less functional decline and improvement in mental health. A meta-analysis of randomized controlled trials of comprehensive GA in the hospital setting was performed in 2011, identifying 22 eligible trials evaluating 10,315 participants in six countries (Ellis et al. 2011). The result of this meta-analysis showed that in the non-cancer setting for hospitalized patients, comprehensive GA

increases patients' likelihood of being alive and in their own homes after an emergency admission to the hospital, and patients were less likely to die or experience deterioration and were more likely to experience improved cognition. However, at present, there is limited data on the utility of GA-guided interventions in older cancer patients.

Several other studies in the non-cancer setting have evaluated the impact of interventions in a single GA domain and shown to improve outcomes. The physical function domain has the most extensive amount of research. In 2014, a meta-analysis was performed to evaluate the impact of exercise in older adults and included 19 studies (Gine-Garriga et al. 2014). Investigators determined that when compared with control, exercise was shown to improve gait speed and the short physical performance battery, an objective measure of physical function. In Finland, a study of 605 community-dwelling older adults age >75 evaluated the impact of GA-based intervention on the ambulation (Tikkanen et al. 2015). Investigators determined that the intervention reduced decline in the ability to ambulate for subjects who were frail or pre-frail. Lihavainen and colleagues performed a randomized, controlled trial evaluating the effects of comprehensive GA with targeted intervention on mobility in subjects age ≥75 (Lihavainen et al. 2012). In this study, 781 subjects were randomized to either GA with multifactorial intervention lasting 2 years or usual care. The intervention had a positive effect on mobility, with a lower percentage of patients with mobility limitation in the intervention group at 1-year and 2-year follow-up. GA-based interventions have also been shown to reduce the risk of falling in community-dwelling older adults. In 2012, a Cochrane review was performed of randomized trials of interventions to reduce falls in community-dwelling older adults including 159 trials (Gillespie et al. 2012). Investigators determined that group and home-based exercise programs and home safety assessment and modifications reduce rate of falls and risk of falling. Luger and colleagues evaluated the feasibility and impact of a home-based physical training, nutritional and social support program on nutritional status, and frailty in older adults in Austria (Luger et al. 2016). The intervention was delivered by volunteers and consisted of six strength exercises and discussion about nutrition and compared to an active control group consisting of social contact. Investigators determined that the intervention was feasible and resulted in improvements in mini-nutritional assessment score, although was not significantly different from the control arm suggesting that the social support alone improved outcomes. Nykanen and colleagues evaluated the effects of individual dietary counseling as part of a comprehensive GA in community-dwelling subjects aged 75 and older (Nykanen et al. 2014). Investigators observed that nutritional counseling resulted in an increase in mini-nutritional assessment scores as well as serum albumin.

In the non-cancer setting, interventions that target multi-domains are felt to be superior as compared to mono-domain, particularly with regard to interventions on frailty and physical function measures. A systematic review was performed evaluating the effects of multi-domain compared to mono-domain interventions in subjects aged ≥65 and included 12 studies which supported this assumption as well (Dedeyne et al. 2017).

GA with Management Interventions in Oncology Care

Given the limited data regarding GA with management interventions in oncology care, a Delphi study was performed to develop consensus among US-based geriatric oncology experts regarding the incorporation of GA and management interventions into clinical care (Mohile et al. 2015). Thirty participants were included; the majority used GA in clinical care with the remainder involved in geriatric oncology research. The expert consensus panel met consensus for how GA could guide non-oncologic interventions and cancer treatment decisions in multiple domains and an algorithm for GA-guided management interventions was developed. A summary of assessment tools and interventions recommended is provided in Table 1. An expert consensus panel with guideline

Table 1 Summary of GA assessment tools and potential management interventions for consideration (Mohile et al. 2015)

GA domain	Assessment tool	Potential management intervention
Physical function/objective physical performance	Gait speed Activities of daily living Instrumental activities of daily living Timed up and go Short performance physical battery	Physical therapy Occupational therapy Home safety evaluation Evaluate fall risk Refer to social work Exercise Rehabilitation Nursing/home health Modify treatment regimen Evaluate fall risk Assure presence of social support Improve functional status prior to treatment Avoid aggressive therapy Recommend personal emergency response service Assess comorbidity/medication Modify dosage of standard Modify delivery of standard
Cognition	Montreal cognitive assessment Blessed orientation-memory-concentration Caregiver burden/support Mini-Cog	Involve caregiver Assess/minimize medications Delirium prevention Refer to social work Assess capacity and ability to consent to treatment Identify health-care proxy Cognitive testing/neuropsychology referral Ensure caregiver involved and present with patient Assess safety of treatment Limit complexity of treatment Modify therapy delivery Avoid aggressive therapy
Psychological	Hospital anxiety and depression scale Mental Health Inventory	Refer to social work Counseling Refer to psychiatry/psychology Consider medication therapy Support programs Spiritual care
Nutrition	History of recent unintentional weight loss Mini-nutritional assessment	Nutrition consult Make specific dietary recommendations Oral care Supplements Refer to social work
Social support	Medical outcomes study survey Social support from medical history	Social work referral Nursing/home health Transportation assistance Caregiver management Home safety evaluation Support groups Spiritual care Psychiatry/psychology Assess patient safety/tolerability Assess caregiver support Modify treatment regimen Consider less aggressive treatment Modify therapy delivery

development was also performed with European-based oncologists regarding the optimal assessment method and interventions recommended for commonly employed domains of the GA (O'Donovan et al. 2015).

In oncology, a select few studies have evaluated GA-guided interventions for older adults with cancer. A randomized, pilot study conducted by Puts and colleagues evaluated the impact of GA with integrated care plan in improving outcomes in 60 older patients with advanced beast, gastrointestinal and genitourinary cancer (Puts et al. 2016). Eligible patients were aged $\geq$70 and randomized to receive usual care versus GA with implementation of tailored, evidence-based interventions using a standardized intervention protocol. The study team implemented GA-guided interventions, and patients were assessed at 3 and 6 months to assess intervention fidelity and outcomes, including quality of life and modification of the cancer treatment plan. Investigators determined that there was less decline in quality of life in the intervention group at the 3-month follow-up time point. A phase III study is planned to further evaluate the intervention. A second pilot study by Magnuson and colleagues also evaluated the effect of GA with management recommendations in a randomized fashion (Magnuson et al. 2016b). In this study, patients aged $\geq$70 with advanced solid tumor malignancy were randomized to receive either GA with management recommendations or usual care. In this study design, the study coordinator administered and scored the GA and then utilized an established algorithm to identify appropriate management interventions based upon impairments identified on GA. Recommendations for GA-guided interventions were then relayed to the primary oncologist who was responsible for implementation. In this study design, the assessment and development and implementation of GA-guided management were done independent of a geriatrician or geriatric oncologist. Investigators designed the study to develop a model of care that could implement GA-guided management independent of a geriatric provider given the limited number of providers available with geriatrics expertise. In this pilot study, it was determined that it was feasible to use an algorithm to guide GA management recommendations; however it was observed that the rate of implementation of the recommendations by the primary oncologists was low, at only 34%. There was no difference in outcomes between the control and intervention groups with regard to toxicity rates, hospitalizations, or treatment changes.

A British study evaluated the impact of GA with management in older adults with cancer receiving chemotherapy that was high risk for complications (Kalsi et al. 2015). Eligible subjects were aged $\geq$70 and determine to be high risk based upon a screening questionnaire (CGA-GOLD). Subjects underwent evaluation by a geriatrician with implementation of geriatric management interventions, and outcomes were compared to a historical observational cohort. Investigators observed that patients who underwent geriatric evaluation with management interventions were more likely to complete their cancer treatment and experienced fewer treatment changes as compared to the historical observational cohort, although rates of chemotherapy toxicity were not different between the two groups. Although this was not a randomized study, it does suggest that it is feasible to develop and implement GA-based interventions by a geriatrician in the oncology setting.

Other studies in geriatric oncology have evaluated interventions in a single GA domain. A study in the Netherlands investigated the utility of a preoperative geriatric consultation with individualized treatment plan targeting risk factors for delirium as well as daily visits by a geriatric nurse during hospitalization in older adults undergoing elective surgical procedures for solid tumor malignancies (Hempenius et al. 2016). Investigators determined that the geriatric intervention did not improve outcomes of mortality, rehospitalization, ADL functioning, cognitive functioning, QOL, or return to prior living situation at 3-month follow-up. A systematic review of studies evaluating physical and nutritional preoperative interventions in older adults with colorectal cancer determined that none of the interventions significantly reduced length of stay, mortality, or readmission rates (Looijaard

et al. 2017). A randomized, controlled trial in France evaluated the impact of a nutritional intervention in older adults at risk of malnutrition during chemotherapy (Bourdel-Marchasson et al. 2014). Patients age ≥70 with solid tumor malignancy at risk of malnutrition and receiving chemotherapy were randomized to receive an intervention consisting of diet counseling to increase energy intake, as compared to usual care. Investigators determined the intervention was effective at increasing caloric intake, but did not impact mortality or chemotherapy outcomes. Other studies have evaluated the impact of a social support intervention for older adults with cancer. McCorkle and colleagues performed a randomized, controlled intervention study evaluating the impact of a home care intervention on survival in postsurgical cancer patients aged ≥60 (McCorkle et al. 2000). The intervention lasted 4 weeks and was comprised of three home visits and five telephone contacts providing clinical assessments, monitoring, and teaching to patients and caregivers. Investigators determined that overall survival was improved in the intervention group as compared to controls, with effects most noticeable in individuals with advanced disease. Goodwin and colleagues evaluated the impact of a nurse case management support in older women with breast cancer (Goodwin et al. 2003). In this multicenter, randomized study, subjects were aged ≥65 with newly diagnosed breast cancer. Women were randomized to receive a nurse case manager intervention for 12 months following diagnosis, versus usual care. Investigators determined that women receiving the intervention were more likely to receive breast-conserving surgery and radiation therapy as well as breast reconstructive surgery. Women with advanced cancer were also more likely to receive chemotherapy in the intervention group. At 2 months post-surgery, women randomized to the intervention group were more likely to have return of normal arm function and report a sense of "choice" in their treatment. Investigators also determined that women with indicators of poor social support were most likely to benefit from the case management intervention.

GA with management intervention has also been shown to improve equality of life and pain management for older cancer patients. In a subset analysis of a larger geriatric assessment intervention study, 99 patients with cancer were analyzed. Investigators determined that patients randomized to inpatient geriatric assessment had improved quality of life at time of discharge (Rao et al. 2005). Patients were also more likely to receive evaluation by consultative services as well as physical and occupational therapy (Nipp et al. 2012).

GA can also be used to intervene on treatment decisions and help identify the appropriate level of cancer therapy for an individual. The ESOGIA-GFPC-GECP 08-02 study was a multicenter, phase III study evaluating the utility of using GA to allocate cancer therapy in patients age ≥70 with advanced non-small cell lung cancer (Corre et al. 2016). Patients were randomized to GA-guided treatment decision (standard doublet-based chemotherapy for "fit" patients, single-agent docetaxel for "vulnerable," and best supportive care for "frail" patients) versus treatment allocation based upon performance status and age (platinum-based doublet if aged ≤75 and Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 0–1, single-agent docetaxel for aged >75 or ECOG PS of 2). Patients randomized to GA-guided therapy had experienced less treatment toxicity and had lower rates of treatment failures. Overall survival was not different between the two groups, despite 23% of patients in the GA-guided arm receiving best supportive care only (all patients in the usual care arm received chemotherapy). Although this study did not evaluate traditionally geriatric supportive care interventions, it did demonstrate the potential benefit of using GA to guide management decisions about cancer therapy (Gajra et al. 2016).

Although early data suggests a possible benefit from GA-based management in oncology care, it is unclear the optimal model of care for delivery of such interventions. This topic was discussed at a geriatric oncology conference, "Design and Implementation of Intervention Studies to Improve or Maintain Quality of Survivorship in Older and/or Frail Adults with Cancer" in 2015

(Mohile et al. 2016; Magnuson et al. 2016a). Multiple options for clinical trial design exist, each with specific benefits and limitations. For example, a clinical trial could be developed to explore a comprehensive approach with a multicomponent intervention targeting all impaired GA domains identified for a particular subject. Alternatively, trials could be designed to investigate the benefit of a particular intervention (e.g., nutritional supplements) or the benefit of multicomponent interventions in a single GA domain (e.g., for individuals with impaired nutrition, a multicomponent intervention including nutritional supplements, nutritional counseling, exercise, etc.). Additionally models of care should be explored, such as development and delivery of interventions by an independent geriatrics team versus the primary oncology team, or physician-based development of interventions versus a team approach with geriatric-specific nursing and other allied health professionals.

Currently, there are multiple ongoing trials to further evaluate the benefit of GA with management intervention in older cancer patients. A large, phase III study in the United States of GA with algorithm-guided management intervention in community-based oncology practices is underway (NCT02054741). A second, large, phase III randomized study of approximately 1200 patients in France is also underway, which will evaluate the effect of a multidimensional GA and interventions tailored for the patient on overall survival and quality of life (NCT02704832) (Soubeyran et al. 2016). Disease-specific studies are also underway. A randomized phase II trial, GERICO, is evaluating the benefit of GA and management intervention before and during chemotherapy in older adults with colorectal cancer (NCT02748811) (Lund et al. 2017). The benefit of GA and geriatrician involvement in treatment planning, geriatric therapeutic intervention, and follow-up is also being evaluated in older adults with head and neck cancer (EGeSOR, NCT02025062) (Brugel et al. 2014). Another large, phase III study is evaluating how GA with management recommendations influences communication between older cancer patients and their oncologists (NCT02107443).

In summary, older adults represent an increasing proportion of oncology patients. Often these individuals have coexisting medical, psychological, or social concerns that require attention and management concurrent with their cancer treatment. A GA can be used to detect these potential issues and has been shown to be feasible to implement the GA in both academic and community oncology settings. GA has been shown to influence decision-making when developing an oncology treatment plan, and elements of the GA are predictive of chemotherapy toxicity. GA can be used to develop specific management interventions for identified impairments. There is considerable data in the non-cancer population about the feasibility and utility of GA-guided management, as outlined above, and it is reasonable to extrapolate this data to the oncology setting for older adults with cancer. Preliminary evidence suggests that it is likely feasible to incorporate GA with management recommendations into oncology care, although the optimal model of care for delivery remains unclear. Multiple studies are ongoing to evaluate the feasibility, benefit, and optimal model for delivering GA-guided management interventions in cancer care.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Population Trends in Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management

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Organizing the Clinical Integration of Geriatrics and Oncology

28

Silvio Monfardini

Contents

Abstract

The management of cancer in the elderly requires attention to the oncological aspects as well as to those age-associated. Due to the complexity of the clinical aspects on both sides, the practice of the interdisciplinarity involving Clinical Oncologists, Geriatricians, and other actors is needed, but this is difficult to be achieved without a proper organization with dedicated time and space, since this integrated activity cannot rely only on good will.

A structured approach to the problem has been attempted through the so-called Geriatric Oncology Programs with different characteristics in various countries on the basis of the local health organization and available resources.

No uniform universal model can then be proposed; therefore, here the most common models have been presented as possible alternatives to those who would like to enter in this field. A description of the activities carried out in various countries may also help in

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suggesting solutions for situations similar to those described.

Keywords
Integrating oncology and geriatrics · Organizing the clinical activity · Geriatric Oncology Programs

Introduction

Due to the progressive aging of the population, cancer in the older person has become an increasingly common global problem. More than half of all tumors occur over 65 years with 70% of cancer deaths in people older than 65 years (Yancic and Ries 2000). The projected increase of older cancer patients in the next decades due to the aging of the population will pose more challenges on the health care. But this does not simply mean an expansion of our cancer care resources, rather the need of a care centered on the peculiar needs of elderly cancer patients (Holmes and Allbrand 2013). Taking care of older patients with cancer will require a competence in dealing with comorbidity and disability, understanding that age-associated conditions have a significant influence on the therapeutic approach and impact on survival. And recalling that the desired outcome of treatment by elderly cancer patients are different from those of adult patients, since by the old patients the emphasis is more often placed on the maintenance of quality of life rather than on survival. This means that the increasing and peculiar needs of management of cancer in the elderly should require solutions taking into account a specific patient-oriented care.

Significant progress has been made in recent years to identify specific problems in the elderly cancer population with the development and validation of the Comprehensive Geriatric Assessment (CGA). However, this approach does not substitute for the Geriatricians contribution, but, at the contrary, calls for their presence and intervention in several clinical situations. While the needs of older cancer patients can be optimally addressed by the integration of Geriatrics with Oncology, the majority of patients worldwide in the routine practice is not managed with this interdisciplinary approach, as was already underlined some few years ago (Monfardini and Aapro 2007).

Conceptual Models of Integration

Although there is presently no widely accepted and uniform clinical model for the delivery of cancer care to frail and vulnerable elderly, in the year 2006 an International Society of Geriatric Oncology (SIOG) Task Force report on the organization of the clinical activity of Geriatric Oncology (Monfardini et al. 2007) mentioned that ideally a dedicated Geriatric Oncology Program should have the following Goals:

- To provide comprehensive care through a multidisciplinary approach that considers age-associated conditions which influence cancer management
- To conduct clinical trials in representative older patients
- To reduce adverse outcomes such as nursing home placement and hospitalizations
- To allow patients to continue to live in their primary area of life either at home, hospice, or in nursing home
- To educate health professionals, the public, older patients, and their families about cancer therapy and research

The International Society for Geriatric Oncology (SIOG) launched then in 2011 an initiative to define what, in the experts' opinion, should be the top ten priorities for the development of Geriatric Oncology worldwide (Extermann et al. 2011). Concerning in particular the clinical practice, the first stressed issue was again that of developing interdisciplinary Geriatric Oncology Clinics, especially in academic institutions and comprehensive cancer centers.

In theory, the interdisciplinary approach for each tumor type should take place at the initial therapeutic decision (tumor board), also during the therapy administration, as well as during the follow up. It is assumed that this approach may

allow the best therapeutic choice and the appropriate geriatric interventions.

The team of the health professional should be composed essentially by Clinical Oncologists (Medical Oncologist, Surgical Oncologist, Radiotherapist) and Geriatricians, but also ideally by the Dietician/Nutritionist, Social worker, Nurse, Physiotherapist, Pharmacist, Palliative Care Therapist (Hurria 2014), and of course Primary Care Physician.

In any hospital or academic Institution where the units and/or services of Clinical Oncology (Surgery, Medical Oncology, Radiotherapy) and Geriatrics are present, these physician and nurses could be involved in the development of the clinical activity of Geriatric Oncology. Other units and services may be required to cover optimally the request for supportive therapy, nutrition, and palliation.

This model can vary depending on the needs of the individual patient, family, and caregiver; the availability and expertise of the involved professionals; and support services (Cohen 2009).

Working Examples of Integration

Efforts for the integration of Geriatrics with Oncology are present in all continents but with different degrees of development. The most important results have been achieved in countries where the decisions taken by the Governments has been that of funding and supporting the multidisciplinary clinical activity and research on cancer in the elderly. This happened principally in the USA and in France, but many other efforts in other Countries deserve also to be mentioned.

USA and Canada

In the USA, the initial effort began in the year 2001 with the Geriatrics/Oncology Training Program Development Grant supported by the ASCO with the John A. Hartford Foundation. The emphasis was put on a dual training in Oncology and Geriatrics.

The Recipients of the Geriatrics/Oncology Training Program Development Grant were the Boston Medical Center, the Duke University Medical Center, the Johns Hopkins University, the Northwestern University, the Universities of California, of Chicago, of Colorado, of Michigan, of Rochester, and of Texas. In each of these centers, a training Program Director was appointed.

After 4 years in 2005, the emphasis on the development of Geriatric Oncology was placed on research and acquisition of data with the Grants to NCI–NIA (National Institute of Aging) designated Cancer Centers to study age-integrated aspects. The establishment of these initiatives provided a marked impulse to the development of the research and of the clinical multidisciplinary activity in the field of Geriatric Oncology.

A further step in the USA was the development in the year 2010 of the U13 conference series of Cancer and Aging Research Group NCI-NIA and the Alliance Clinical Trials in Oncology (2010–2014). The U13 grant, "Geriatric Oncology Research to Improve Clinical Care," was a cooperative conference grant between the Cancer and Aging Research Group in collaboration with the Geriatrics and Clinical Gerontology branch of the National Institute on Aging (NIA) and the National Cancer Institute (NCI). The mission of this conference grant program was to provide a forum for a multidisciplinary team of investigators in Geriatrics and Oncology to review the present level of evidence in Geriatric Oncology, identify areas of highest research priority, and develop research approaches to improve clinical care for older adults with cancer. One of the most important contributions of this conference were the recommendations on designing therapeutic clinical trials for older and frail adults with cancer issued in 2014 (Hurria et al. 2014) and subsequently those at improving the quality of life and survivorship of older and frail adults with cancer (Mohile et al. 2016).

Since research in the field of Geriatric Oncology requires integration of the clinical activity between Oncologists and Geriatricians, the availability of all these grants at the beginning of this millennium have been acting as a potent

leverage for the development of Geriatric Oncology Programs.

Several centers in Canada and the USA have developed Geriatric Oncology clinics or consultation services (Soto-Perez-de-Celis et al. 2017). But looking at the present situation, a consistent diversity of designed activities exists across the USA. Some centers provide consultative Geriatric services with Oncology care provided by an Oncologist (McGill University; Memorial Sloan Kettering; Thomas Jefferson University; University of Chicago; University of Rochester; University of Toronto). For example at the specialized oncology care and research in the elderly (SOCARE) of the Rochester and Chicago University through a pretreatment assessment, the risks and benefits of multiple treatment options are evaluated and weighed. In the preoperative setting, a geriatric evaluation prior to cancer surgery is carried out, while in the adjuvant setting risks and benefits of adjuvant therapy are quantified. During the survivorship management of geriatric-related conditions is also provided (Magnuson et al. 2014).

Others centers provide comprehensive care including assessment, treatment, and follow-up of cancer patients within a dedicated Geriatric Oncology team such as the Moffitt Cancer Center, where the Senior Adult Oncology Program of Balducci and Extermann (Overcash 2013) was the first to be developed in the early 1990s. At Moffit, there is in fact a separate clinic within the center with physicians, nurse, pharmacist, social worker, dietitian, and support staff. CGA is performed by a nurse. Cases are discussed at weekly team meeting. Other features of this program are the external grant funding, the fellows training activity, and the international visiting scholarship.

Many other centers consist of Geriatricians or Geriatric Oncologists providing services within a larger cancer center (City of Hope; Royal Columbian Hospital; University of Alabama).

The development of these Geriatric Oncology Programs nationwide has given a big impulse to the production of publications essential to guide the clinical practice, as for example in the case of the development of tools to estimate chemotherapy toxicity in adults, such as the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) (Extermann et al. 2012) and the Cancer and Aging Research Group (CARG) tool (Hurria et al. 2011).

Latin America

Geriatric Oncology Clinics on a consultative model with Geriatricians performing the Geriatric assessment and make recommendations to the treating Oncologist exist in Brazil, five in the city of S Paulo and one in Recife (Soto-Perez-de-Celis et al. 2017).

In Mexico, only one multidisciplinary clinic is located in Mexico City (Soto-Perez-de-Celis et al. 2017).

France

The Oncogeriatric Coordinations Units (UCOG)

In Europe, France has been the first country focusing on the need for older cancer patients to be followed though a cooperation between Clinical Oncologists and Geriatricians. Here, the 2003–2008 Cancer Control Plan enabled the selection, via calls for proposals from the French National Cancer Institute (INCa), of 15 pilot *Oncogeriatrics units designed to bring Oncologists and Geriatricians together around the older cancer patien*t (Brechot 2013).

The specific organization for older people with cancer was enhanced and extended during the 2009–2013 Cancer Control Plan, with a new INCa call for proposals enabling the deployment of oncogeriatric coordination units (UCOG) headed by an Oncologist and a Geriatrician in every region. This scheme currently comprises 24 UCOG. The objective of this specific organization was to provide appropriate care to every cancer patient aged $\geq$75 years receiving care in the facilities authorized to

treat cancer. The UCOG were encharged the following roles:

- To develop collaboration between Geriatricians and Oncologists
- To structure care in all countries to disseminate, in the region under their control, recommendations for good practice in oncogeriatrics
- To develop professionals and encourage training in Oncogeriatrics for all professionals involved (Oncologists, organ specialists, Geriatricians, general physicians, pharmacists, nurses, mobile geriatrics units)
- To encourage specific research projects in oncogeriatrics, with dedicated clinical trials for this population
- To inform elderly patients, their families, and the general public of the advances made in cancer care, also in older patients, the importance then of early and reliable diagnosis, and insisting on the participation in clinical trials allowing access to innovative treatments

At the first evaluation in 2010, an increase in the use of the CGA was noted, however, with a great heterogeneity among the different Pilote Units and many patients not benefitting from this organization (Brechot 2013).

The next step of the Program consisted in selecting 376 health facilities that had admitted 80% of older people with cancer. Of these 376 facilities, 277 were contacted by the UCOG. Among the actions conducted by UCOG in these facilities, training of health professionals in the G8 geriatric prescreening test (Soubeyran et al. 2014) constituted the first phase of training in oncogeriatric care. G8 training was established in 173/277 facilities contacted by the UCOGs (Brechot and Balandier 2015).

University Training

Three university diplomas and two inter-university diplomas were established providing specific teaching in Oncogeriatrics.

Also an optional certificate in oncogeriatrics as part of medical studies was developed in Paris. An active role in the University training was played by the UCOG, coordinators in 46% of them being responsible for university training in oncogeriatrics. In total, 830 health professionals were trained in this context in the year 2013. Thus 399 (48%) Geriatricians and 66 (8%) Oncologists had this training as well as 92 general physicians (11%) and 85 pharmacists (10%).

Training as Part of Continuing Professional Development (CPD)

Nineteen hundred health professionals had oncogeriatrics training in 2013 as part of CPD. Of these, 29% were Geriatricians, 12% Oncologists, 14% general physicians, and 17% nurses. As for the university training, Geriatricians were much more numerous than Oncologists.

The positive consequence of this activity was that in several public and private facilities, an effective cooperation between Oncologists and Geriatricians took place.

The Geriatrician's participation in organ multidisciplinary consultations made possible, via the simultaneous presentation of oncological and geriatric assessments, to share proposals for care. Private Oncologists were noted increasingly moving into the Oncogeriatrics field.

The main difficulty, however, identified by the UCOG in trying to spread the practice of geriatric oncology to the surrounding regional hospital was the lack of funding for the geriatric consultation, since this was not covered by any specific official pricing. The assessment activity for this population was thus less valued, impeding so the geriatric assessments. This could then be poorly developed in some regional hospitals, despite the motivation of the physicians.

Research

The establishment of the UCOG provided a marked impulse to the oncogeriatric research. The number of older patients entered in a clinical trial made a strong progress in the last few years. The enrolled cases were over 800 in 2008, while in 2013, a total of over 5380 older patients were enrolled in clinical trials, 4710 in institutional trials, and 670 in an industry-sponsored trials. Although an INCa report on the Geriatric Oncology publications after the

birth of the UCOG is not yet available, the increase of the scientific articles and proffered papers at the main international meetings (ASCO, ESMO, SIOG) produced in France by the clinicians of these units has been impressive.

Other European Countries

In Europe, other successful models of care delivery and cooperation between Clinical Oncologists and Geriatricians have been developed in Belgium, Holland, Norway, and Switzerland, but with less governmental support and on a less larger scale than in France. In Belgium, the national cancer plan has provided significant financial support for geriatric assessment projects in 30 hospitals. In Netherlands, collaboration between Oncologists and Geriatricians exist mostly in general hospitals, as well as a formalization of education programs: a foundation for Geriatric Oncology is active with taskforces aimed at research activity, care, and education programs with one center of Geriatric Oncology and collaboration between Geriatricians and Oncologists in several centers. In Norway, there are three centers, including one at a geriatric and another at a surgical site, where clinical cooperation of Geriatricians with Clinical Oncologist and research activity is carried out. In Switzerland, there are three centers with an activity of Geriatric Oncology, two at a geriatric site, with weekly multidisciplinarity discussions and research activity (Soubeyran et al. 2014; Monfardini et al. 2013). In Italy, a considerable activity in the field of Geriatric Oncology is carried out on a goodwill base in 12 Medical Oncology units and in two Geriatrics units. The cooperation of Medical Oncologists with Geriatricians, in few hospitals where they are present, is good, but without structured periodical case discussion. The research activity is in some units the most prominent strength point (Brechot and Balandier 2015; Monfardini et al. 2012a).

Spain has three Geriatric Oncology clinics (two in Madrid and one in Cuenca).

Ireland has two pilote Geriatric Oncology Programs ongoing respectively in Waterford and Dublin.

In Greece there are two Geriatric Oncology clinics (Patras and Heraklion).

Israel

In Israel, two Geriatric Oncology clinics have been created within tertiary medical centers (Soto-Perez-de-Celis et al. 2017).

Australasia

Australia

Geriatric Oncology services have been established in Adelaide, Perth, Brisbane, Canberra, Melbourne, and the Gold Coast. These clinical services operate slightly differently in accordance with available local infrastructure and skills of the clinicians. The majority of these teams are hospital based, but service delivery is also available to ambulatory outpatients (Soto-Perez-de-Celis et al. 2017).

Concerning New Zealand, only in Hamilton has been developed a program for older cancer patients.

Singapore

There is a Geriatric Oncology clinical service at the National Cancer Centre Singapore.

Possible Models in Different Situations and Settings

Different Situations

For the practice of interdisciplinary activity of Geriatric Oncology, at least three different solutions for different situations have been followed worldwide. These have been published (Wildiers et al. 2014) or simply presented at SIOG meetings (Hurria 2016).

Geriatric Oncologist

The Geriatric Oncologist is the treating physician for cases where the Geriatric Oncology expertise is needed. The CGA is performed by him/her and therapeutic recommendations are given after oncological multidisciplinary discussion, if indicated systemic therapy is administered in the Geriatric Oncology Unit. This type of organization has the major advantage that geriatric expertise is centralized. The other advantage provided by this approach is that of having the patient followed during all his disease trajectory. However, the disadvantage is that this model can only reach a limited number of patients who are willing and able to travel to the Geriatric Oncology unit for consultation. Also the lack of financial incentives might drive general Oncologists not to refer patients. And a general Geriatric Oncologists might miss the details, rapidly evolving knowledge in the broad field of Oncology.

Geriatric Consultation

A consultation is provided to the Clinical Oncologist referring patients to the Geriatricians: this means to bring Geriatric consultation teams to the patients. These remain under supervision of their treating Oncologists. As a consequence, geriatric assessment result and recommendations are provided to the clinical Oncologist and selected patients can also be referred to appropriate specific geriatric programs.

This model has the potential advantage of reaching a large proportion of older patients with cancer with the consequence of a cross-fertilization of Oncology and Geriatric principles. However, if not well applied, treating Clinical Oncologists might not know what to do with CGA results. It may also be difficult to provide multiple geriatric consultations through all the disease trajectory of the old patient. On the Geriatrician's side, a possible limitation can be that of being involved with other multiple role within their Institutions and to suffer from a time constraint due to overwhelming number of elderly cancer patients. Of course, this approach can be easy if Geriaticians and Clinical Oncologists are present in the same hospital, more difficult if they work in the same city but in different hospital, and apparently impossible if Geriatrics does not exist in a region or in a country, as may happen in Europe. To overcome this difficulty, teleconferences with geriatric consultation on special cases may be of help in these instances.

Geriatric Oncology Team Collaboration with the Treating Clinical Oncologist or Shared Care Model

The Geriatrician or the Geriatric Oncologist performs the geriatric assessment and provides the therapeutic recommendations and geriatric interventions. The therapeutic and care plan is provided through a multidisciplinary team discussion with the participation of the treating specialist. The Geriatric Oncology team can then provide a concurrent care across the disease trajectory. This approach implies a periodical assessment and multidisciplinary discussions with different specialists. Therefore, it requires a well-established organization since there should be, where needed, also the participation of nurse, social workers, pharmacists, palliative and supportive care specialist and a general practitioner.

Since the nurse is often a core member of the multidisciplinary team, it has been stressed that the leadership role of the Geriatric Oncology nurse should be extended to the construction and ongoing maintenance of the multidisciplinary activity (Overcash 2013).

The choice of the model preference should be given to the best-designed model of activity that fits with the local health care.

Different Settings

For which cases, when, and where the interdisciplinary activity should be carried out?

Cases with Interdisciplinary Approach Needed

Not all cases of elderly with cancer need to be seen by the Geriatricians (Holmes and Allbrand 2013), while probably all oncological cases encountered by Geriatricians should be seen by Clinical

Oncologists. To identify which cases should be seen by Geriatricians, several screening tests have been developed, and on these a detailed and a thorough review updating the SIOG recommendations has been made by De Coster et al. (2014). However in this review considering the G8 (the screening test mandatory for all EORTC trials and the most used tool in Europe), the percentage of abnormal screening test ranges, according to the various Authors, from 68% to 82% of all older patients. This means that out of ten screened patients, only two or three could be spared of the geriatric evaluation. Then not all cases, but the majority of patients could need a full geriatric evaluation.

Timing

The time of the interdisciplinary activity is initially that of the therapeutic decision. Also during the treatment of systemic treatment or after surgery, a reassessment may be necessary, although the optimal timing in these instances has never been clearly established. Often it happens that patients receive a mutidisciplinary consultations not before the oncologic decision but during therapy (Lazarovici et al. 2011). Concerning the follow up period after the end of treatment, it has been stressed that in elderly cancer survivors an assessment of persistent and coexisting health problems should be carried out. This approach should imply a referral to Geriatricians and a relationship of Clinical Oncologists with Geriatricians. Therefore, a clinical dialogue between Oncology and Geriatric specialists other than cross-training of clinical researchers should be encouraged (Rowland and Bellizzi 2014). However, in this field, issues are still open concerning delivering optimal post-treatment care (Monfardini et al. 2017).

The possibility of following older patients at a variety of time points, during their oncological trajectory has been, however, shown by the specialized Oncology Care and Research in the Elderly (SOCARE) clinic (Magnuson et al. 2014).

Place

The place of the interplay should be that of the Units of Clinical Oncology (Medical, Surgical Oncology, and more rarely Radiotherapy) within a general Hospital, an Academic Center or a Comprehensive cancer center. Attention should also be paid to the possibility of bringing Oncology into Geriatrics. There can be in fact a setting (Geriatric Department, Geriatric or Medicine Unit) where Geriatricians can propose for consultation cancer patients to Medical Oncologists. In this situation, Geriatricians are not "reduced to make simple assessments, their opinion and proposals being ignored" (Sifer-Rivière et al. 2011). This can provide a definite advantage for the management of the old frail cancer patient (Monfardini et al. 2012b).

Since nursing homes also hosted older cancer patients, the possibility of bringing also here Medical Oncologists for consultation should not be missed (Cutolo et al. 2012).

Suggestions/Recommendations for Starting a Geriatric Oncology Program

The possible partners to be involved in the development of a Geriatric Oncology Program should be made aware by the proponent of the dimension of the problem of cancer in the elderly. For this goal, a considerable amount of epidemiological information is available in the English literature: the demographic change has consisted in a rapid increase of the population of adults older than 65 years of age. Since older patients with cancer, particularly those older than age 70 years, have specific health needs, the possible partners should be convinced that Geriatric Oncology is no longer a niche field with only a few dedicated clinician and researchers but instead an established field of activity. And that this activity takes place in several countries worldwide.

They should be informed that a scientific society – The SIOG – as a multidisciplinary society that unites experts in the field of Geriatric Oncology from throughout the world has been founded and is active since the year 2000. Concerning the clinical practice, the SIOG aims then at integrating geriatric evaluation (including comorbidities) into Oncology decision-making and has been

so providing guidelines for all tumor types. To implement this process, interdisciplinary Geriatric Oncology clinics should be developed.

The common discussion of the most difficult and interesting cases has been acting as a leverage of many Geriatric Oncology Programs. If the participants are convinced of the usefulness of case discussion and keep on in carrying it periodically, this can be the core business of this activity. Since this work requires an extra time, the health administrators should be convinced that this activity produces better clinical results. Also sparing on the costs is possible by reducing treatment complications and readmissions to the hospital, as well as the admission to the nursing homes, even if at this time no published information is available on this issue. Raising public awareness on the problem of cancer in the elderly will help in achieving the support of administrators.

A positive stepwise progression could be suggested for Medical Oncologists willing to establish a Geriatric Oncology Program through these successive phases:

1. If a Medical Oncologist is interested in Geriatrics (Geriatric Oncologist), he could initially collect the information on the CGA domains (ADL, comorbidity, MMS, GDS) before deciding on treatment.
2. This Geriatric Oncologist could then have somebody else (e.g., a nurse) collecting for him the information on G8 and/or CGA. He should also look the availability of a geriatric consultation for a help in the interpretation of the results of the collection of the CGA items and for a deeper Geriatric assessment, as well as for the planning of the geriatric interventions and supportive therapy.
3. This Geriatric Oncologist should then try to have an integrated framework consisting in a formally established and recognized relationship with the Geriatricians (interdisciplinary case discussion at the tumor board) and scheduled case conferences.
4. The further progression should be that of having a fully established multidisciplinary activity, possibly funded. This program should carry out of clinical, training, and research projects with scheduled case and research interdisciplinary discussion in connection with other specialists (Surgical Oncologists, Radiotherapists, nurses, social workers, pharmacists, palliative and supportive care specialists, and general practitioners). The Program should be coordinated by a Medical Oncologist, or by a Medical Oncologist and a Geriatrician.

If the possible proponent of a Geriatric Oncology Program is a Geriatrician, it should be firstly taken into account that recruiting other Geriatricians may be difficult, since there is a Geriatricians shortfall in Europe but also in the USA.

But, there is often a more insidious handicap such as the fact that the Geriatrician's tools and know-how may be often perceived ambiguously by the Clinical Oncologists, who may be unclear as to the Geriatricians role. On their side, Geriatricians may feel confined to the periphery of organization of cancer treatment and being involved with other multiple role within their Institutions suffer from a time constraint due to an overwhelming number of elderly cancer patients (Sifer-Rivière et al. 2011). Mainly for this reason on the Geriatricians side, it has been stressed a proper selection of cases to be proposed to the Geriatricians (Karnakis et al. 2016). Karnakis et al. have in fact quite well presented the point of view the Geriatricians who have been embarking in the organization of a Geriatric Oncology Program in a large Cancer Center. To them, the major challenges in establishing collaboration in Geriatric Oncology are the evaluation of the resources of the center, to know the role of each member of the team, to establish a good communication both within the team and with the patients, to determine the referral criteria, and to use the screening tests to select which patients can benefit the most from the multidisciplinary evaluation and a thorough GA. Their conclusion is also that multidisciplinary care models must be studied and standardized, according to the sociocultural and healthcare services of each country.

Finally, since the practice of Interdisciplinarity may not be easy at the beginning, it is important

that Clinical Oncologists in starting a collaboration get acquainted with the minimum basic principles of Geriatrics, and the same for Geriatricians concerning the basic oncological information. And that at both sides is in advance clarified what, in discussing clinical cases, Clinical Oncologists can ask to Geriatricians and vice - versa, as for example has been attempted in the Treviso SIOG advanced courses (Colloca and Monfardini 2017).

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Predictive Tools for Older Cancer Patient Management

29

Ki Hyang Kim and Martine Extermann

Contents

Abstract

Because older cancer patients are very heterogeneous, decision-making is difficult for physicians. Predictive tools can help provide objective data support to inform treatment decisions. Such tools exist to predict tolerance to chemotherapy, estimate treatment benefit in view of other life-limiting conditions, or assess surgical risk, for example. In this chapter we will review several of them: the Chemotherapy Risk Assessment Score for High-age patients (CRASH score), the Cancer and Aging Research Group score (CARG), various proposed risk stratification models for surgical risk, and the Lee-Schonberg Index.

Keywords

Predictive tools · CRASH score · CARG score · Geriatric oncology · Clinical decision-making

Introduction

Oncology care entails complex decisions. This is even more the case in older patients, who are very heterogeneous in terms of health, functional, psychological, social, cultural, and economic status

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(Puts et al. 2015). Yet, decision analysis studies demonstrate that oncologists have a hard time integrating more than three to four variables in their decisions (Magnuson et al. 2016; Hurria et al. 2016; Huisman et al. 2016; Luciani et al. 2013; Yourman et al. 2012; Extermann 2011). Furthermore, geriatric assessment (GA) is a key component of decision-making in older cancer patients. GA includes functional status, comorbidity, cognition, psychological state, social support, nutritional status, and a review of medications (Hurria 2015; Extermann 2010; Inouye et al. 1998; Lee et al. 2006). For these various reasons, predictive tools to summarize the information and assist benefit and risk prediction can be highly useful in geriatric oncology. In geriatric oncology practice, brief decision tools were developed to assess robustness or frailty for chemotherapy by integration of geriatric instruments (Extermann 2010, 2012; Extermann et al. 2012; Hurria et al. 2011). This chapter reviews predictive tools for older cancer patient management: chemotherapy and surgery.

Chemotherapy Toxicity Predictive Tools in Older Cancer Patients

Tailoring chemotherapy to the tolerance of a patient is a frequent challenge in geriatric oncology. However, it is often difficult to estimate clinically the extent of that risk. Historically, oncologists tend to underdose chemotherapy in older patients (Field et al. 2008; Shepherd et al. 1994). This topic has therefore seen quite a bit of research. Several studies, both prospective and retrospective, have demonstrated the association of various parameters with toxicity from chemotherapy. Yet few have led to formal externally validated indexes. Two such indexes are available to date for older patients.

The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score

The CRASH score predicts grade 4 hematologic and grade 3 or 4 non-hematologic toxicity. This study was a prospective, multicenter study of patients aged $\geq$70 years who were starting chemotherapy. In total, 562 patients were accrued, and 518 patients, who were 2:1 randomly assigned to the derivation cohort or the validation cohort, were evaluated. The median age of participants was 75.5 years.

Baseline variables tested represented four categories: (1) clinical variables included age, sex, body mass index (BMI), diastolic blood pressure, comorbidity measured with the Cumulative Illness Rating Scale-Geriatric (CIRS-G), and polypharmacy; (2) laboratory variables included white blood count, hemoglobin, lymphocyte count, aspartate aminotransferase, creatinine clearance, albumin, and lactate dehydrogenase (LDH); (3) geriatric and functional assessment variables included self-rated health, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), the Lawton 9-item Instrumental Activities of Daily Living (IADL), nutritional assessed with the Mini Nutritional Assessment (MNA), cognition assessed with the Folstein Mini-Mental Status (MMS), and depression assessed with the Geriatric Depression Scale (GDS)-short form; and (4) cancer-specific variables included disease stage, bone marrow invasion, prior chemotherapy, and response. Tumor type was not included because (1) tumor type has minimal influence on the patient chemotherapy toxicity risk (Extermann et al. 2002); (2) no good system exists for grouping tumor types to predict chemotherapy toxicity; (3) the main effects on the patients' general condition are likely better accounted for by measuring other factors (e.g., performance status); (4) the toxicity of the chemotherapy regimens varies over time and practice settings for a given tumor type; and (5) the group had validated a method for ranking the toxicity of chemotherapy regimens (Chemotox) valid across tumor types: the MAX2 index (Table 1) (Extermann et al. 2004). The MAX2 index describes the overall risk of severe toxicity of a regimen using the highest frequency of both grade 4 hematologic toxicity and grade 3–4 non-hematologic toxicity reported in the published literature. It correlates with the overall risk of severe toxicity in ECOG trials (Fig. 1) (Extermann et al. 2004).

As different predictors were identified for hematologic and non-hematologic toxicity, the CRASH score was developed along two sub-scores: hematologic score and non-hematologic score. The hematologic score included a clinical variable, diastolic blood pressure; a laboratory variable, LDH; a geriatric and functional assessment variable, IADL; and the toxicity of the regimen. The non-hematologic score included geriatric and functional assessment variables: ECOG-PS, MMS, MNA, and the toxicity of the chemotherapy (Table 2). Items are rated on a 0–2 point scale, and summing the points stratifies patients into four risk categories (low, medium-low, medium-high, and high). The CRASH score is available online (www.moffitt.org/eform/crashscoreform). The CRASH score was validated by two methods which were bootstrap internal validation of 200 randomly selected samples from the derivation cohort of 331 patients and independent sample validation of 187 patients. Figure 2 showed risk percentage of grade 4 hematologic toxicity and grade 3 or 4 non-hematologic toxicity based on each validated methods. The risk of hematologic toxicity was 7% in the low-risk categories and 100% in the high-risk categories ($p < 0.001$). The risk of non-hematologic toxicity was 33% in the low-risk categories and 93% in the high-risk

Table 1 The MAX2 index (Extermann et al. 2012)

(Most frequent grade 4 hematological toxicity + most frequent grade 3 + 4 non-hematological toxicity)/2
25% grade 4 neutropenia, 13% grade 3 + 4 diarrhea MAX2 = (0.25 + 0.24)/2 = 0.19 Notes Alopecia is not counted When only white blood cell nadirs are reported, ANC is extracted as follows: 0.6∗G3 + 4 leucopenia, if G4 leukopenia <30% 0.8∗G3 + 4 leucopenia, if 30% above
The formula that correlates the MAX2 index with actual risk of severe toxicity (Chemotox) is:
All patients $\text{Prob} = \frac{\exp(-0.94+6.16*\text{MAX2})}{1+\exp(-0.94+6.16*\text{MAX2})}$
Patients >70 years old $\text{Prob} = \frac{\exp(-0.94+8.30*\text{MAX2})}{1+\exp(-0.94+8.30*\text{MAX2})}$

Abbreviation: MAX2, the average of the highest frequency of both grade 4 hematologic toxicity and grade 3/4 non-hematologic toxicity (the "maximum 2" toxicities)

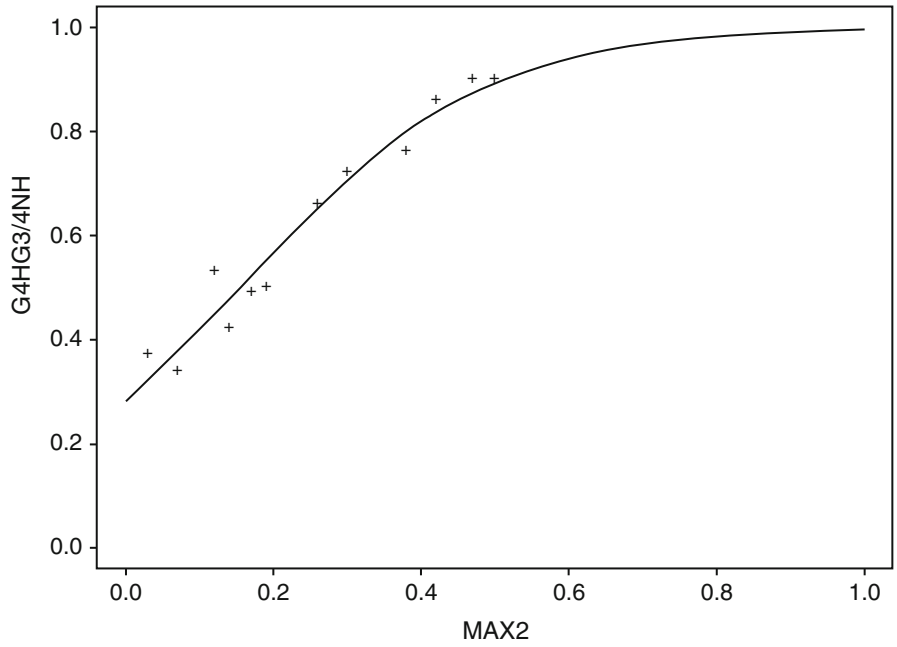

Fig. 1 MAX2 index correlation graph in ECOG trials (Extermann et al. 2012)

Table 2 CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) score (Extermann et al. 2012)

Points			
Predictors	0	1	2
Hematologic score			
Diastolic BP	≤72	>72	
IADL	26–29	10–25	
LDH (if UUN 618 U/L; otherwise, 0.74L[a] UNL)	0–459		>459
Chemotox[a]	0–0.44	0.45–0.57	>0.57
Non-hematologic score			
ECOG-PS	0	1–2	3–4
MMS	30		<30
MNA	28–30		<28
Chemotox[a]	0–0.44	0.45–0.57	>0.57

Abbreviation: BP, blood pressure; Chemotox, toxicity of the chemotherapy regimen; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; IALD, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MMS, Mini-Mental Health Status; MNA, Mini Nutritional Assessment; ULN, upper limit of normal
[a]Percent of risk of severe toxicity of a chemotherapy based on the MAX2 score (see Table 1)

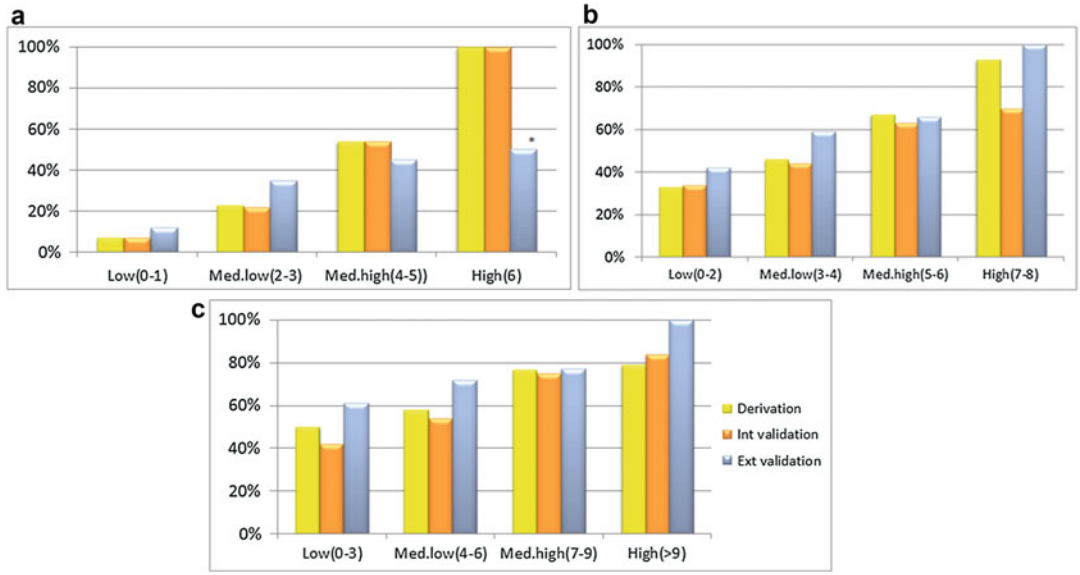

Fig. 2 The percentage of patients who experienced grade 4 hematologic toxicity (**a**), grade 3 or 4 non-hematologic toxicity (**b**), and combined toxicity (**c**) according to the CRASH score. Med indicates medium. ∗ indicates only two patients (Extermann et al. 2012)

categories ($p < 0.001$). However, in the combined risk category, the low-risk categories were 50% and the high-risk categories were 79% ($p < 0.001$). In a validation study of the CRASH score in an Italian cohort, the CRASH score was significantly associated with hematologic toxicity ($p = 0.005$) (Luciani et al. 2015). Another French study showed that the CRASH score was validated in non-Hodgkin lymphoma (Fargeas et al. 2014; Trarieux-Signol et al. 2013). One should note that even patients in the low-risk categories of the CRASH score have a residual risk of severe toxicity and therefore should be adequately monitored.

The Cancer and Aging Research Group (CARG) Chemotherapy Toxicity Assessment

The CARG score predicts the risk of grade 3–5 hematologic and non-hematologic toxicities. This study was a prospective, multicenter study of patients age ≥65 years who were starting chemotherapy. In total, 500 patients were evaluated. The mean age of participants was 73 years.

Baseline variables tested included (1) sociodemographic factors (age, sex, education, marital status, household composition, employment status, race/ethnicity), (2) study site, (3) cancer type (breast, GI, genitourinary, gynecologic, lung, and other), (4) cancer stage, (5) chemotherapy dosing (standard or dose reduced), (6) number of chemotherapy drugs (mono- or polychemotherapy), (7) line of treatment, (8) chemotherapy duration, (9) receipt of primary prophylaxis WBC growth factor, (10) prechemotherapy laboratory value (WBC, hemoglobin, liver function tests, albumin, creatinine clearance), and (11) the geriatric assessment measures (Table 3) (Hurria et al. 2005, 2011). The geriatric assessment measure included a healthcare provider portion and a patient portion. The healthcare provider portion had the patient's Karnofsky Performance Status (KPS), the Timed Up and Go measure (a performance-based measure of functional status), and the Blessed Orientation-Memory-Concentration test (a screening measure of cognitive function). The patient portion had self-reported measures of functional status, comorbidity, medications nutrition, psychological state, and social support/function (Hurria et al. 2016).

The CARG investigators identified geriatric variables associated with prognosis and narrowed down the relevant items within each to design a score that included 11 questions: factors obtained in everyday oncology practice – patient age, number of chemotherapy drugs, dosing, and laboratory values – and factors not used in everyday oncology practice-geriatric assessment questions (Table 4) (Hurria et al. 2011, 2016). The CARG score calculates the sum of the scores. The total risk score ranges from 0 (lowest toxicity risk) to 19 (highest toxicity risk). The total risk score was divided into three categories: low risk (0–5 points), medium risk (6–9 points), and high risk (10–19 points). Figure 3 shows the risk percentage of grade 3–5 hematologic and non-hematologic toxicity. The lower-risk category had a 30% risk of chemotherapy toxicity, and the high-risk category had a 83% risk ($p < 0.001$). The CARG score was validated using internal and external validation model (Hurria et al. 2011, 2016). Internal validation used the tenfold cross-validation process. External validation was performed in 250 patients who were over 65 years old. The results showed a risk of 36.67%, 62.41%, and 70.18% in the low-, medium-, and high-risk groups, respectively (Hurria et al. 2016). Another group compared the CARG tool, the VES-13, and oncologist judgment in men with prostate cancer and found lower toxicity than predicted (Alibhai et al. 2017). Analogous to the CRASH score, patients in the low-risk group still have a residual risk of severe toxicity and need proper monitoring.

Although some parameters of the CRASH score and CARG score have differences (Table 5), these two scores are available methods in oncology practice to stratify the personal risk of chemotherapy toxicity in older cancer patients. They can be useful notably as dilemma breakers when conflicting clinical impressions make a physician hesitate between treatments. More work needs to be done to define decision thresholds or changes in supportive care linked to this risk stratification. Extending the validation of these tools to targeted therapies and immunotherapies would also be a useful development. The impact of those scores on the efficacy and outcomes of chemotherapy beyond toxicity also needs additional study.

Predicting the Risk of Perioperative Complications

Although surgery is an effective cancer-ablative therapy, the increase in complication rate, mortality, length of hospital stay, and intensive care unit admission with age is a barrier to treatment for

Table 3 Measures in the Geriatric Assessment Questionnaire (Hurria et al. 2011)

Domain	Measure	No. of items	Description	Range of scores
Functional status	Activities of Daily Living (subscale of MOS physical health) (Stewart 1992)	10	Measure limitation in a wide range of physical functions (from bathing/dressing to vigorous activities such as running)	0–100 (higher score: better physical function)
	Instrumental Activities of Daily Living (subscale of the OARS) (Fillenbaum and Smyer 1981)	7	Measure ability to complete activities required to maintain independence in the community (shopping, meal preparation, making telephone calls, money management)	0–14 (higher score: less need for assistance)
	Karnofsky Self-Reported Performance Rating Scale	1	Global indicator of patient function determined by patient self-report ranging from "normal" to "severely disabled"	40–100 (higher score: better physical function)
	Karnofsky Physician-Rated Performance Rating Scale (Loprinzi et al. 1994)	1	Global indicator of patient function determined by physical report ranging from "normal" to "dead"	0–100 (higher score: better physical function)
	No. of falls in the last 6 months	1	Indicates number of times fallen in the last 6 months	0–100 (higher score: better physical function)
Comorbidity	Physical Health Section (subscale of the OARS) (Fillenbaum and Smyer 1981)		Presence/absence of 13 comorbid illness: number of comorbid illness	
Psychological state	Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983)	14	Assesses the level of depression and anxiety experienced in the past week	0–100 (higher score: poorer psychological state)
Social activity	MOS Social Activity Survey (Stewart 1992)	4	Measure the degree in which physical or emotional problems interfere with level of social activity	0–100 (higher score: better social activity)
Social support	MOS Social Support Survey: Emotional/Information and Tangible Subscales (Sherbourne and Stewart 1991)	12	Measure the perceived availability of social support	0–100 (higher score: better social support)
Nutrition	Body mass index	1	Weight in kg/(height in m)^2	
	Percent unintentional weight loss in last 6 months	1	(Unintentional weight lost in the last 6 months/baseline body weight) × 100	

Abbreviations: MOS, Medical Outcomes Study; OARS, Older American Resources and Services

older patients (Korc-Grodzicki et al. 2014). Especially, emergency surgery due to delay of cancer diagnosis causes an increase in mortality and morbidity of this population (Korc-Grodzicki et al. 2014). Optimizing perioperative management is important to increase long-term survival in this population. The data show that elderly patients who survive the first year after surgery have the same cancer-related survival as younger patients (Dekker et al. 2011). Geriatric surgical patients are heterogeneous and have various vulnerabilities. Therefore, to develop assessment tools to predict various vulnerabilities in these populations is a challenge. The comprehensive geriatric assessment (CGA) is a multidisciplinary, multidimensional assessment tool to analyze a

Table 4 CARG (Cancer and Aging Research Group) scoring tool to calculate chemotherapy toxicity risk (Hurria et al. 2016)

Variable	Value/response	Score
Age of patient	≥72 years	2
	<72 years	0
Cancer type	GI or GU cancer	2
	Other cancer type	0
Planned chemotherapy dose	Standard dose	2
	Dose reduced upfront	0
Planned no. of chemotherapy drugs	Polychemotherapy	2
	Monochemotherapy	0
Hemoglobin	<11 g/dL (male), <10 g/dL (female)	3
	≥11 g/dL (male), ≥10 g/dL (female)	0
Creatinine clearance (Jelliffe, ideal weight)	<34 mL/min	2
	≥34 mL/min	0
How is your hearing (with a hearing a gearing aid, if needed?)	Fair, poor, or totally deaf	2
	Excellence or good	0
No. of falls in the past 6 months	≥1	3
	None	0
Can you take your own medicine?	With some help/ unable	1
	Without help	0
Does your heath limit you in walking one block?	Somewhat limited/ limited a lot	2
	Not limited at all	0
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	Limited some of the time, most of the time, or all of the time	1
	Limited none of the time or a little of the time	0

Abbreviation: GI, gastrointestinal; GU, genitourinary

biologic age of the elderly. This tool helps to identify who is at risk for postoperative adverse events and provides a possible opportunity to implement perioperative interventions (Korc-Grodzicki et al. 2014). The International Society of Geriatric Oncology recommends that CGA should be used in older patients with cancer to detect unaddressed problems (Extermann et al. 2005). Several studies showed the importance of the geriatric assessment (Table 6).

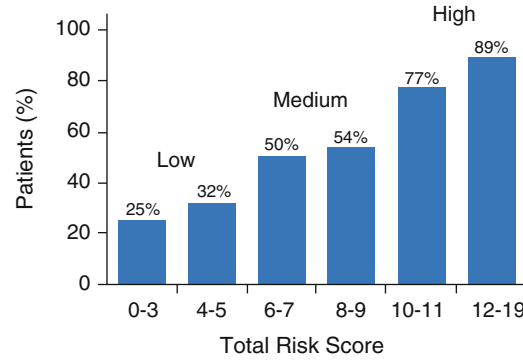

Fig. 3 Risk of grade 3–5 toxicity based on the CARG score (Hurria et al. 2011)

Table 5 Comparison of the CARG score and CRASH score

Parameter	CARG score	CRASH score
Number/ age	500 patients/ ≥65 years	518 patients/ ≥70 years
Geriatric assessment	Cancer-specific CGA, KPS	ECOG-PS, MNA, IADL, Folstein MMSE, GDS
Predictors chosen	Tumor type and stage included	Tumor type not included
Chemo adjustment	Tumor type, standard dose, poly/monotherapy	MAX2, dose, and regimen of chemotherapy

CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients

The practice guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society recommends the preoperative assessment of geriatric patients; these are summarized in checklist form (Table 7) (Chow et al. 2012). It is important to assess the decision-making capacity in older cancer patients. Cognitive ability should be assessed, and short tools such as the Mini-Cog maybe helpful in quickly screening out cognitive issues (Oresanya et al. 2014). After that, the physician could have patients articulate their personal treatment goals (Oresanya et al. 2014). In patients treated with major thoracic and abdominal surgery, preoperative impaired cognition, low albumin level, previous falls, low hematocrit level, any functional dependence, and a high burden of comorbidities were related to 6-month mortality

Table 6 Geriatric assessment as predictor of surgical outcomes in elderly patients (Korc-Grodzicki et al. 2014)

Reference	Age (years)	No. of patients	Type of surgery	Predictor	Outcome
Robinson et al. (2009)	68–80	110	Elective surgery requiring postoperative ICU admission	Impaired cognition, recent falls, lower albumin, greater anemia, functional dependence, and increased comorbidities	6-month postoperative mortality and post-discharge institutionalization
Robinson et al. (2012)	67–79	186	Elective surgery requiring postoperative ICU admission	Cognitive impairment	Increased postoperative complications, length of stay, and long-term mortality
Preoperative Assessment of Cancer in the Elderly (PACE) (Audisio et al. 2008)	≥70	460	Cancer surgery for solid tumors	Disability, fatigue, and abnormal performance status	Postoperative complication
Dale et al. (2014)	80% were older than 60	76	Pancreaticoduodenectomy for pancreatic tumors	Fried's exhaustion	Major complications, longer hospital stay, and ICU admissions
Large et al. (2013)	≥65	49	Radical cystectomy for bladder cancer	Cognitive impairment and older age	Post-cystectomy delirium
Fukuse et al. (2005)	60–84	120	Thoracic surgery, multiple causes	Functional dependency and cognitive impairment	Postoperative complications
Makary et al. (2010)	65–94	594	Multiple surgeries	Frailty	Postoperative complications, length of stay, and discharge to skilled nursing or assisted living facility
Kim et al. (2013)	≥65	141	Multiple surgeries	Functional dependency, poor nutrition, and cumulative impairment in geriatric assessment	In-hospital death, post-discharge institutionalization, adverse in-hospital events, and prolonged length of stay
Revenig et al. (2013)	19–86	189	Oncologic, urologic, and general surgery procedures	Intermediately frail or frail on the Hopkins Frailty Score	30-day postoperative complications
Huisman et al. (2014)	Older than 70	180	Elective surgery for solid tumor	Timed Up and Go test	30-day postoperative complications

and post-discharge institutionalizations (Robinson et al. 2009).

In the Preoperative Assessment of Cancer in the Elderly (PACE) study, poor health in relation to functional dependency, fatigue, and abnormal performance status was associated with a 50% increase in the relative risk of postoperative complications (Audisio et al. 2008). PACE is used as a

tool for surgical risk assessment in onco-geriatric patients (Audisio et al. 2005). PACE included these factors: Mini-Mental Status, Satariano's modified index of comorbidities, Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Geriatric Depression Scale (GDS), Brief Fatigue Inventory (BFI), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), American Society of Anesthesiologists (ASA) physical status system, physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) and in the elderly (Elderly POSSUM) (Audisio et al. 2005). In the patients aged 65 and older, a lower Mini-Mental Status score and older age were related with the development of post-cystectomy delirium (Large et al. 2013). Table 8 shows results of PACE interim analysis with 30-day morbidity (Ramesh et al. 2006). In patients treated with pancreaticoduodenectomy, older age and worse scores in geriatric assessment were related with longer hospital stays and surgical intensive care unit admission (Dale et al. 2014). These tools are to identify high-risk patients and improve communication between the surgeon and patients. However, they are still limited in their use in real practice because of the resources and time needed to complete them (Korc-Grodzicki et al. 2014; Chow et al. 2012). Another study showed that a preoperative multi-domain frailty measure based on a CGA was useful compared to the frailty measure based on physical phenotype of frailty in predicting postoperative complications (Kristjansson et al. 2012). In the UK, Enhanced Recovery after Surgery (ERAS) programs have

Table 7 Checklist for the optimal preoperative assessment of the geriatric surgical patient in elderly patients

In addition to conducting a complete history and physical examination of the patient, the following assessments are strongly recommended:
Assess the patient's cognitive ability and capacity to understand the anticipated surgery.
Screen the patient for depression.
Identify the patient's risk factors for developing postoperative delirium.
Screen for alcohol and the other substance abuse/dependence.
Perform a preoperative cardiac evaluation according to the American College of Cardiology/American Heart Association algorithm for patients undergoing noncardiac surgery.
Identify the patient's risk factors for postoperative pulmonary complications and implement appropriate strategies for prevention.
Document functional status and history of falls.
Determine baseline frailty score.
Assess patient's nutritional status and consider preoperative interventions if the patient is at severe nutritional risk.
Take an accurate and detailed medical history and consider appropriate perioperative adjustment and monitor for polypharmacy.
Determine the patient's treatment goals and expectations in the context of the possible treatment outcomes.
Determine patient's family and social support system.
Order appropriate preoperative diagnostic tests focused on elderly patients.

Table 8 PACE (Preoperative Assessment of Cancer of the Elderly) interim analysis with 30-day morbidity

Components	Complications (64 patients)	No. of complications (149 patients)	*p*
Median (IQR)			
Comorbidities	2 (0–3)	1 (0–2)	0.024
MMS	28 (27–30)	28 (26–30)	0.917
GDS	3 (1–6)	2 (1–4)	0.018
BFI	2.2 (0.2–4.4)	1.2 (0–4.4)	0.156
Number of patients (%)			
PS = 0	30 (46.9)	122 (81.9)	<0.0001
ADL (Dependent)	38 (59.4)	55 (36.9)	0.005
IADL (Independent)	38 (59.4)	114 (76.5)	0.443
ASA = 1 or 2	29 (45.1)	72(49.0)	0.449

Abbreviation: ADL, Activities of Daily Living; ASA, American Society of Anesthesiologists' scoring system; BFI, Brief Fatigue Inventory; GDS, Geriatric Depression Scale; IADL, Independent Activities of Daily Living; IQR, interquartile; MMS, Mini-Mental State; PS, performance status

been implemented to optimize recovery for elective surgical patients (Parks et al. 2015). According to the type of surgery, it delivers optimal recovery and discharge for patients from preoperative stage to postoperative stage. Also, it includes nutritional status, mobility, monitoring, and analgesia. In a Cochrane review, although it was mentioned that the quality of data was low, the ERAS group had a significant risk reduction for all complications and shorter length of hospital stay than conventional methods care groups in colorectal surgery (Parks et al. 2015; Spanjersberg et al. 2011). Another asystemic review data showed that ERAS programs may reduce length of hospital stay for colorectal surgery between 0.5 and 3.5 days compared with standard care (Parks et al. 2015; Paton et al. 2014).

Frailty Identifying Tools

The definition of frailty has been a debate until now. Many authors have reported a set of scales and screening tools for defining this syndrome. Frailty can be thought of as a decreased physiological reserve across multiple organ systems, broadly (Partridge et al. 2012). The most commonly used in oncology are Fried frailty criteria and the Balducci frailty criteria (National Comprehensive Cancer Network 2015). Fried defines frailty as the clinical syndrome with three or more of the following conditions: unintentional weight loss (10 Ib or more in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity (Fried et al. 2001; Hamaker et al. 2012). However, Kristjansson et al. evaluated frailty for 74 elderly colorectal cancer patients in both Fried and Balducci frailty criteria (Kristjansson et al. 2008). It showed that 9 patients were frail in Fried frailty criteria and 28 were in Balducci frailty criteria. Fried frailty was not measured in the same way as Balducci criteria. The Balducci criteria were originally offered as a concept to identify vulnerable or frail patients and predicted quality of care in older cancer patients based on component of CGA (age >85, dependence in one or more ADLs, three or more major comorbid conditions, and one or more geriatric syndromes) (Balducci and Stanta 2000). The concept has been operationalized by various groups, most frequently using grade 3 or 4 on the Cumulative Illness Rating Scale-Geriatric (CIRS-G) to define a severe comorbidity. Table 9 presents examples of this adaptation. These "Balducci criteria" have proven surprisingly robust in the oncology context, including when compared to Fried frailty criteria to predict complications from surgery (Kristjansson et al. 2010, 2012) or to the oncologists' clinical judgment to choose chemotherapy for high-grade lymphoma (Tucci et al. 2009). According to the Balducci criteria, Mohile et al. evaluated 12,480 community-dwelling individuals aged 65 years and older. Mohile et al. found that the cancer patients had more commonly frailty than the non-cancer patients (80% vs. 73%, $p < 0.001$) (Mohile et al. 2009). Although both frailty measures were available for prediction of OS, the Balducci frailty criteria were more useful than the modified version of the Fried frailty criteria in predicting postoperative complications in a prospective study that compared the Balducci frailty criteria and the modified version of Fried frailty criteria in 176 patients (age 70–94 years) who underwent elective surgery for colorectal cancer (Kristjansson et al. 2012; National Comprehensive Cancer Network 2015). Other measures of frailty exist and can be used as part of a geriatric assessment (GA). Groningen Frailty Index (GFI), Vulnerable Elders Survey (VES-13), Triage Risk Screening Tool (TRST), and the Geriatric 8 (G8) are used as screening tools (Huisman et al. 2016).

Predictive Tools for Life Expectancy

An accurate estimate of a patient's life expectancy is important to make a clinical decision in managing older cancer patients. The life expectancy of the healthy person is different from that of frail person. For example, the average life expectancy of a healthy 90-year-old woman is still more than 2 years longer than the life expectancy of a same age person with moderate dementia, repeated falls, dependence in one or more ADL, or severe

Table 9 Examples of operationalization and use of the Balducci criteria

Study	Age	ADL dependence	Comorbidity	Geriatric syndrome	Outcome
Soubeyran et al. (2011)	≥70	ECOG-PS 3–4	Severe/low LVEF, CrCl, cytopenia	N	Efficacy of COP-based regimen in NHL
Monfardini et al. (2005)	>80	Y	≥3 grade 3 CIRS-G or 1≥ grade 4 CIRS-G	Y	Efficacy of vinorelbine and prednisone in NHL
Tucci et al. (2009)	>80	Y	≥3 grade 3 CIRS-G or ≥1 grade 4 CIRS-G	Y	Response/survival in DLBCL
Olivieri et al. (2012)	>85	Y	≥1 grade 3 CIRS-G or 3≥ grade 2 CIRS-G	Y	Tailored therapy in DLBCL
Spina et al. (2012)	≥70	Y/IADL	Selected group (fit vs. unfit vs. frail)	N	Tailored therapy in DLBCL
Balducci and Stanta (2000)	>85	Y	3 + major	Y	N
Kristjansson et al. (2010)	≥70	Y	≥3 grade 3 CIRS-G or 1≥ grade 4 CIRS-G	Y	Post-op 30 days complications in colorectal cancer
Corsetti et al. (2011)	>80	Y/IADL	≥3 grade 3 CIRS-G or 1≥ grade 4 CIRS-G	N	AML response/overall survival

Abbreviation: Y, yes; N, no; LVEF, left ventricular ejection fraction; CrCl, creatinine clearance; COP, cyclophosphamide, vincristine, and prednisone

comorbid conditions (Balducci and Stanta 2000). Many prognostic indices were developed but several are of limited quality. A team at the University of California San Francisco conducted a systematic review of 21,593 titles (Yourman et al. 2012). They could identify 16 indices that predict risk of mortality from 6 months to 5 years for older adults in a variety of clinical settings: the community (6 indices), nursing home (2 indices), and hospital (8 indices) (Yourman et al. 2012). They assembled them into a convenient online tool for clinical practice named ePrognosis (eprognosis.ucsf.edu/). For oncology patients, taking out the points related to the cancer intended for treatment (points would still be counted for second tumors), it offers a practical estimate of the non-cancer mortality of the patients.

Recent work has tried to identify predictors of early death in older patients with cancer. In a study which enrolled a total of 348 patients in France, patients were scheduled for first-line chemotherapy and previously untreated patients greater than 70 years of age (Soubeyran et al. 2012). This study showed that high-risk early death predictors (<6 months) after initiation of chemotherapy treatments were male gender, advanced tumor stage, a low Mini Nutritional Assessment (MNA) score ≤23.5, and long Timed Get Up and Go (GUG) >20 s (Soubeyran et al. 2012). Another study showed predictor factors of early death in older patients with cancer during 100 days (Boulahssass et al. 2014). A total of 547 patients were analyzed, and a geriatric comprehensive assessment (CGA) has been done. Predictors of early death at 100 days were poor nutritional status with MNA <17, metastatic cancers, and gait speed <0.8 m/s (Boulahssass et al. 2014).

Future Needs

These predictive tools include various perspectives. However, there are some limitations to expect that these predictive tools would improve patient's outcomes. There are no validated methods for management based on predictive tool score that have been shown to improve outcomes. In view of chemotherapy toxicity tools, current tools have not been validated with recently approved targeted or immunologic therapies to inform dose modification. These predictive tools were not considered according to goals of cancer treatment (curative vs. palliative intent). Predictive tools have not been routinely incorporated into clinical trials. Future studies should consider these points.

Conclusions

Older cancer patient management is difficult because older persons are heterogeneous in health, function, psychological, social, culture, and economic status. Predictive tools could help the treatment decisions of older cancer patients. This chapter reviewed predictive tools of chemotherapy toxicity, perioperative management, life expectancy, and frailty. We could use these CGA-based tools to decide the management of older cancer patients. First of all, it is important that physicians consider the life expectancy and frailty level of their patients. They could use the ePrognosis for predicting a life expectancy. Frailty is not definitely defined, but the most commonly used tools in oncology are the Fried frailty criteria and the Balducci frailty criteria. Predictive tools for chemotherapy toxicities include two validated scores: the CRASH score and the CARG score. For perioperative management, several CGA-based systems are available, although standardized tools are still lacking. Predictive CGA-based tools often involve some time to be administered and calculated. However, this is time well spent if they contribute to improve the targeting of cancer treatment in older patients. Future developments should bring shorter instruments, and clinical multidisciplinary trials will help develop pathways using these tools more systematically.

Cross-References

- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Decision Making and Safety Issues in Older Cancer Patients
- Frailty in Cancer Patients
- Geriatric Interventions in Oncology
- Geriatric Oncology in Tropical and Developing Countries
- Geriatric Screening in Cancer Patients
- Integrating Geriatric Oncology into Clinical Pathways and Guidelines
- Principles of Cancer Surgery in Older Adults
- Principles of Cancer Targeted Therapy in Older Adults
- Principles of Chemotherapy in Older Adults
- Principles of Radiation Therapy in Older Adults
- Research Methods: Clinical Trials in Geriatric Oncology
- Research Methods: Outcomes and Survivorship Research in Geriatric Oncology

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Part V

Heme Malignancies

Heidi D. Klepin

Myelodysplastic Syndrome

30

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Abstract

Myelodysplastic syndrome (MDS) is a heterogeneous, clonal hematologic malignancy of the elderly defined by morphologic dysplasia and ineffective hematopoiesis, resulting in uni- or multilineage cytopenias. Driven by genetic mutations and immune deregulation, MDS patients commonly present with cytopenias, which manifest in transfusion dependency, bleeding, and/or recurrent infections, and eventually progress into acute myeloid leukemia (AML). The International Prognostic Scoring System (IPSS) and revised IPSS (R-IPSS) are paramount in risk-stratifying patients and guiding treatment decisions, which include observation, erythropoiesis-stimulating agents (ESA), hypomethylating agents (HMA), immunosuppressive therapy, lenalidomide, and allogeneic hematopoietic stem cell transplant (allo-HSCT). Allo-HSCT remains the only curative treatment modality in MDS and should be considered in the elderly population in the right setting. While genetic mutations play an important role in prognosis, none are MDS-defining or guide treatment decisions to date. Novel therapies are being investigated in clinical trials, including oral HMAs, checkpoint inhibitors, TGF-beta inhibitors, and targeted therapies.

Keywords

Acute myeloid leukemia (AML) · Familial MDS · Treatment-related MDS (t-MDS) · Hypoplastic MDS · Idiopathic cytopenia of unknown significance (ICUS) · Idiopathic dysplasia of unknown significance (IDUS) · Ring sideroblasts (RS) · Chronic myelomonocytic leukemia (CMML) · 5q minus syndrome · Deletion (del) 5q syndrome · TP53 mutation · Lenalidomide · SF3B1 · International Prognostic Scoring System (IPSS) · Revised-IPSS (R-IPSS) · Global MD Anderson model · Allogeneic hematopoietic stem cell transplant (allo-HSCT) · WHO-based prognostic scoring system (WPSS) · WHO classification · Erythropoietin-stimulating agents (ESA) · Hypomethylating agent (HMA) · Azacitidine (AZA) · Decitabine (DAC) · Immunosuppressive therapy

Introduction

Myelodysplastic syndrome (MDS) is a clonal hematologic malignancy characterized by morphologic dysplasia, ineffective hematopoiesis, and a predisposition to progress to acute myeloid leukemia (AML). Uni- or multi-lineage cytopenias and bone marrow hypercellularity are present in early stage MDS, as a consequence of increased apoptosis and proliferation of hematopoietic stem cells. As the disease progresses, hematopoietic cell maturation is further impaired and the proportion of myeloblasts increases. Alterations at the genetic and epigenetic level, altered innate immunity, and immune deregulation play an important role in the pathogenesis of MDS. MDS can present as an indolent disorder initially; however, progressive cytopenias can result in symptomatic anemia,

transfusion dependency, recurrent infections, and bleeding. Eventually, patients progress into AML or develop fatal complications due to the underlying cytopenias (Vardiman et al. 2009).

Epidemiology

MDS is a rather common hematologic malignancy. Based on Surveillance, Epidemiology, and End Results (SEER) data, the age-adjusted incidence rate of MDS is 4.8 per 100,000 population per year (Ma et al. 2007). MDS is a disease of the elderly with a median age of onset of 72 years. It has a preponderance to affect males with a male to female ratio of 1.8 to 1. These statistics are similar in Europe, while the Asian MDS population has a younger age, lower incidence, and can present as pathologically distinct subtypes (Strom et al. 2008; Komrokji 2006). Similar incidence rates are reported for white, black, and Hispanic populations, representing 4.9, 4.1, and 3.7 MDS cases yearly per 100,000 capita, respectively. MDS has a higher frequency in the elderly population with a yearly incidence as high as 55.5 per 100,000 in patients over the age of 80 (Ma et al. 2007).

Etiology

The etiology of MDS is believed to be multifactorial. Factors such as senescence, genetic predisposition, environmental triggers, and immunologic derangements play a role and accumulate to the multi-hit sequence of events that culminate to the development of MDS.

Another well-known but uncommon risk factor is familial MDS or MDS in the setting of a genetic predisposition (Churpek et al. 2013). Certain bone marrow failure syndromes, including dyskeratosis congenital, Fanconi anemia, Shwachman-Diamond syndrome, and severe congenital neutropenia, are predisposing conditions for the development of MDS (Churpek et al. 2013). Two molecularly distinct familial MDS syndromes have been described in the literature. A familial platelet disorder with a propensity to develop myeloid malignancy, associated with an autosomal-dominant RUNX-1 germline mutation manifesting as thrombocytopenia and MDS/AML has been recognized (Liew and Owen 2011). Another familial MDS/AML syndrome associated with GATA2 mutation is inherited in an autosomal dominant pattern but with variable penetrance (Ostergaard et al. 2011).

Environmental risk factors that stimulate the development of MDS include exposure to benzenes and cigarette smoking (International Agency for Research on Cancer 2012; Schnatter et al. 2012; Tong et al. 2013). One meta-analysis demonstrated an odds ratio of 1.81 in active smokers and 1.67 in former smokers compared to non-smokers (Tong et al. 2013). According to a European study, a history of infections and autoimmune diseases also increased the probability of acquiring MDS with odds ratios of 1.3 and 2.1, respectively (Kristinsson et al. 2011).

In the current era of chemotherapy and radiation, it has become evident that these exposures in itself contribute to MDS pathology. Treatment-related MDS (t-MDS) is a recognized entity and comprises up to one fifth of all MDS cases (Park and Koeffler 1996; Smith et al. 2003). t-MDS is characterized by complex cytogenetics, has an increased risk of progressing to AML, and portends a dismal overall prognosis. Certain chemotherapeutic agents have a stronger carcinogenic potential and incidence can vary anywhere from 1% in adjuvant breast cancer chemotherapy to 15% in refractory lymphoma patients receiving multiple lines of chemotherapy (Park and Koeffler 1996; Smith et al. 2003). The overall carcinogenic effect is multifactorial and depends upon the age of the patient, the class of antineoplastic agent, and the duration of cytotoxic therapy. There are two distinct subtypes of t-MDS, characterized by different mechanisms, cytogenetic profiles, and latency periods. Type I t-MDS develops after a latency period of 3–5 years post exposure to alkylating agents. Monosomy 5 and monosomy 7 are often seen on the cytogenetic level. Type II t-MDS arises shortly after exposure to topoisomerase II inhibitors and evolves rapidly into AML. Cytogenetically, type II t-MDS is typified by chromosome 11q23 derangements involving the MLL gene (Bennett et al. 2004). Radiation-induced MDS

tends to have a better prognosis than chemotherapy-related MDS, with outcomes comparable to de novo MDS (Nardi et al. 2012).

Diagnosis

In order to make the diagnosis of MDS, a complete blood count (CBC) with differential, peripheral blood smear, bone marrow aspirate or touch prep, Wright-Giemsa stain, iron stain, bone marrow biopsy, and bone marrow karyotype are imperative.

Sustained cytopenia in the absence of correctable causes such as nutritional deficiencies is required for diagnosis of MDS. Cytopenia is defined by an absolute neutrophil count $<1.8 \times 10^9$/L, hemoglobin <10 g/dL, platelet count $<100 \times 10^9$/L. Milder thresholds for cytopenia are permitted if definitive diagnostic criteria for MDS are met. Milder hematological parameters include hemoglobin <12 g/dL in females and <13 g/dL in males or platelet count $<150 \times 10^9$/L (Arber et al. 2016). In addition, one of the following criteria has to be fulfilled: (1) presence of uni- or multilineage cytologic dysplasia involving ≥10% of cells, (2) demonstration of increased myeloblasts (5–19%), or (3) a specific cytogenetic abnormality in the setting of persistent unexplained cytopenia (Arber et al. 2016; Valent et al. 2007).

Secondary causes of cytopenia and dysplasia need to be excluded clinically. Cytologic dysplasia must affect at least 10% of the cell lineage. Table 1 summarizes the classic dysplastic changes in the peripheral blood and bone marrow that define myelodysplasia.

In case of excess marrow blasts, bone marrow recovery or growth factor effect needs to be ruled out. The percentage of myeloblasts in the bone marrow is calculated as a percentage of the total cells regardless of the amount of erythroid precursors present, which is a change per the 2016 revised World Health Organization (WHO) criteria (Arber et al. 2016). While the aspirate blast count remains the gold standard, CD34 immunostaining can be useful in cases with fibrosis or suboptimal aspirate (Malcovati et al. 2014).

Table 1 Dysplastic features in peripheral blood and bone marrow characteristic of MDS (Padron and Komrokji 2015)

Cell lineage	Peripheral blood	Bone marrow
Erythroid	Poikilocytosis Anisocytosis Nucleated red blood cells Basophilic stippling	Multinuclearity Nuclear fragments Megaloblastoid changes Cytoplasmic abnormalities Ringed sideroblasts Increased erythroblasts
Myeloid	Hypolobulation Nuclear sticks Ring-shaped nuclei Hypogranulation	
Megakaryocytic	Micromegakaryocytes Large mononuclear forms Multiple small nuclei	

Approximately 50% of all MDS patients have a karyotype abnormality. Per the WHO 2016 criteria, there are several MDS-defining cytogenetic abnormalities recognized as diagnostic for MDS in the presence of sustained cytopenia. These cytogenetic profiles are summarized in Table 2 with their relative frequencies (Arber et al. 2016).

Iron stains are imperative to determine the degree of ring sideroblasts. Reticulin stains address medullary fibrosis, which can be of prognostic value. Bone marrow core biopsy adds additional information to the bone marrow aspirate and is a key in establishing the diagnosis. Bone marrow core biopsy determines cellularity, identifies dysmegakaryopoiesis, and can home clusters of abnormal localization of immature precursors (ALIP). ALIPs represent immature cells such as myeloblasts and promyelocytes displaced from the paratrabecular space to the intertrabecular areas, forming abnormal clusters (Malcovati et al. 2006; Della Porta et al. 2009).

Of note, flow cytometric abnormalities are not sufficient for diagnosis of MDS but can support the diagnosis when suspected by other observations. Similarly, MDS-type mutations are not defining MDS but may support the diagnosis in the right clinical context (Arber et al. 2016).

Table 2 MDS-defining cytogenetic abnormalities per the World Health Organization (WHO) 2016 criteria and its relative incidences in primary MDS and therapy-related MDS (Arber et al. 2016)

Cytogenetic profile	Primary MDS	Therapy-related MDS
Unbalanced		
−7 or del(7q)	10%	50%
−5 or del(5q)	10%	40%
i(17q) or t(17p)	3–5%	
−13 or del(13q)	3%	
del(11q)	3%	
del(12p) or t(12p)	3%	
del(9q)	1–2%	
idic(X)(q13)	1–2%	
Balanced		
t(11;16)(q23;p13.3)		3%
t(3;21)(q26.2;q22.1)		2%
t(1;3)(p36.3;q21.2)	1%	
t(2;11)(p21;q23)	1%	
inv(3)(q21q26.2)	1%	
t(6;9)(p23;q34)	1%	

+8, -Y, and del(20q) are common cytogenetic abnormalities in MDS; however, they can occur in non-malignant conditions and hence are not MDS-defining karyotypes

Differential Diagnosis

Up to one fifth of MDS cases are hypocellular, also known as hypoplastic MDS, and often pose a challenge upon clinicians in distinguishing these from aplastic anemia. Idiopathic cytopenia of unknown significance (ICUS) is a term that defines cases with sustained cytopenia(s) with dysplasia affecting less than 10% of any cell lineage in the absence of cytogenetic abnormalities. Patients without cytopenia or cytogenetic aberrations and a mild degree of dysplasia below 10% are recognized as idiopathic dysplasia of unknown significance (IDUS) (Steensma 2012).

Classification

French-American-British (FAB) Classification

MDS was originally classified under the French-American-British or FAB classification, which included two subtypes. This was expanded in 1982 to five distinct entities consisting of refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), refractory anemia with excess blasts (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML) (Bennett et al. 1982).

Original WHO Classification

The WHO later established the WHO classification which refined the existing FAB classification. Categories of refractory cytopenia with multilineage dysplasia (RCMD) and RCMD with ring sideroblasts (RCMD-RS) were coined, delineating groups with dysplasia in either myeloid or megakaryocytic cell lineages in addition to erythroid dysplasia. RAEB was further subdivided into RAEB I (5–9% blasts) and RAEB II (10–19% blasts), while RAEB-t was omitted from the classification (Bennett 2000; Komrokji and Bennett 2003). The blast percentage to diagnose progression to AML was decreased from a threshold of 30% to 20% (Bennett 2000; Komrokji and Bennett 2003; Vardiman et al. 2002). A new entity, the 5q minus syndrome, was introduced, which is a less aggressive form of MDS characterized cytogenetically by isolated del(5q) and less than 5% myeloblasts in the bone marrow. MDS/myeloproliferative neoplasm (MPN) overlap syndromes were recognized, including CMML-1, CMML-2, juvenile myelomonocytic

leukemia (JMML), and atypical chronic myeloid leukemia (aCML) (Bennett 2000; Komrokji and Bennett 2003; Vardiman et al. 2002). CMML-1 is defined as 0–4% blasts and/or promonocytes in the peripheral circulation or <10% in the bone marrow, while CMML-2 represents 5–19% blasts and/or promonocytes in the peripheral circulation or <20% in the bone marrow (Bennett et al. 2002).

2008 Revised WHO Classification

In 2008, a revision of the WHO classification took place resulting in further modification of the categories. Refractory cytopenia with unilineage dysplasia (RCUD) was introduced as a separate category, which includes patients with peripheral monocytopenia or bicytopenia. MDS unclassified (MDS-U) was defined as a group of MDS disorders that did not meet criteria for other categories, including unilineage dysplasia with pancytopenia, cytogenetic evidence of MDS without overt dysplasia, RCUD or RCMD with 1% circulating blasts. Per the WHO 2008 revisions, RAEB-1 also comprised variants that have 2–4% circulating blasts and RAEB-2 included those that have 5–19% circulating blasts. The identification of Auer rods was determined to be diagnostic for RAEB-2 or CMML-2 regardless of the blast count. Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) was a novel category for patients with RARS with persistently elevated platelet count over 450,000/mm^3 (Vardiman et al. 2008). Myeloid neoplasm with eosinophilia was added as a distinct category consisting of CMML patients with eosinophilia and genetic mutations in platelet-derived growth factor receptor alpha (PDGFRα) or beta (PDGFRβ) (Orazi et al. 2008).

2016 Revised WHO Classification

In 2016, the most recent revision of the WHO criteria was published. A detailed overview of the updated classification is summarized in Table 3. While the prognostic impact of molecular mutations is recognized, most data are still too immature to determine how to incorporate mutational data into the existing morphologic classification. New data, however, help refine definitions of MDS with isolated del(5q) and MDS with ring sideroblasts (MDS-RS). Isolated del(5q) syndrome can have one additional cytogenetic abnormality without affecting its prognosis, with the exception of −7 and del(7q). TP53 mutation confers a poor prognosis in patients with 5q minus syndrome treated with lenalidomide. Hence, TP53 mutation testing or p53 immunostaining is recommended in all patients with del(5q) syndrome for prognostic purposes (Mallo et al. 2011; Jadersten et al. 2011; Germing et al. 2012). MDS-RS has a strong association with mutant SF3B1, a RNA splicing factor. SF3B1 is mutated in 70–80% of MDS with >15% RS and is rarely mutated in MDS lacking RS. SF3B1 appears to be an early founding mutation and is associated with a prolonged survival (Papaemmanuil et al. 2011; Patnaik et al. 2012; Bejar et al. 2012; Malcovati et al. 2011, 2015; Woll et al. 2014). MDS-RS is expanded to include RARS, cases with RS and multilineage dysplasia, cases with SF3B1 mutation and ≥5% RS, and cases with ≥15% RS if SF3B1 wildtype or unknown.

Acute erythroid leukemia was omitted as a category and was mostly merged with MDS with excess blasts. RCUD was renamed to MDS with single lineage dysplasia (MDS-SLD), RCMD to MDS with multilineage dysplasia (MDS-MLD), RARS, and RCMD-RS were replaced by MDS-RS with SLD and MDS-RS with MLD, respectively. RAEB was changed to MDS with excess blasts (MDS-EB) (Arber et al. 2016).

MDS-U is redefined as a heterogeneous group consisting of MDS-SLD with pancytopenia, low-grade MDS with exactly 1% circulating blasts measured on two separate occasions, and MDS with an MDS-defining cytogenetic abnormality without excess blasts or dysplasia.

MDS-EB is defined as ≥5% blasts in the marrow or ≥2% blasts in the peripheral blood and is subdivided into MDS-EB-1 and MDS-EB-2 based on marrow and peripheral blood blast percentages. Increased blast levels are a very strong indicator of aggressive behavior in MDS, independent of cytogenetics, cytopenias, and mutations (Malcovati et al. 2014).

Lastly, a new WHO category was added: myeloid neoplasms with germline predisposition. This category includes conditions with pre-existing

Table 3 The World Health Organization 2016 revised classification of MDS

Classification	Dysplastic lineages	Cytopenias[a]	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%[b]	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1–3	<15%/<5%[b]	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%[b]	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1–3	≥15%/≥5%[b]	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del (5q)	1–3	1–2	None or any	BM <5%, PB <1%, No Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0–3	1–3	None or any	BM 5–9% or PB 2–4%, No Auer rods	Any
MDS-EB-2	0–3	1–3	None or any	BM 10–19% or PB 5–19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
With 1% blood blasts	1–3	1–3	None or any	BM <5%, PB = 1%,[c] No Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, No Auer rods	Any
Based on defining cytogenetic abnormality	0	1–3	<15%[d]	BM <5%, PB <1%, No Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1–3	1–3	None	BM <5%, PB <2%	Any

From Arber et al. (2016)
BM bone marrow, *PB* peripheral blood
[a]Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L
[b]If *SF3B1* mutation is present
[c]One percent PB blasts must be recorded on at least two separate occasions
[d]Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia and are classified as MDS-RS-SLD

platelet disorders (germline RUNX1, ANKRD26, and ETV6 mutations), with associated organ dysfunction (germline GATA2 mutation among other syndromes), and without a preexisting platelet disorders or organ dysfunction (germline CEBPA and DDX41 mutations). It is imperative to sequence

non-hematopoietic tissue to distinguish a germline mutation from a somatic one. Newly arising mutations can occur in adulthood in the absence of a positive family history. MDS/AML with DDX41 germline mutation typically presents in adulthood (Czuchlewski and Peterson 2016; West et al. 2014).

Clonal Hematopoiesis of Indeterminate Potential

Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the presence of an MDS-type mutation in the absence of MDS-related cytopenias. The somatic mutation involves a gene that is recurrently mutated in hematologic malignancies and has an allele fraction of at least 2%. The allele burden is characteristically of a low fraction. These individuals typically have normal blood counts, but can have mild cytopenias not meeting criteria for MDS, or cytopenias related to other causes. Somatic mutations in hematopoietic cells affecting DNMT3A, TET2, ASXL1, TP53, JAK2, and SF3B1 have been described in a proportion of otherwise healthy older individuals (Jaiswal et al. 2014; Genovese et al. 2014; Xie et al. 2014; Steensma et al. 2015). The frequency of these somatic mutations increases with age and averages 10% in the population over age 70. The presence of such somatic mutation is associated with an increased risk of acquiring a hematologic malignancy and an increased overall mortality, with the latter most probably attributed to the increased risk of coronary heart disease and ischemic stroke (Jaiswal et al. 2014). Patients with cancer who have CHIP are at increased risk of developing therapy-related myeloid neoplasms (Gillis et al. 2017).

Pathogenesis

MDS is a clonal disorder driven by underlying genetic abnormalities. Approximately one-half of MDS patients carry chromosomal alterations, with del(5q), monosomy 7, del(7q), and trisomy 8 being the most well described. While certain chromosomal deletions and duplications are critical in the evolution of the disease, particular gene mutations have been proven to play a major role in the disease pathway as well. As high as 90% of MDS patients will have evidence of clonal genetic abnormalities. An array of such somatic mutations has been uncovered, affecting epigenetic regulators (TET2, ASXL1), RNA splicing (SF3B1, SRSF2, U2AF1), transcription factors (RUNX1, ETV6), tyrosine kinase signaling (RAS), and tumor suppressor genes (TP53) (Papaemmanuil et al. 2013). Figure 1 depicts the diversity of commonly mutated genes in MDS and their relative frequencies in the different categories of the MDS spectrum.

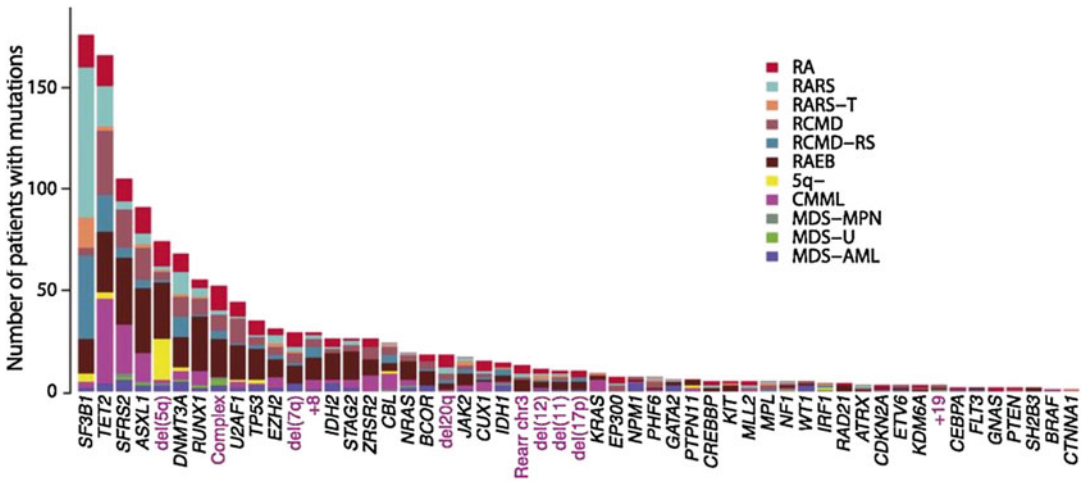


Fig. 1 Relative frequencies of driver mutations by MDS subtype. (From Papaemmanuil et al. (2013))

Inactivating TET2 mutations lead to DNA methylation and epigenetic repression, and are among the most frequently mutated genes (Ko et al. 2010). The ASLX1 gene is also frequently mutated in MDS and acts as an epigenetic regulator (Grossmann et al. 2010; Gelsi-Boyer et al. 2009; Bejar et al. 2011; Jankowska et al. 2011). Up to date, there is no MDS-defining mutation however. RNA splicing mutations occur early in the disease pathogenesis and are prognostic (Wu et al. 2012; Meggendorfer et al. 2012; Itzykson et al. 2013). SF3B1 and SRSF2gene mutations are associated with ring sideroblast subtypes and monocyte expansions (CMML), respectively (Papaemmanuil et al. 2011; Meggendorfer et al. 2012). Emerging data have shown that the type of gene mutation and number of genetic events affect the clinical course of MDS and its progression to AML, and hence impact survival (Walter et al. 2012). It has been well described that these and certain other genetic alterations are driver mutations resulting in overt MDS.

Immune dysregulation has been hypothesized to contribute to the pathogenesis of MDS. Evidence demonstrates that adaptive and innate immunity are deregulated in MDS and its resulting inflammatory changes may act as a driver in its pathogenesis. Inflammation in itself may be permissive for the emergence of a mutational burden or alternatively, an expanded clone may fuel inflammatory changes. Furthermore, studies have demonstrated a strong correlation between chronic immune stimulation and autoimmune diseases with MDS development (Kristinsson et al. 2011; Miller et al. 1994; Kulasekararaj et al. 2013; Tabata et al. 2010).

Dysregulation of T-cell lymphocytes is another hallmark of the disease. Nearly half of all T-cells are clonal and the majority of T-cells have impaired telomerase activity, which may explain their early senescence (Zou et al. 2009; Epling-Burnette et al. 2007; Yang et al. 2013). Proliferation of effector memory T-regulator cells portends a worse prognosis and manifests as anemia and elevated blast count (Mailloux et al. 2012). Upregulation of the innate immunity system leads to activation of nuclear factor kappa B (NF-κB), which further stimulates the inflammatory milieu in MDS (Wei et al. 2013; Dimicoli et al. 2013). Myeloid-derived suppressor cells (MDSC) are critical components in innate immunity. MDSCs act as effector cells and infiltrate the bone marrow in MDS. As MDSCs oversecrete hematopoietic inhibitory cytokines, their expansion results in ineffective hematopoiesis (Chen et al. 2013).

5q Minus Syndrome

The 5q minus syndrome, also known as deletion (del) 5q syndrome, is a genetically and phenotypically distinct entity within the spectrum of MDS. The 5q minus syndrome encompasses approximately 5–15% of MDS cases and is encountered more commonly in females. Bone marrow biopsy shows a preponderance of megakaryocytes with hypolobated nuclei. Clinically, these patients present with refractory anemia with or without thrombocytosis. They have a relatively indolent disease course and have an overall better prognosis compared to other categories of MDS (Giagounidis et al. 2004). Genetically, del 5q syndrome is characterized by an isolated deletion of part of the long arm of chromosome 5 in hematopoietic stem cells. Specifically, it is the result of haploinsufficiency of multiple genes located within the critical deleted region (CDR) at 5q32 (Boultwood et al. 2002). Of the 40 genes located within CDR, only haploinsufficiency of RPS14 inactivates erythroblast expansion in del 5q MDS samples, while overexpression of RPS14 results in restoration of erythropoiesis (Ebert et al. 2008). Haploinsufficient RPS14 results in defective ribosome assembly, which leads to accumulation of MDM2, and ultimately causes p53 stabilization. Inactivation of p53 in del 5q murine models confirmed the restoration of hematologic abnormalities (Barlow et al. 2010).

Clinical Presentation

The initial manifestation of MDS typically consists of cytopenia affecting one or multiple cell lines. As cytopenias progress, patients become symptomatic with infections, fatigue, or bleeding. The hallmark is macrocytic anemia. It is important to exclude alternative causes of macrocytic anemia including cyanocobalamin deficiency, folic acid deficiency,

among other etiologies. Thrombocytopenia and platelet dysfunction affect up to 65% of all MDS patients and is more prevalent in patients with high risk MDS. Platelet dysfunction is evidenced by a prolonged bleeding time and an increase in atypical megakaryocytes. Fatal bleeding events have been documented in up to 24% of patients (Kantarjian et al. 2007a; Raman et al. 1989).

While over one-third of all MDS patients will eventually transform into AML with a high fatality rate, the vast majority of patients will succumb to cytopenia complications. MDS patients are at increased risk of infections due to a multitude of factors including neutropenia, granulocyte dysfunction, and iron overload in the setting of transfusion dependency (Boogaerts et al. 1983). Common infections include bacterial pneumonias and skin abscesses; however, opportunistic infections with Mycobacterium avium-intracellulare, *Aeromonas hydrophila* endocarditis, bacterial thyroiditis, and Epstein-Barr virus hepatitis have been documented (Tsukada et al. 1994; Ong et al. 1991; Pomeroy et al. 1991). Autoimmune diseases and autoimmune cytopenias can be profound. In particular, Coombs-positive autoimmune hemolytic anemia, Sweet syndrome, seronegative arthritis, cutaneous vasculitis, necrotizing panniculitis, and polymyalgia rheumatica may arise (Al Ustwani et al. 2013; Fain et al. 2011; Enright and Miller 1997; Sanz et al. 1990).

MDS/MPN overlap syndromes, predominantly CMML, may manifest with hepatosplenomegaly, lymphadenopathy, or pleural effusions (Parikh and Tefferi 2013). RARS-T subtypes can develop substantial thrombocytosis which results in an elevated rate of thromboembolic events, comparable to patients with essential thrombocythemia (Malcovati et al. 2009).

Risk Stratification Models

As with any disease process, appropriate risk stratification and prognostic assessment is a crucial initial step in the management of MDS, particularly in the elderly population. By stratifying patients into subgroups, one is better able to get a sense of the disease trajectory thus allowing physicians the opportunity to appropriately tailor therapy. In general, the goal of therapy in low-risk patients is to alleviate symptomatic cytopenias, decrease MDS-associated complications, and most importantly, improve quality of life. In contrast, the goal of therapy in the more advanced high-risk population is to alter the natural history of the disease by delaying the potential of progression to acute myeloid leukemia in an effort to extend survival and preserve an optimal quality of life. Having open, frank discussion with elderly patients regarding their prognosis, goals, and values is critical to fostering honest communication and guiding treatment decision agreements between patients and providers.

While several prognostic models for MDS exist, the two most widely used prognostic stratification systems are the International Prognostic Scoring System (IPSS, Table 4) (Greenberg et al. 1997) and the revised-IPSS (R-IPSS, Table 4). The Global MD Anderson model (Table 4) developed in 2008 is another frequently used prognostic model and is particularly useful as it can be applied to MDS/MPN overlap syndromes (Greenberg et al. 1997; Voso et al. 2013).

The International Prognostic Scoring System

The IPSS remains the most widely used staging system in MDS. This system has been adopted by community oncology physicians, implemented in many clinical trials and remains an integral part in determining the timing of allogeneic stem cell transplant (allo-HSCT). This scoring system was developed from a multivariate analysis of an untreated cohort of more than 800 patients with MDS and incorporates bone marrow and peripheral blood blast percentage, using previously defined FAB cut points, the number of cytopenias, and cytogenetic patterns (Greenberg et al. 1997). There are four prognostic categories: low, intermediate-1, intermediate-2, and high; the IPSS low-risk category comprises low and intermediate-1–risk groups and the IPSS high-risk category includes intermediate-2 and high-risk (see Table 4). The overall survival (OS) in the low-risk group ranges from 3.0 to more than 5.5 years,

while the OS for the high-risk group averages about a year (Greenberg et al. 1997).

While the IPSS has remained a commonly used prognostic model, it is important to note that the IPSS-predicted outcomes are only relevant to the time of initial disease diagnosis and/or de novo disease, rather than patients who are experiencing disease progression. In addition, another shortcoming of the IPSS is that it does not account for the severity of the cytopenias and the cytogenetic risk groups are not comprehensive. Furthermore, the IPSS was only studied in patients with MDS, so this scoring system is not applicable to patients with t-MDS or those with MDS/MPN overlap syndromes (Voso et al. 2013; Greenberg et al. 2012).

The Revised IPSS

The R-IPSS emerged in 2012 as a refinement to adjust for the deficiencies of the original IPSS, as

Table 4 Risk stratification models in MDS

IPSS			R-IPSS			Global MDAS		
Variable	Score		Variable		Score	Variable		Score
BM blasts (%)			**BM blasts (%)**			**PS > 2**		2
<5	0		<2		0	**Age (year)**		
5–10	0.5		>2 to <5		1	60–64		1
11–20	1.5		5–10		2	≥65		2
21–30	2.0		>10		3			
Karyotype[a]			**Karyotype**[b]			**Platelets** (109/L)		
Good	0		Very good		0	<30		3
Intermediate	0.5		Good		2	30–49		2
Poor	1		Intermediate		4	50–199		1
			Poor		6			
			Very poor		8			
Cytopenia[c]			**Hgb (g/dL)**			**Hgb < 12 g/dL**		2
0/1	0		≥10		0	**BM blasts (%)**		
2/3	0.5		8 to <10		1	5–10		1
						11–29		2
			<8		1.5	**Transfusion**		1
			ANC ≤ 0.8		1	**WBC ≥20 × 109/L**		2
			Platelets			**Karyotype**		
			≥100		0	Chromosome & Abn or complex ≥3 Abns		3
			50–100		0.5			
			<50		1			
Risk Group	**Sum Score**	**OS (year)**	**Risk Group**	**Sum Score**	**OS (year)**	**Risk Group**	**Sum Score**	**OS (mos)**
Low	0	5.7	Very good	0–2	8.8	Low	0–4	54
Int-1	0.5–1	3.5	good	3–5	5.3	Int-1	5–6	25
Int-2	1.5–2.0	1.1	Int	6–7	3.0	Int-2	7–8	14
High	≥2.5	0.4	Poor	8–9	1.6	High	≥9	6
			Very poor	10–18	0.8			

Hgb hemoglobin, *WBC* White Blood Cell count, *ANC* absolute neutrophil count, *BM* bone marrow, *OS* overall survival

[a]Good is normal, -Y, del(5q), del(20q). Intermediate is other karyotypic abnormalities. Poor is complex (≥ three abnormalities) or chromosome 7 abnormalities

[b]Very good –Y, del(11q). Good is normal, single del(5q), del(12q), del(20q), or double including del(5q). Intermediate includes single del(7q), +8, I (17q), +19, or any double not including del(5q). Poor includes der(3q), monosomy 7, double including −7/7q, or three abnormalities. Very poor is more than three abnormalities

[c]Hgb <10 g/dL; ANC <1800/μL; platelets <100,000/μ ≥ L

previously outlined (Greenberg et al. 2012). These changes included incorporating a more comprehensive risk assessment based on cytogenetic risk groups, by refining the myeloblasts cutoffs and accounting for the degree of cytopenias in each cell lineage (Voso et al. 2013). The R-IPSS identifies five risk groups: very low, low, intermediate, high, and very high. Several groups have validated the R-IPSS, and it is currently incorporated in the NCCN guidelines (Voso et al. 2013; Mishra et al. 2013).

The Global MD Anderson Model

The MD Anderson Cancer Center risk model was developed in 2008 and represents a more flexible risk model that can be applied at any time during the disease course, unlike the IPSS and R-IPSS (Greenberg et al. 2012). In light of the fact that the MD Anderson model can be used throughout disease course, it does take into account the effects of therapy. In addition, it can be further used to subdivide patients who were initially classified as lower-risk by IPSS into different risk groups with variable outcome. Those models have been validated in several studies (Mishra et al. 2013; Kantarjian et al. 2008), and the MD Anderson risk model was found to be predictive for overall survival and AML transformation, offering a better discrimination for the lowest risk patients. As previously stated, this model can be used in the MDS/MPN overlap syndromes (Kantarjian et al. 2008; Hugo et al. 2009; Komrokji et al. 2012).

Other Risk Models

The lower risk MD Anderson risk model score (LR-MDAS) was developed and validated for patients with lower risk MDS; however, this model is not as commonly used in clinical practice at this time. The WHO based prognostic scoring system (WPSS) is another dynamic model utilized more commonly in Europe (Garcia-Manero et al. 2007; Malcovati et al. 2007).

Comorbidities and Frailty in MDS

Patients with MDS often suffer from other medical comorbidities, which might affect survival, performance status, and limit therapeutic options. This is a realistic challenge because the median age of MDS patients is older than 70 years. In a retrospective review among 600 patients, investigators applied the adult comorbidity evaluator (ACE-27) comorbidity to discern the effect on outcome. The median survival was 31.8, 16.8, 15.2, and 9.7 months for those with none, mild, moderate, and severe comorbidities, respectively ($P < 0.001$). A prognostic model including age, IPSS, and comorbidity score predicted median survival of 43.0, 23.0, and 9.0 months for lower-, intermediate-, and high-risk groups, respectively ($P < 0.001$) (Naqvi et al. 2011).

The Italian group added further refinement by developing an MDS-specific comorbidity index (MDS-CI). Cardiac disease (HR, 3.57; $P < 0.001$), moderate to severe liver disease (HR, 2.55; $P = 0.01$), severe pulmonary disease (HR, 2.44; $P = 0.005$), renal disease (HR, 1.97; $P = 0.04$), and history of solid tumors (HR, 2.61; $P < 0.001$) were found to independently affect the risk of nonleukemic death, and diabetes and cerebrovascular disease did not retain prognostic value. Patients were stratified into three risk groups based on those comorbidities with distinctly different outcomes. The MDS-CI is a flexible model that was predictive of outcome within each subgroup of WPSS (Della Porta et al. 2011).

It is important to keep in mind the difference between comorbidities and frailty in elderly patients. A large cohort of patients with Frailty was assessed by clinical judgment and also with a combination of physical measures such as hand grip strength and ability to get out of a chair 10 times and walk 4 m. Using a schema developed by Rockwood and associates, known as the Clinical Frailty Scale (CFS), patients were assigned scores of 1–9. A score 1 indicates very fit, 4 indicates vulnerable, and 8 indicates very severely frail. Frailty was found to correlate only modestly with Eastern Cooperative Oncology Group (ECOG) performance status ($r = 0.39$; $p < 0.0001$), less with comorbidity as assessed

by the MDS-specific comorbidity index (MDS-CI28; $r = 0.33$; $p < 0.0001$), and minimally with age-adjusted IPSS-R ($r = 0.12$; $p = 0.03$). Frailty improved the prognostication of the IPSS-R in all but the highest-risk group. Frailty was independently associated with survival (hazard ratio [HR] 2.7; 95% CI, 1.7–4.2). Moreover, incorporation of frailty improved MDS risk stratification by 30% (Buckstein et al. 2016).

Molecular Alterations

The heterogeneity of MDS has been elucidated and appreciated even prior to the advent of next-generation sequencing (NGS) and karyotypic analyses and techniques. Important somatic mutations to remember include ASXL1, EZH2, RUNX1, ETV6, and TP53, as these have all been shown to have less favorable outcomes in MDS patients (Bejar et al. 2012; Haferlach 2012). Of particular significance, TP53 alterations carry the worst prognostic significance. Additionally, a study published in *Blood* in 2013 showed that the number of somatic mutations effects prognosis with more than three mutations carrying a particularly unfavorable prognosis in patients with MDS (Papaemmanuil et al. 2013; Garcia-Manero et al. 2007). To date, SF3B1 is the only mutation shown to have a more favorable outcome (Haferlach 2012), and this is the most common mutation observed in patients with ring sideroblast MDS subtypes.

Incorporating somatic mutations into prognostic models enhances their utility; in fact, presence of any of the aforementioned somatic mutations has been demonstrated to upstage patients risk category in the IPSS or R-IPSS (Nazha and Bejar 2017).

Management of MDS: Low, High, and Intermediate Risk

Managing MDS is complicated by the advanced age of the majority of patients, their preexisting nonhematologic comorbidities and their comparative inability to tolerate intensive treatments compared to the younger population. The choice of therapy and treatment indications is based upon the IPSS and/or R-IPSS along with other parameters like performance status, age, patient preference for therapy, frailty, and comorbidities. At this point in time, molecular mutations do not drive treatment decisions but rather they play a role in the prognostication of patients. As further knowledge is elucidated about the significance of certain mutations, there is likely to be changes regarding incorporating these into treatment decisions and tailoring therapy for specific individuals, particularly in the elderly population.

To date, the only curative therapy for MDS remains allo-HSCT. This modality of therapy should be discussed with all elderly patients with a good performance status who have high-risk disease, in addition to those patients with low-risk disease that is refractory to treatment.

The first step in the treatment of the elderly population with MDS requires confirming the diagnosis ad subtype. This may require examination from an experienced hematopathologist at a large tertiary center familiar with MDS. Next, it is of paramount importance to risk-stratify patients, by using the aforementioned indices and molecular profiling, into low and high risk for management decisions. Once patients are stratified into groups, the subsequent step prior to discussion of therapy is to determine if the patient is an allo-HSCT candidate. Only after that should management and therapy options be discussed. A formal geriatric assessment for comorbidities and frailty should be incorporated to tailor therapy accordingly.

Low-Risk

Low-risk MDS patients include those with IPSS low, intermediate-1, and R-IPSS very low, low, and intermediate. The goal of therapy in these patients is to mitigate symptomatic cytopenias. This differs from the goal in high-risk patients, which aims to modify the natural history of the disease. Asymptomatic low risk patients are generally followed

clinically with close observation. Supportive care is an important component of all MDS patients, particularly in the elderly population.

Low-Risk Patients with Isolated del (5q) Syndrome

Patients with isolated del(5q) represent a rare entity but a favorable prognosis, as they respond well to treatment with lenalidomide. In a landmark NEJM publication, 67% of patients with del(5q) treated with lenalidomide had transfusion independence with at least 50% of patients going into a complete cytogenetic remission (List et al. 2006). The dose of lenalidomide is 10 mg po continuously or 10 mg po daily for 21 days of a 28-day cycle. Subsequent placebo controlled study confirmed those observations. Patients who achieve transfusion independence and or cytogenetic response derive survival advantage and less likely to progress to AML (List et al. 2014).

Initially, patients are started on 10 mg once daily dose; however, a majority of patients develop treatment related cytopenias within a few weeks, which then requires holding the drug for 2–3 weeks and restarting at a lower dose. It is important to note, however, that treatment related cytopenias predict a more favorable response. It is crucial to monitor blood counts weekly for the first 8 weeks of therapy. Other common side effects of lenalidomide include scalp itching, pruritic or non-pruritic rash, diarrhea, muscle cramping of the legs, and hypothyroidism.

Low-Risk Patients Without Isolated del (5q) Syndrome

As shown in Fig. 2, low-risk patients with a low erythropoietin level (EPO) <500 μU/mL and a low red cell transfusion burden (<2 units/month) have a 61–74% response rate to erythropoietin-stimulating agents.

Hypomethylating agents (HMA) such as Azacitidine (AZA) or Decitabine (DAC) are also used in the low-risk MDS population after failure of an ESA agent or those patients with serum EPO >500. It is important to note that HMAs do not improve counts immediately; therefore, it is important and considered standard practice to continue with at least 4–6 cycles of HMAs prior to rendering them a treatment failure. When using AZA in the lower-risk subpopulation, many favor a 5-day schedule, rather than the 7-day schedule used for higher risk patients (Lyons et al. 2009). Outcome after HMA failure is poor in the elderly, and they should be considered in patients with bi/pancytopenia and those with higher risk features (Jabbour et al. 2010, 2015).

Lenalidomide in non-del5q patients yields lower response rates compared to del5q patients. However, because of this drugs ability for some patients to attain red cell transfusion independency, it remains an option for patients with pure anemia. Recent studies demonstrated higher and more durable response rates when combined with ESA (Zeidan et al. 2015).

Immunosuppressive therapy (IST) with ATG (equine or rabbit) with or without cyclosporine is most effective in the younger population (<60yo), HLA-DR15+, hypoplasia, normal cytogenetics, and those with a PNH clone (Sloand et al. 2008). If patients are appropriately selected, durable trilineage responses can be observed.

High-Risk

The most important item to assess prior to assessing prognostic score or initiating any kind of therapy in high-risk patients is transplant eligibility. As such, every provider treating high-risk MDS patients should ask "is this patient allogeneic transplant eligible?" This is very important to initially assess, as most patients with MDS are ineligible for transplant given their advanced age, performance status, and underlying non-hematologic comorbidities (Fig. 3).

High-Risk, Transplant Ineligible

For all high-risk patients, including the elderly population, AZA 75 mg/m^2 $\times$ 7 days is considered the standard of care. This is based upon the AZA-001 phase III trial that revealed an improved median OS of 24.5 months versus 15 months with conventional care alone (i.e., best supportive care, low-dose cytarabine or intensive chemotherapy) (Fenaux et al. 2009). Another study comparing low-dose DAC to best supportive care in high-risk elderly

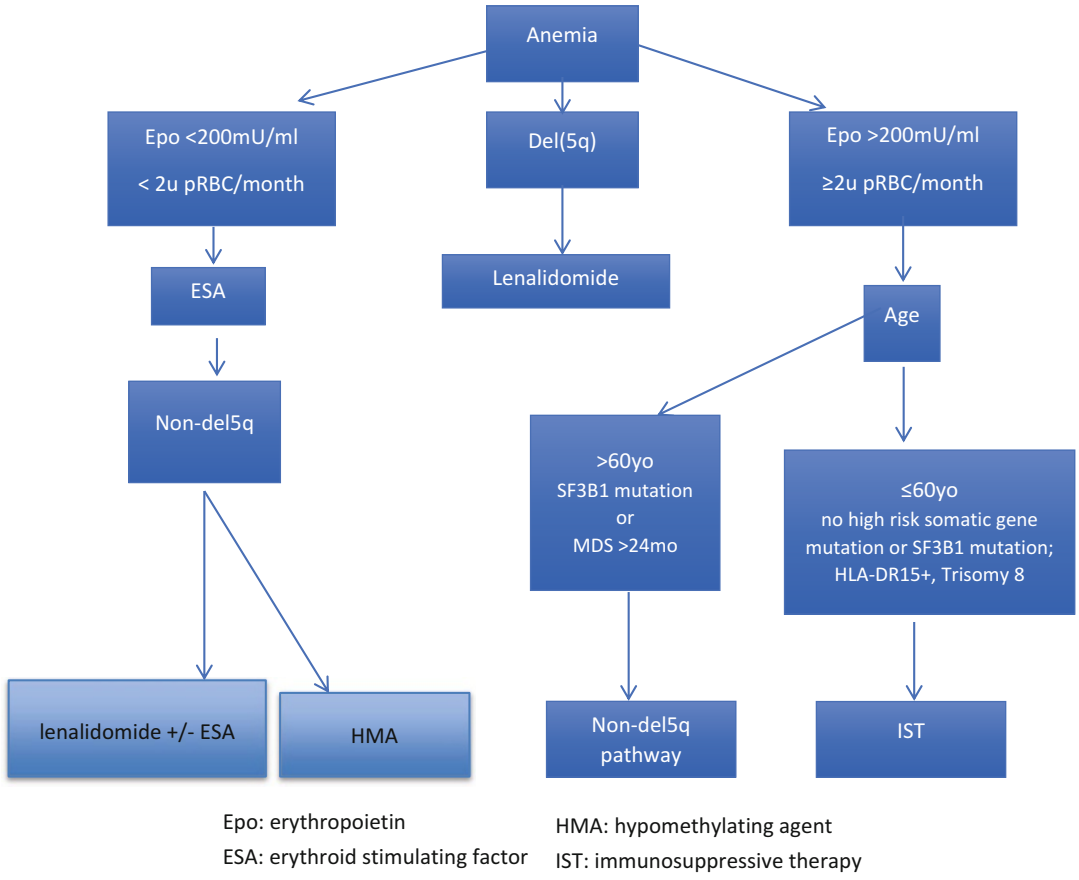
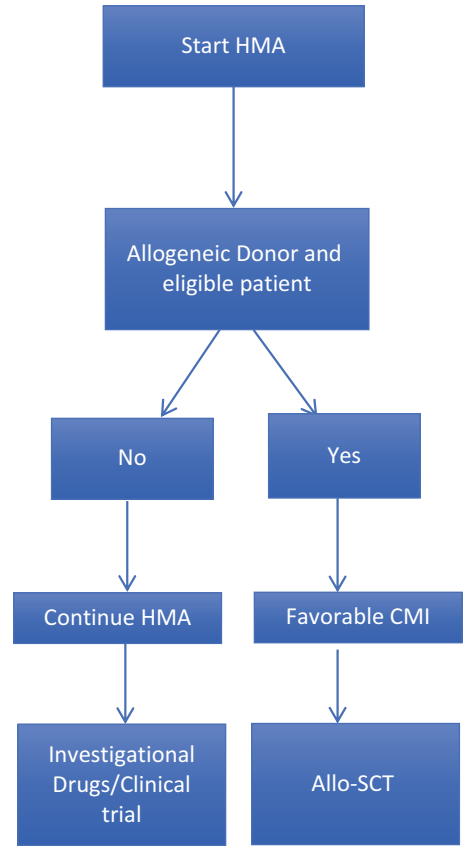


Fig. 2 Anemia management in low-risk MDS. *Epo* erythropoietin, *ESA* erythroid stimulating factor, *HMA* hypomethylating agent, *IST* immunosuppressive therapy

(60–90yo) transplant and intensive chemotherapy ineligible patients showed no statistically significant improvement in OS, but did improve PFS and AML transformation at 1 year (33% w/BSC to 22% with DAC) (Lubbert et al. 2011). Decitabine treatment was associated with improved patient-reported quality of life (QOL) parameters. Decitabine used at 20 mg/m^2 IV for 5 days every 28 days as outpatient was reported to have median overall survival of 19–20 month (Kantarjian et al. 2007b). It is crucial to allow 4–6 cycles of HMA therapy, patients with stable disease or better should continue on therapy as some patients will achieve better response later and even those with stable disease have better outcome than those who progress on therapy. Rarely, intensive chemotherapy can be utilized in this subset of patients as well, although these patients tend to have a lower response rate and shorter duration of remission.

High-Risk, Transplant Eligible

Since allo-HSCT is the only curative therapy for MDS, all patients who are <75 years of age with limited comorbidities should be considered for transplant at the time of initial diagnosis (Rowe et al. 2004). Currently, there remains inconclusive evidence that treatment prior to allo-HSCT improves outcomes. HMA compared to induction is an acceptable therapeutic option prior to allo-HSCT and often is used as a bridge to allo-SCT. As discussed below, the most important predictor of response to transplant is the disease status (blast percentage) and cytogenetics going into transplant (Damaj et al. 2012).



HMA: hypomethylating agents

Allo-SCT: allogeneic hematopoietic stem cell transplantation

Fig. 3 High-risk MDS treatment algorithm. *HMA* hypomethylating agents, *Allo-SCT* allogeneic hematopoietic stem cell transplantation

Low-dose HMA maintenance therapy (32 mg/m^2 × 5 days) posttransplant can be well tolerated although definitive clinical trial is warranted to confirm benefit of HMA maintenance (Jabbour et al. 2009).

It is important to note that a particular subset of high-risk patients, those with a TP53 mutation, have a particularly poor prognosis and to date, the benefit of allo-HCT has not been elucidated. For these patients, a clinical trial would be preferable (Lindsley et al. 2017).

Relapsed/Refractory Disease

There is a general paucity of effective treatments for the management of recurrent or refractory MDS. As such, patients with recurrent or refractory disease should be encouraged to participate in clinical trials whenever possible (Prebet et al. 2011). Any risk patient with HMA failure generally has a poor outcome (Garcia-Manero et al. 2013).

Intermediate-Risk R-IPSS

The intermediate-risk R-IPSS patients represent a challenging subset of patients. At this time, there is no defined consensus regarding the optimal treatment of patients with intermediate-risk MDS. As such, the management of this group of patients is ill-defined and is individualized based upon other factors such as age, LDH, ferritin, and perhaps somatic mutations (Tefferi et al. 2017). A choice among the therapeutic options, particularly in the intermediate-risk patients, must take into consideration the patients' own preferences and interpretation regarding what ascertains a reasonable quality of life, survival, and individualized goals.

The Role of Allogeneic Stem Cell Transplant

At this time, allo-HCT remains the only potentially curative therapy for patients with MDS. Unfortunately, as the median age of patients with MDS is 72 years old, most of these patients – even the higher risk patients – are ineligible for allo-HCT given other medical comorbidities and the baseline transplant-related mortality. It is interesting to note that since 2008, when Medicare began to provide coverage for the procedure in MDS patients, the number of allo-HCT performed in the United States for patients with MDS, particularly those older than 60 years, has significantly increased over the last decade.

The timing of allo-HCT is of paramount importance in MDS but is incompletely defined. In general, early transplant is recommended for all-comers with higher risk MDS to maximize survival potential, whereas for lower-risk MDS patients delaying allo-HCT until disease progression is often the norm as this is associated with prolonged OS in this subset of patients (Cutler et al. 2004). A subsequent study utilizing data from reduced intensity allo-HCT in the elderly (60−70yo) population confirmed the recommendation of early allo-HCT for high-risk disease and delayed allo-HCT for those patients with lower-risk MDS (Koreth et al. 2013). It is important to note, however, that age is *not* the most important predictor of outcome after allo-HCT. A retrospective multicenter analysis of 1333 MDS patients ≥50 years, the 4-year estimated treatment-related mortality (TRM) was 36% in the 50–60-year-old cohort, and 39% in patients older than 60 years (Lim et al. 2010). Interestingly, age is not the most important predictor of outcome after allo-HCT, rather it is the disease status prior to transplant (Damaj et al. 2012; Cutler et al. 2004).

Therapies on the Horizon

MDS is a particularly challenging entity given the heterogeneity of this disease and the complicated elderly patients that compromise the majority of those afflicted. Newer and more efficacious therapies are needed to advance the overall outlook of elderly patients with MDS. In higher risk MDS patients, new HMA such as oral azacitadine, oral decitabine, and SGI-110 are being tested in clinical trials. Checkpoint inhibitors are currently in clinical studies in combination with HMA or after HMA failure.

In the lower risk MDS population, novel TGF-B inhibitors luspatercept and sotatercept showed promising results in patients with ring sideroblasts. Those molecules are fusion trap proteins that neutralize activin receptor ligands (Platzbecker et al. 2017; Komrokji et al. 2014).

Targeted therapies including splicing inhibitors, IDH-2 inhibitors, and p53 modulators are being investigated in clinical trials.

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Acute Myeloid Leukemia in Older Adults

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Contents

Abstract

Acute myeloid leukemia (AML) is a disease of older adults, and approximately 58% are diagnosed in those aged ≥65 years. Outcomes in older adults with AML are poor due to a combination of factors including disease biology, under-referral, undertreatment, and poor treatment tolerability. For selected older patients with AML, treatment is associated with improved survival. The optimal treatment for older patients with AML is unclear. While

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intensive induction chemotherapy has been used for the last few decades, it has been associated with high treatment-related morbidity and mortality. In the last decade, many advances in the treatment of AML have been made, including the use of targeted agents and novel combinations of lower-intensity treatments, the latter of which may have better tolerability and similar or better efficacy compared to intensive chemotherapy. Nonetheless, to help personalize therapies for older adults with AML, it is important to assess individual fitness through the use of a geriatric assessment. Improving outcomes of older adults with AML will rely on both development of novel therapies and targeting therapy to their physiologic fitness and disease biology.

Keywords
Acute myeloid leukemia · Older adults · Geriatric assessment

Introduction

Acute myeloid leukemia (AML) is an aggressive cancer of the myeloid linage of leukocytes. It is of particular interest to geriatric oncologists as it is a disease of older adults which has been characterized by dramatic age-related outcome disparity. There is no consensus regarding optimal therapy for older adults (frequently defined as ≥60 or ≥ 65 years). Older adults are commonly treated differently than younger patients due to concerns related to both decreased treatment efficacy and lower treatment tolerance. Available evidence supports an individualized approach to treatment accounting for both the heterogeneity of tumor biology and the variability of patient characteristics which better define physiologic age and resilience. A recent expansion of therapeutic strategies spanning more and less intensive treatment approaches provide opportunities to improve outcomes for older adults with AML.

Epidemiology

AML is a disease most commonly diagnosed in older adults. The median age at diagnosis is between 68 and 72 years; approximately 57% are ≥65 years and 33% are ≥75 years. The Surveillance, Epidemiology, and End Results (SEER) Program estimates 19,520 new cases in 2018 in the United States with 10,670 deaths from the disease (SEER 2019).

Risk factors for the development of AML include a history of preceding myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPNs), exposure to certain chemotherapy drugs (alkylating agents, topoisomerase II inhibitors, and nitrosoureas), radiation, benzene exposure, and a history of Down's syndrome. The majority of diagnosed cases of AML, however, are not associated with any known risk factor.

Diagnosis and Risk Stratification

The presentation of AML can vary and initial symptoms are non-specific. The most common objective findings are anemia, thrombocytopenia, and/or leukopenia. Fatigue, dyspnea, bleeding, fever, and infection are common presenting symptoms secondary to cytopenias. Leukemic infiltration of tissues outside the bone marrow such as the liver, spleen, skin, lymph nodes, and central nervous system (CNS) can manifest a variety of other symptoms specific to the site of involvement. Some patients present with severe leukocytosis, which can produce symptoms of leukostasis due to the large blast fraction in the peripheral blood. Peripheral blood findings range from pancytopenia with or without circulating blasts cells to severe leukocytosis with circulating blasts often accompanied by anemia and thrombocytopenia.

Diagnosis of AML depends primarily upon detection of an abnormal accumulation of leukemic blasts of myeloid lineage ≥20% in the bone marrow. Additionally, presence of certain genetic abnormalities t(8;21), inv(16), or t(15;17) and myeloid sarcoma are considered diagnostic of AML regardless of marrow blast count. AML classification by genetic abnormality is presented in Table 1 (Döhner et al. 2017).

Table 1 Risk stratification by genetics for acute myeloid leukemia per European Leukemia Network 2017

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;122.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or 1(16;16)(p13.1; q22); *CBFB-MYH11*
	Mutated NPM1 without FLT3-ITD or with FLT3-ITD[low(a)]
	Biallelic-mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD[high(b)]
	Wild-type NPM1 without FLT3-ITD or with FLT3-ITD[low(a)] (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3; q26.2); GATA2, MECOM(EVI1)
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype or monosomal karyotype
	Wild-type NPM and FLT3-ITD[high(b)]
	Mutated RUNX1[c]
	Mutated ASXL1[c]
	Mutated TP53

Reference: Dohner et al. (2017)
[a]Low allelic ratio (<0.5)
[b]High allelic ratio (≥0.5)
[c]Not used as an adverse prognostic marker if co-occur with favorable-risk AML subtypes

Outcome and Treatment Disparity by Age

Outcomes for older adults are poor. In the United States, a 5-year relative survival reported by Surveillance, Epidemiology, and End Results (SEER) Program is 46.3%, 26.3%, 10.8%, and 2.7% for ages 20–49, 50–64, 65–74, and > 75 years, respectively (SEER 1988–2014). While survival rates have improved over time, the magnitude of improvement decreases with increasing age and has remained fairly stagnant for those diagnosed above age 75 (representing approximately one-third of newly diagnosed patients) (SEER, Fig. 1). Clinical trial data have also documented low 5-year survival estimates among adults aged ≥65 years (<10%) (Appelbaum et al. 2006). The Alliance for Clinical Trials in Oncology recently published long-term outcomes of patients treated intensively who did not undergo allogeneic transplantation post-remission and showed a complete remission rate of 60.3% among older patients (>60 years, N = 944) and a 10-year disease-free survival rate of 2.4% (Vasu et al. 2018).

Population-based data have indicated that a large proportion of older adults with newly diagnosed AML receive no antileukemic therapy at all (Medeiros et al. 2015; Oran and Weisdorf 2012). For example, SEER data indicated that only 40% of adults ≥65 years of age received any antileukemic therapy within 3 months of diagnosis (years 2000–2010). Forty percent of the population were aged >80 years, and only 20% received any therapy in this age group (Medeiros et al. 2015). Indicators of poor performance (i.e., claims for oxygen, wheelchair, home health supplies, skilled nursing; poor performance indicators) and comorbidity were associated with lack of therapy. However, it is notable that indicators of poor performance were only present in 13% of the population and only a quarter had such a comorbidity. In a more recent analysis (2000–2013), it appears that the percentage of older patients who received antileukemic therapy has increased from 37% to 55% (Medeiros et al. 2018).

Importantly, receipt of any treatment is associated with improved survival. Swedish registry data has also observed a survival advantage for older adults who receive therapy for AML (Juliusson 2011; Juliusson et al. 2009). In general, these population-based studies do show a trend for increased use of antileukemic therapy over time among older patients, particularly among those between ages 65 and 80 years. Given the recent availability of new therapies, it is likely that the proportion of older adults receiving any antileukemic therapy will continue to increase in the coming years. However, it will be important to continue observing practice patterns in the community and to pay close attention to those aged ≥75 years.

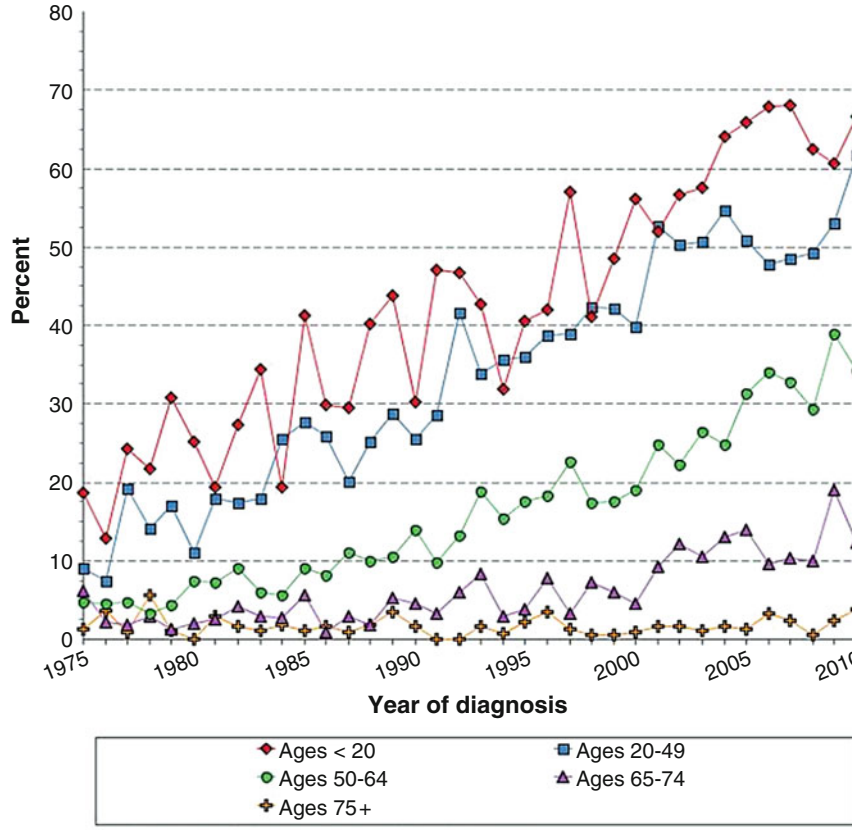

Fig. 1 Surveillance, epidemiology, and end results (1975–2014) 5-year relative survival for newly diagnosed acute myeloid leukemia by year of diagnosis and by age

Age-Related Changes in Tumor Biology

Age-related changes in tumor biology contribute to poor outcomes for older adults. Older adults with AML are less likely to have favorable cytogenetic abnormalities (i.e., t(8;21), t(15;17), and inv(16)) compared to younger patients. In addition, they are more likely to have unfavorable cytogenetic abnormalities (i.e., chromosome 5 and 7 abnormalities and/or complex karyotypes) (Appelbaum et al. 2006; Grimwade et al. 2001; van der Holt et al. 2007). Unfavorable cytogenetic abnormalities are associated with decreased rates of remission and decreased overall survival (OS) (Appelbaum et al. 2006; Grimwade et al. 2001; Farag et al. 2006; Frohling et al. 2006; Gupta et al. 2005). Other risk factors include expression of a multidrug resistance (MDR1) phenotype which are more commonly seen in older patients with AML (Leith et al. 1997). This membrane-associated glycoprotein actively pumps out conventional chemotherapies such as anthracyclines reducing intracellular concentrations, compromising treatment efficacy. Older patients are also more likely to harbor unfavorable mutations in their leukemic clone when compared to younger patients. This was particularly true for mutations in the tumor suppressor gene *TP53* and the epigenetic regulator *DNMT3A*. Mutations in both of these genes were independent predictors of adverse prognosis among older adults (Tsai et al. 2016). Finally, older adults are more likely to present with secondary AML, often with a

preceding hematologic disorder such as myelodysplastic syndrome, which is associated with lower remission rates and higher rates of relapse (Godwin and Smith 2003).

Studies have demonstrated the influence of these risk factors on remission rates for older adults. For example, a study of older adults with newly diagnosed AML treated with intensive induction therapy conducted by the Southwest Oncology Group demonstrated that patients with none of these adverse risk factors (i.e., de novo AML, MDR1-negative phenotype, favorable or intermediate cytogenetics) had high complete response (CR) rates (81%), while those with multiple risk factors (i.e., secondary AML, MDR1-positive phenotype, unfavorable cytogenetics) had extremely low CR rates (12%) (Leith et al. 1997). Another study of older patients with favorable cytogenetics (t(8;21), inv. (Tsai et al. 2016)) demonstrated remission rates of 80% and 5-year survival of 30% (Prebet et al. 2009), resulting in some consensus that this uncommon subgroup should be offered intensive therapy if their Eastern Cooperative Oncology Group (ECOG) performance status is <3.

The majority of older adults fall into the category of cytogenetically normal AML. This category is, however, molecularly diverse. The prognostic implication of gene mutations (i.e., FMS-like tyrosine kinase-3 internal tandem duplication (*FLT3-ITD*), nucleophosmin 1 (*NPM1*), CCAAT-enhancer-binding protein alpha *(CEBPA)*, DNA methyltransferase *3 (DNMT3)*, isocitrate dehydrogenase *1* (*IDH1)* and *IDH2*, Wilms tumor suppressor gene 1 (*WT1*)), and gene overexpression (i.e., erythroblast transformation-specific-related gene (*ERG*), brain and acute leukemia, cytoplastic (*BAALC*)) is an area of active research (Becker et al. 2010; Marcucci et al. 2012; Mendler et al. 2012; Schwind et al. 2010, 2011; Whitman et al. 2012; Whitman et al. 2010; Eisfeld et al. 2018). The most well-defined molecular risk factors are *FLT3-ITD* mutation (poor prognosis), *NPM1* without *FLT3-ITD* mutation (good prognosis), and biallelic *CEBPA* mutation without *FLT3-ITD* (good prognosis). The prognostic implications of these mutations appear similar across ages. Molecular changes have been observed between older and younger patients, and analysis of gene expression data comparing younger and older patients has demonstrated age-specific dysregulation of oncogenic pathways (Rao et al. 2009).

Treatment

Induction Chemotherapy

The standard treatment for older adults with AML is an ongoing debate. Induction chemotherapy with anthracycline and cytarabine (given over 7 and 3 days, respectively) has been a standard upfront treatment for AML since the 1970s (Yates et al. 1973). In the CALGB study published by Rai et al., it was established that 7 days of cytarabine administered as a continuous confusion along with 3 days of daunorubicin given as intravenous injection was superior to 5 + 2 (Rai et al. 1981). The CR rate was 59% in patients aged <60 years and 45% in patients aged ≥60 years. In 1989, Löwenberg et al. confirmed the benefits of intensive chemotherapy in patients aged ≥65 years (Lowenberg et al. 1989). In this trial, patients who received 7 + 3 vs. supportive care had a superior CR (58% vs. 0%) and median survival (21 weeks vs. 11 weeks, P = 0.015).

Since then, various other strategies have been investigated with the goal of improving outcomes. These strategies include the use of different anthracyclines (e.g., idarubicin or mitoxantrone) (Rowe et al. 2004; Goldstone et al. 2001; Pautas et al. 2010; Lowenberg et al. 1997, 1998), new agents added to standard 7 + 3 (e.g., etoposide, midostaurin, or gemtuzumab) (Goldstone et al. 2001; Baer et al. 2002; Cripe et al. 2010; Castaigne et al. 2012; Stone et al. 2017; van der Holt et al. 2005), alternative agents (e.g., clofarabine alone) (Foran et al. 2015), novel combinations (e.g., clofarabine with cytarabine) (Faderl et al. 2006; Burnett et al. 2017), various doses of anthracycline and cytarabine (Pautas et al. 2010; Lowenberg et al. 2009; Dillman

et al. 1991), and growth factors (Rowe et al. 2004; Lowenberg et al. 1997; Godwin et al. 1998; Stone et al. 1995). Some of these strategies have yielded improvement in outcomes although the majority did not (Table 2).

In terms of the types and doses of anthracycline, Löwenberg et al. compared daunorubicin 45 mg/m^2 vs. 90 mg/m^2 given with cytarabine in patients aged 60–82 years; CR rates were 54% vs. 64% (P = 0.002) (Lowenberg et al. 2009). No difference in OS, 30-day mortality, or adverse events was noted. Nonetheless, in subgroup analyses, patients aged 60–65 years who received higher dose of daunorubicin (90 mg/m^2) had improved CR (73% vs. 51%) and 2-year OS (38% vs. 23%, P < 0.01). On the other hand, Pautas et al. did not demonstrate superiority of daunorubicin 80 mg/m^2 vs. idarubicin 12 mg/m^2 given over 3 or 4 days (Pautas et al. 2010). In fact, the CR rate was lower in the daunorubicin arm (70% in the daunorubicin arm vs. 83% in the 3-day idarubicin arm vs. 78% in the 4-day idarubicin arm, P = 0.04) (Pautas et al. 2010). Burnett et al. also failed to show any difference in the daunorubicin 60 mg/m^2 vs. 90 mg/^{2} arm (over a quarter were aged ≥60 years) (Burnett et al. 2015). Taken together, daunorubicin 60–90 mg/m^2 or idarubicin 12 mg/m^2 can be considered for patients aged ≥65 years.

In recent years, emerging studies have demonstrated the utility of adding targeted agents to intensive chemotherapy. Castaigne et al. demonstrated that in patients aged 50–70 years, adding gemtuzumab ozogamicin, an anti-CD33 antibody conjugate, during induction on days 1, 4, and 7 and during consolidation for two doses at 3 mg/m^2 improved OS (34.0 months vs. 19.2 months, P = 0.0368) (Castaigne et al. 2012). Burnett et al. also showed that adding gemtuzumab at 3 mg/m^2 on day 1 of induction chemotherapy improved survival (Burnett et al. 2012). However, both studies did not show a difference in CR rates.

Another targeted agent is midostaurin, a multikinase inhibitor with activity against FLT3. In a study of patients aged 18–60 years, Stone et al. showed that midostaurin added to standard induction chemotherapy for those with a FLT3 mutation improved median OS (74.7 months vs. 25.6 months, P = 0.009), compared to chemotherapy alone (Stone et al. 2017). CR was similar (58.9% vs. 53.5%, P = 0.15). Even though the trial did not include older patients, midostaurin was approved by the US Food and Drug Administration (FDA) for use in all patients with FLT3 mutations.

Even with intensive chemotherapy, the outcomes of older patients with AML are poor, especially in those with secondary or therapy-related AML (Granfeldt Ostgard et al. 2015). In this population, a liposomal capsulation of cytarabine and daunorubicin, known as CPX-351, was evaluated. Lancet et al. compared CPX-351 to standard 7 + 3 in patients aged 60–75 years with secondary AML, therapy-related AML, or AML with MDS-related cytogenetic abnormalities (Lancet et al. 2018). CPX-351 improved the median OS and remission rate compared to standard 7 + 3 (median OS, 9.6 months vs. 6.0 months, P = 0.003; remission rate, 47.7% vs. 33.3%, P = 0.016). It is worth noting that the time taken to neutrophil and platelet count recovery in the CPX-351 arm was longer (around 35 to 37 days vs. 26 days in the 7 + 3 arm), which may translate to a longer hospitalization.

Lower-Intensity Treatments

Intensive chemotherapy is associated with an early mortality rate of 10–30% in older adults (Foran et al. 2015; Lowenberg et al. 2009; Kantarjian et al. 2006, 2010). Therefore, it is typically reserved for patients who are considered "fit" and have no major comorbidities. In addition, some older patients may prioritize receiving treatments in the outpatient setting. Therefore, lower-intensity treatments that are outpatient, such as low-dose cytarabine and hypomethylating agents (azacitidine and decitabine), have been actively investigated.

Tilly et al. compared low-dose cytarabine (LDAC) to intensive chemotherapy in patients aged ≥65 years (Tilly et al. 1990). CR was 32% in the low-dose cytarabine group vs. 52% in the intensive chemotherapy group, though OS was

Table 2 Selected clinical trials for older adults with acute myeloid leukemia

Author	Year	Age (years)	N	Treatment	CR (%)	Median OS (months)	P value for OS	Induction death rate (%)
Standard dose induction								
Lowenberg et al. (1989)	1989	>65	31	Ara-C, daunorubicin, vincristine	58	5.3	<0.05	9.7
			29	Supportive care	0	2.8		N/A
Lowenberg et al. (1998)	1998	>60	242	Ara-C, daunomycin	38	9.0	0.23	6.0
			247	Ara-C, mitoxantrone	47	9.7		6.0
Dose-attenuated induction								
Tilly et al. (1990)	1990	>65	46	Rubidazone, Ara-C	52	12.8	0.12	31
			41	Low-dose Ara-C	32	8.8		10
Growth factor support								
Lowenberg et al. (1997)	1997	>60	157	Daunomycin, Ara-C, GM-CSF	56	No difference	0.55	14
			161	Daunomycin, Ara-C	55			10
Stone et al. (1995)	1995	>60	195	Ara-C, daunorubicin	54	9.4	0.10	16
			193	Ara-C, daunorubicin, GM-CSF	51	9.4		20
MDR1 modulation								
Baer et al. (2002)	2002	≥60	61	Ara-C, daunorubicin, etoposide	46	No difference	0.48	20
			59	Ara-C, daunorubicin, etoposide, PSC-833	39			44
Van der Holt et al. (2005)	2005	≥60	211	Daunorubicin, Ara-C	48	No difference	0.52	Not reported
			208	Daunorubicin, Ara-C, PSC-833	54			
Dose intensification								
Lowenberg et al. (2009)	2009	≥60	411	Ara-C, daunorubicin 45mg/m^2	54	No difference	0.16	11
			402	Ara-C, daunorubicin 90mg/m^2	64			12
Addition of gemtuzumab ozogamicin								
Castaige et al. (2012)	2012	50–70	139	Ara-C, daunorubicin, gemtuzumab ozogamicin	75[a]	34.0	<0.05	4
			139	Ara-C, daunorubicin	81[a]	19.2		6
Burnett et al. (2012)	2012	>60 (or not suitable for the trial for younger patients)	556	Daunorubicin, Ara-C, or clofarabine	68			8
			559	Daunorubicin, Ara-C or clofarabine + gemtuzumab ozogamicin (GO)	70	Improved with GO	0.05	9

(*continued*)

Table 2 (continued)

Author	Year	Age (years)	N	Treatment	CR (%)	Median OS (months)	P value for OS	Induction death rate (%)
Addition of FLT-3 inhibitor								
Stone et al. (2017)	2017	18–59[b]	160	Ara-C, daunorubicin, midostaurin	59	74.7	<0.05	5
			357	Ara-C, daunorubicin	54	25.6		3
Drug delivery modification								
Lancet et al. (2018)	2018	60–75 (secondary AML)	156	7+3	33	6.0	<0.05	6
			153	CPX-351	48	9.6		11
Lower-intensity therapy								
Kantarjian et al. (2012)	2012	≥65	243	Supportive care or low-dose Ara-C	8	5	0.2	8
			242	Decitabine	18	8		9
Burnett et al. (2007)	2007	≥60[c]	103	Low-dose Ara-C ± ATRA	18	Improved with low-dose Ara-C	<0.05	26
			99	Hydroxyurea ± ATRA	1			26
Dombret et al. (2015)	2015	≥65	241	Azacitidine	28	10.4	0.10	8
			247	Conventional care arm	25	6.5		12
Dinardo et al. (2019)	2019	≥65	145[d]	Venetoclax with decitabine or azacitidine	67	17.5	–	3
Cortes et al. (2019)	2019	≥55	88	Glasdegib	17	8.8	<0.05	6
			44	Low-dose Ara-C	2	4.9		13

Abbreviations: *AML* acute myelogenous leukemia, *N* number of patients enrolled, *CR* complete remission, *OS* overall survival, *Ara-C* cytarabine, *N/A* not applicable, *GM-CSF* granulocyte macrophage colony-stimulating growth factor
[a]Rates represent CR with incomplete platelet count recovery
[b]Trial did not include older adults but is an important recent advance in the field
[c]2% <60 with comorbidity
[d]Single-arm study

similar. Burnett et al. compared low-dose cytarabine to hydroxyurea in patients with AML or MDS (most patients were aged ≥60 years) not considered "fit" for intensive treatment (Burnett et al. 2007). CR was 18% in the low-dose cytarabine group vs. 1% in the hydroxyurea group ($P < 0.00006$), with improvement in OS noted in the former group (odds ratio (OR), 0.60; 95% CI, 0.44–0.81). These studies supported that the utility of low-dose cytarabine in older patients with AML was not considered candidates for intensive chemotherapy.

Additional low-intensity options are the hypomethylating agents, azacitidine and decitabine. These drugs are cytidine and deoxycytidine analogues, respectively. Unlike cytarabine, these agents are incorporated into the growing DNA strand and do not cause DNA polymerase stalling or replication fork collapse. Once incorporated into the newly synthesized DNA strand, DNA methyltransferases become covalently attached when they attempt to methylate them. This adduct is recognized by the base excision repair machinery, and its resolution results in the degradation of the DNA methyltransferase. The result is a cell depleted of DNA methyltransferase and hypomethylated DNA leading to aberrant gene expression and differentiation or apoptosis (Stresemann and Lyko 2008).

These agents have demonstrated activity in older adults with AML (van der Helm et al. 2013; Gardin and Dombret 2017) and have been shown to be superior to conventional care regimens (Dombret et al. 2015). Overall, these agents have demonstrated a lower CR rate but increased tolerability and comparable survival when compared to intensive chemotherapy (Gardin and Dombret 2017).

Fenaux et al. compared azacitidine with conventional care regimens (CCR, best supportive care only, low-dose cytarabine, or intensive chemotherapy) in patients (72.7% were $\geq$ 65 years) with low bone marrow blast count AML (median, 22.5–27.0%) (Fenaux et al. 2010). Compared to CCR, those who received azacitidine had improved median OS (24.5 months vs. 16.0 months, $P = 0.005$) and fewer days in hospital (26.0 days vs. 50.9 days per patient year, $P < 0.0001$). CR was not different between the azacitidine and CCR groups (18% vs. 16%, $P = 0.80$). Of note, the median OS was also not different between patients who received azacitidine vs. intensive chemotherapy (not reached vs. 14.2 months, $P = 0.97$), although the study was not powered to detect a difference (Fenaux et al. 2010). Dombret et al. further evaluated azacitidine vs. CCR in patients aged $\geq$65 years with high bone marrow blast count (>30%) (Dombret et al. 2015). Compared to CCR, those who received azacitidine had improved median OS, though this was not statistically significant (10.4 months vs. 6.5 months, $P = 0.1009$). When adjusted for subsequent AML therapy, azacitidine was superior compared to CCR. Overall response rate (CR + CRi) was not different between the azacitidine vs. CCR groups (27.8% vs. 52.1%, $P = 0.5384$). Kantarjian et al. compared decitabine vs. supportive care or low-dose cytarabine in patients aged $\geq$65 years (Kantarjian et al. 2012). Like azacitidine, after censoring for subsequent AML therapy, decitabine was found to be superior to its comparative arm (median OS: 8.5 vs. 5.3 months, $P = 0.044$). CR was higher in the decitabine arm (17.8 vs. 7.8%, $P = 0.001$). To date, there is no published randomized trial powered to compare low-dose therapy vs. intensive therapy although such a study is ongoing (NCT02172872).

Recently, novel combinations with lower-intensity therapies have been tested leading to new drug approvals specific to older adults. Two combination therapies with LDAC have been recently approved in the United States. The first of these is an oral hedgehog pathway inhibitor, glasdegib. This was tested in a randomized trial of older patients with AML not fit for intensive chemotherapy (97.7% were $\geq$ 65 years; 53% had ECOG performance status of 2). The study showed a doubling of survival for patients treated with combination compared to LDAC alone (4.9 months vs. 8.8 months, $P = 0.0004$) (Cortes et al. 2019). This led to the approval of this combination for older AML patients unfit for intensive therapy due to comorbidities or age. The B-cell leukemia/lymphoma 2 (BCL2) antagonist venetoclax was also tested in combination with LDAC in a single-arm phase I/II study of 82 patients (median age not reported) with previously untreated AML that were unfit for induction chemotherapy (Wei et al. 2018a). The phase I portion of the study determined the recommended phase II dose of venetoclax to be 600 mg daily given continuously. The combination resulted in a CR/CRi rate of 54% with a median survival not yet reached at the time the abstract was presented (Wei et al. 2018b). These data led to the approval of venetoclax in combination with LDAC for the treatment of unfit patients with AML. Finally, the combination of venetoclax with either azacitidine or decitabine for older adults not fit for chemotherapy was conducted. In this phase Ib study of 145 previously untreated, unfit patients, the recommended venetoclax dose was determined to be 400 mg daily (DiNardo et al. 2019). The overall CR/CRi rate was 67% for all doses tested. The median survival was a remarkable 17.5 months given the median age of the patients was 74 (DiNardo et al. 2019). These outstanding results led to the approval of this combination by the FDA for the treatment of unfit patients with AML and may result in this combination becoming the standard of care for these patients. In elegant translational experiments on AML cells taken from treated patients, it was determined that the combination of venetoclax and azacitidine acts by impairing the activity of complex II of

the electron transport chain leading to disruption of oxidative phosphorylation (ox/phos) and apoptosis particularly in the leukemia stem cell population (Pollyea et al. 2018). Of note neither agent alone has this activity; it is only the combination that results in ox/phos inhibition.

While recent approvals have included a specific indication for "unfit" adults, the criteria for "unfitness" vary among trials and remain to some extent dependent upon physician perspective. To a large extent, "unfitness" in this context has been described by chronologic age >75 years. The trial testing glasdegib did include additional specific criteria including PS 2, heart disease, and creatinine >1.3. No characterization of functional status was required except that patients were excluded if PS was >3.

Extrapolating Clinical Trial Data

In reviewing available clinical trial data to support treatment decisions for older adults, consideration must be given to how results can be extrapolated to patients seen in practice. Careful attention should be paid to inclusion and exclusion criteria in addition to characterization of patients. It is well known that those older adults who are enrolled on clinical trials are typically healthier than patients seen in practice (Hurria et al. 2015; Scher and Hurria 2012; Singh et al. 2017; Levit et al. 2018). In the case of AML, referral bias is also an important consideration. Clinical trials commonly enroll patients from referral centers, yet most older adults with AML are never referred (Alibhai et al. 2009a). Referral bias and unmeasured confounders (related to the patients themselves or the environment in which they are treated) can influence treatment outcomes at a high-volume referral center vs. smaller-volume community practice (Ostgard et al. 2016; Juliusson et al. 2012).

Post-remission Therapy

No studies have demonstrated the benefits of post-remission therapy vs. no therapy in older patients. However, most clinical trials evaluating induction therapies have incorporated post-remission therapies given a high risk of relapse in these patients (Cassileth et al. 1988). Therefore, it is an accepted standard to administer consolidation therapy to older patients with AML. Consolidation therapy usually consists of chemotherapy, allogeneic stem cell transplant, or both.

Mayer et al. showed that patients who received high-dose cytarabine (3 gm/m^2) every 12 hours on days 1, 3, and 5 for four courses had the best OS and disease-free survival, compared to lower doses (100 mg/m^2 or 400 mg/m^2 given continuously over 5 days) (Mayer et al. 1994). However, only 29% of patients aged >60 years were able to tolerate four courses, and 45% were able to receive more than one course. Central nervous toxicity occurred in 32% of these patients; 40% had permanent disability. Gardin et al. compared a single intensive consolidation course (i.e., second course of induction therapy) vs. a 6 monthly course of daunorubicin/idarubicin and cytarabine at lower doses. The latter regimen appears to be better in terms of disease-free survival and OS (Gardin et al. 2007). In contrast, Schlenk et al. showed that consolidation with idarubicin and etoposide was better than oral maintenance with the same drugs over a year (Schlenk et al. 2006). Stone et al. showed that a combination of cytarabine at higher dose and mitoxantrone was no better than cytarabine alone at a lower dose given over 4 months (Stone et al. 2001).

Overall, the aforementioned studies suggest that cytarabine may be beneficial in older patients with AML who achieve CR after induction chemotherapy, although the exact dosing and frequency are unclear. There are various regimens used in clinical trials and practice. The National Comprehensive Cancer Network recommends several strategies: cytarabine at 100–200 mg/m^2/day over 5–7 days for one to two cycles with or without anthracycline or intermediate-dose cytarabine at 1.0–1.5 gm/m^2/day for 4–6 doses given for 1–2 cycles for those who were not CD-33 positive, did not have FLT3 mutation, and did not have secondary or therapy-related AML (National Comprehensive Cancer Network 2018). In these patients, gemtuzumab, midostaurin, or CPX-351 should be incorporated as part of the consolidative treatments.

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is generally considered in younger patients who have high-risk cytogenetics and potentially in those with intermediate-risk cytogenetics (Oliansky et al. 2008). However, the lack of evidence for allo-HSCT in older adults, coupled with the high treatment-related mortality, has contributed to its low utilization. With improvement in conditioning regimens and supportive care, an increasing number of older patients are considered for allo-HSCT (Muffly et al. 2017). Several studies have suggested improvement in outcomes in older patients with AML who underwent allo-HSCT (Muffly et al. 2017; Rashidi et al. 2016; Devine et al. 2015). Nonetheless, studies are needed to select older patients who will most benefit from this highly intense treatment.

Acute Promyelocytic Leukemia (APL)

Acute promyelocytic leukemia (APL) represents a unique AML subset. Treatment recommendations differ for APL. Patients with APL were largely excluded from the trials reviewed above and therefore warrant separate discussion. APL is defined by a translocation between chromosomes 15 and 17, which leads to fusion of the promyelocytic leukemia (*PML*) gene with the retinoic acid receptor α (*RARα*) gene and results disruption of normal cell differentiation (Sanz et al. 2019). This block to differentiation is the result of the fusion gene, PML-RARα, no longer able to bind to physiological levels of retinoic acid recruiting transcriptional repressors to genes normally activated by the wild-type RARα receptor (The and Chen 2010). APL is less common among older adults (only approximately 30% are over age 60) (Chen et al. 2012), but the response and cure rates are higher than in most AML subtypes with induction regimens that include use of all-*trans* retinoic acid (ATRA) that overcomes the differentiation block by providing pharmacological levels of ATRA to force binding to the fusion receptor resulting in the restoration of gene activation. A clinical feature of APL is presentation with bleeding secondary to disseminated intravascular coagulation, which is a frequent cause of early death. When the diagnosis is suspected, treatment with ATRA should begin immediately.

APL is a curable disease. Treatment options have expanded in the past decade which is particularly relevant for older patients. Common curative treatment regimens include induction therapy with ATRA+anthracycline (for patients with high-risk disease defined by white cell count greater than 10,000) versus ATRA+arsenic trioxide (ATO) induction (chemotherapy-free regimen for intermediate and low-risk disease). A paradigm changing randomized trial compared ATRA+chemotherapy induction with ATRA+ATO alone in 156 patients with low- and intermediate-risk disease and showed CR rates of 95% versus 100% (ATRA+ATO) with a 2-year event-free survival of 86% and 97%, respectively (Lo-Coco et al. 2013). Consolidation therapy post induction is recommended with ATRA+ATO where available. The role of maintenance therapy is less clear. This treatment option provides highly effective therapy with lower toxicity rates providing an option for most older adults diagnosed with APL.

Survival rates for APL have been improving over time although there remains a persistent age-related survival disparity. For example, in a report from the Netherlands, relative 5-year survival rates for those 61–70 years of age at diagnosis improved from 38% (2001–2006) to 54% (2007–2012), while those for aged over 70 increased from 16% to 37% during those years (Dinmohamed et al. 2016). Early death rates (typically defined as 30-day mortality) are high for all ages in population-based data but significantly worse among those diagnosed at an older age, with poor performance status, or comorbidity (Lehmann et al. 2011). Registry data from Sweden reported an early death rate of 15% for ages 16–50 and 50% for those over age 60 years (Lehmann et al. 2011). It is expected that this age-related gap in outcomes may continue to improve with use of chemotherapy-free regimens, but it remains critical that older adults are diagnosed in a timely manner, offered therapies, and carefully monitored to address unique supportive care needs during management.

Individualizing Therapeutic Decisions

Risk Prediction Models

A critical issue when making treatment decisions for older adults with AML is estimating risks and benefits of therapy. Several models have been developed to inform risk stratification particularly when considering intensive therapy. Most of these incorporate chronologic age, tumor biology characteristics, and oncology performance status (PS). For example, a model predicting early mortality (death within 8 weeks of induction) among patients 70 years of age or older receiving intensive therapy includes age > 80, complex karyotype, poor ECOG performance status ≥2, and elevated creatinine (>1.3 mg/dl) (Kantarjian et al. 2010). Early mortality rates were 16%, 31%, 55%, and 71% for patients with none (28%), 1 (40%), 2 (23%), or ≥ 3 (9%) of these risk factors, respectively (Kantarjian et al. 2010). A model developed to predict OS after induction includes chronologic age, karyotype, NPM1 mutation status, white blood cell count, lactate dehydrogenase (LDH) levels, and CD4 expression (Rollig et al. 2010). Three-year OS rates of 39.5%, 30%, 10.6%, and 3.3% illustrate the impact of favorable, good intermediate, adverse intermediate, and high-risk categories based on this model. Another validated web-based application predicts CR and early death using both laboratory and clinical variables (body temperature, age, secondary leukemia or antecedent hematological disease, hemoglobin, platelet count, fibrinogen, and LDH). CR rate predictions range from 12% to 91% if cytogenetic information is available (Krug et al. 2010). More recently, two additional models were developed. The first model was developed to predict therapeutic resistance. Factors including age, performance status, white blood cell count, secondary AML, cytogenetic risk, and *FLT3*-ITD/*NPM1* mutation status were independently associated with failure to achieve CR despite no early death (area under receiver operator characteristic curves of 0.78). The second model was the AML composite model (AML-CM) which includes albumin levels, platelet counts, and LDH level, in addition to comorbidities as assessed in the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (Sorror et al. 2017). Four risk groups were derived, and 1-year survival among patients aged 60–75 years were 86% (scores 1–4), 50% (scores 5–6), 46% (scores 7–9), and 23% (scores ≥10). All of the above models demonstrate that outcomes for older adults vary widely and provide a foundation for improving risk stratification at the time of diagnosis. With the exception of the AML-CM, each model relies on chronologic age as a surrogate for measureable underlying impairments (i.e., comorbidity, physical function, cognition) that if accounted for may further improve estimates of reserve capacity during or after treatment (Loh and Klepin 2018a).

Assessing Fitness: A Role for Geriatric Assessment

Characterization of "fitness" is central to personalizing therapies for older adults with AML. To do so the heterogeneity of aging needs to be measured including assessments of patient-specific characteristics such as comorbidity and functional status. Clinical trials have incorporated knowledge gained from characterizing the biologic diversity of AML but have not routinely adopted rigorous characterization of the diversity of the older adult population. Older age is a risk factor for poor outcomes but remains a surrogate marker for other unmeasured characteristics. Older adults of the same chronologic age present with varying comorbidity, functional status, emotional health, cognitive performance, polypharmacy, social support, and presence of geriatric syndromes. These factors can influence aspects of care including communication, decision-making, treatment tolerance/resilience, treatment responsiveness, and survival.

Performance of standardized, validated measurement of patient characteristics can inform fitness in the context of specific therapies. For the purposes of this discussion, fit older adults could be considered robust enough to treat similarly to a middle-aged patient. Frailty, on the other hand, is characterized as a state of decreased physiologic

reserve associated with adverse health outcomes usually arising from decreased organ reserve, lack of activity, poor nutritional intake, stress, and/or physiologic changes of aging. In geriatric medicine, frailty is most commonly assessed using a phenotype method such as the Fried Frailty Index (weight loss, weakness, slow gait speed, low physical activity, and exhaustion) (Fried et al. 2001) or using a cumulative deficit burden approach (Rockwood and Mitnitski 2007). The implications of frailty may differ in hematology practice as it relates to treatment decisions (Abel and Klepin 2018). For example, a phenotypically frail person is unlikely to tolerate aggressive therapy but may tolerate and benefit from low-intensity therapy depending upon the toxicity profile. Frailty is also not a static process. In some cases frailty may improve with therapy if the disease was a primary contributor to the phenotype. Alternatively, frailty can develop as a consequence of treatment complications. Finally, there is a middle category of patients, who meet neither extreme, often termed "vulnerable," "unfit," or "pre-frail." These patients may benefit from aggressive supportive care targeting specific vulnerabilities to enhance fitness or prevent frailty.

Current evidence has not defined a gold standard for assessment of fitness, "unfitness," or frailty categorization in AML. Recent studies, which have tested new drugs in "unfit" older adults, maintained some subjectivity. Several studies left characterization of "unfit" to the discretion of physicians and/or patients. Common criteria cited include age $>$ 75 years and comorbidity (Dombret et al. 2015; DiNardo et al. 2019). Most studies have continued to exclude those patients with the worst performance status (ECOG $\geq$3) even when testing less-intensive therapies (DiNardo et al. 2019). Most clinical trials do not routinely characterize comorbidity although many studies investigating the relationship between comorbidity and outcomes in AML have shown a relationship between increased comorbidity burden and worse outcomes (Sorror et al. 2017; Wass et al. 2016; Sorror et al. 2007; Etienne et al. 2007; Giles et al. 2007).

Geriatric assessment is a promising strategy to improve characterization of older patients enrolled on clinical trials and treated in practice. Geriatric assessment is a method used to evaluate multiple characteristics in a standardized fashion and commonly includes physical function, comorbidity, cognitive function, psychological state, social support, polypharmacy, and nutritional status. This robust assessment strategy could help define fitness, "unfitness," or frailty in AML studies (Loh and Klepin 2018b; Loh and Klepin 2018c). Geriatric assessment is recommended by the National Comprehensive Cancer Network, the International Society of Geriatric Oncology (SIOG), and the American Society of Clinical Oncology (ASCO) guidelines statement due to the growing evidence that it can predict chemotherapy toxicity and survival in varied settings (Mohile et al. 2018; NCCN 2019; Extermann et al. 2011; Hamaker et al. 2014a; Hurria et al. 2011; Soubeyran et al. 2012; Wildiers et al. 2014).

There are data to support use of geriatric assessment in the AML setting. Pretreatment geriatric assessment is feasible to perform for newly diagnosed AML patients and detects vulnerabilities not otherwise captured (Deschler et al. 2013; Klepin et al. 2011). A single institution study assessing older patients ($\geq$60 years of age) with good ECOG performance status considered fit to receive intensive therapy found the following impairments when performing bedside geriatric assessment: cognitive impairment (24%), depression (26%), distress (50%), activity of daily living (ADL) dependence (34%), impaired objectively measured physical performance (31%), and significant comorbidity (40%) (Klepin et al. 2011). In this cohort (N = 74) testing, the utility of inpatient geriatric assessment prior to intensive chemotherapy, baseline impaired objectively measured physical performance (assessed using the Short Physical Performance Battery [SPPB], score $<$9), and cognitive impairment (modified Mini-Mental State Exam score $<$77) were independently associated with worse survival (Klepin et al. 2013). The SPPB is a validated measure of lower extremity function that predicts disability, hospitalizations, and mortality among older patients with demonstrated reliability across varied populations

(Guralnik et al. 1994, 1995, 2000; Ostir et al. 2002; Studenski et al. 2003; Volpato et al. 2011). The European Medicines Agency recommends use of the SPPB as a frailty measure (European Medicines Agency 2018). The SPPB consists of a short walk (4 m at usual speed), five repeated chair stands, and three balance tests. Gait speed is as a robust marker of frailty and may be an alternate strategy to use in practice (Studenski et al. 2011).

The utility of geriatric assessment data has been shown in the non-intensive setting as well (Sherman et al. 2013; Molga et al. 2018). A multi-site observational study evaluated pretreatment geriatric assessment among patients with MDS or AML who were treated with best supportive care, hypomethylating agents, or intensive therapy per clinician discretion. Three characteristics were associated with worse survival among those receiving low-intensity therapy or best supportive care: assistance with activities of daily living (ADLs), high fatigue score, and impaired PS (Sherman et al. 2013). These three variables were used to create a frailty score ranging from 0 (low risk), 1–2 (intermediate), and 3 impairments (high risk) which predicted survival. A multi-site study designed to validate this frailty score in the setting of non-intensive therapy has been completed in Europe (Grishina et al. 2015).

While larger studies are ongoing, evidence is sufficient to support incorporation of brief validated assessment tools, ideally a geriatric assessment, to characterize patients both in clinical trials and in practice. Available evidence supports assessing physical function, comorbidity, cognition, and fatigue (Abel and Klepin 2018; Hamaker et al. 2014a, 2017). Integration of core measures to assess fitness can facilitate personalized treatment planning (Abel and Klepin 2018; Hamaker et al. 2014a, 2017).

Quality of Life, Survivorship, and Communication

When making a treatment decision, it is important to consider patients values and to inform patients on expectations for both disease control and quality of life. This communication is made more difficult by both a lack of data on key quality of life outcomes (i.e., functional independence, time spent at home (El-Jawahri et al. 2015), emotional well-being, financial considerations) and the stressful circumstance in which these conversations need to be undertaken. Characterization of how patients feel and function during and after AML therapy is limited largely to observational studies, and data collection in this setting is challenging due in part to attrition (Buckley et al. 2018). This is consistent with studies of older adults with cancer in varied settings; therapeutic trials do not routinely assess functional and QOL outcomes (Hamaker et al. 2014b; Wildiers et al. 2013). Observational studies have provided some insights, highlighting both short-term negative functional consequences of AML treatment and observations of improved QOL and functional resilience among older adult survivors (Aaldriks et al. 2013; Alibhai et al. 2007, 2009b; Klepin et al. 2016; Timilshina et al. 2019; Kayastha et al. 2018). Continued attempts to collect and compare outcomes that can inform "quality" are needed to inform treatment decisions. Finally, communication challenges faced by providers and patients at the time of AML diagnosis are significant. A small study was conducted among AML patients who were enrolled within 72 hours after initiating therapy and their oncologists. Older patients with AML consistently overestimated both the risks and the benefits of treatment they were receiving compared to estimates provided by their oncologists (Kayastha et al. 2018). Studying the decision-making process from the perspective of patients, caregivers, and their providers is important to ensure that patient-centered decisions are optimized (Loh et al. 2018).

Future Strategies

There is no one-size-fits-all treatment strategy for older adults with AML. While outcomes remain suboptimal, treatment options are expanding. Individualized treatment decisions required careful characterization of patient fitness to tolerate a given therapy and targeting of therapy to the

unique disease biology. Rapid advances in the field will be supported by testing of therapies which target biologic disease subsets and account for patient subsets (fit, vulnerable, frail).

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Chronic Lymphocytic Leukemia in Older Adults

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Abstract

The typical patient with chronic lymphocytic leukemia (CLL) is old. For proper choice of therapy, older adults with CLL in need of treatment must be examined towards biological characteristics of their disease (presence or absence of 17p deletion or TP53 mutation) and their age (presence or absence of comorbidities or geriatric syndromes). Comorbidity scores and geriatric assessments could be supportive during fitness evaluation. Chemoimmunotherapy is a standard of care for older adults with previously untreated CLL lacking 17p deletion and TP53 mutation/dysfunction. Choice of the chemotherapy backbone (chlorambucil, bendamustine, fludarabine) and the antibody (rituximab, ofatumumab, obinutuzumab) depends on the fitness of the patient. The kinase inhibitor ibrutinib is a new therapeutic option in such patients and the treatment of choice for older adults with previously untreated CLL harboring 17p deletion or TP53 mutation. In addition to ibrutinib, idelalisib plus rituximab and venetoclax are preferred therapies for older adults with relapsed or refractory CLL. Readministration of chemoimmunotherapy is an option in older adults with late recurrence of CLL.

Keywords

Chronic lymphocytic leukemia · Age · Comorbidity · Geriatric assessment · Chemoimmunotherapy · Antibody · Kinase inhibitor

Introduction

The incidence of chronic lymphocytic leukemia (CLL) in western countries is 4–6 per 100.000 men and women per year, but it increases by more than tenfold with advancing age. Therefore, individuals affected by this disease are typically old. The median age of newly diagnosed subjects is 71 years – with approximately 25% of patients being older than 75 years and 10% being older than 85 years at the time of diagnosis (Howlader et al. 2016). The absolute number and the relative proportion of older adults with CLL are expected to rise during the next decades. Such patients differ considerably from younger ones with regard to several aspects, thereby posing growing challenges to physicians and medical staff involved in the care of CLL. This chapter will discuss features of the disease as well as features of aging in older adults with CLL, followed by a review of the currently available evidence regarding the optimal management in this patient population.

Disease Features in Older Adults with CLL

Similar to younger subjects, disease courses vary remarkably between individual older adults with CLL. In daily practice, some patients will present with indolent and asymptomatic CLL without any need of antileukemic therapy over many years, while others will suffer from rapidly progressive and symptomatic CLL with unsatisfying responsiveness to conventional treatment efforts. According to the observational data, older adults with CLL will present with advanced disease stage twice as often as younger patients. In a Spanish study of 949 subjects with CLL, Binet stage C and Rai stage III–IV was found at rates of 10% and 12% among patients older than 70 years, respectively, but only of 5% in patients younger than 70 years (Baumann et al. 2014). A study of 2487 North American patients with newly diagnosed CLL found Rai stage III–IV in 11% of patients over 75 years but only 4–6% below that

age (Shanafelt et al. 2010). Molecularly defined poor risk features such as presence of a deletion of the short arm of chromosome 17 (del(17p)) or a mutation/dysfunction of the tumor suppressor gene p53 (TP53mt) appear more frequent in older than in younger patients with CLL. A recent study of 909 subjects with CLL demonstrated continuous increase of frequency rates of del (17p), TP53mt, or other adverse prognostic markers such as unmutated IGHV (immunoglobulin heavy chain variable region) gene with each age decade, being lowest in patients younger than 60 years (3%) and highest in patients over 90 years (21%) (Truger et al. 2015). Overall, these data suggest that advanced disease stage and unfavorable risk are more frequently observed among older than younger patients with CLL. Nevertheless, the majority of older adults with newly diagnosed CLL will still present with early or intermediate disease stages and lack of high risk features.

Aging Features in Older Adults with CLL

Physiological decline of functional organ reserve (e.g., aging-driven decline of the glomerular filtration rate or reduction of the hematopoietic stem cell pool in the bone marrow), pathological occurrence of aging-related chronic diseases (e.g., cardiovascular, musculoskeletal, or neurodegenerative disorders), as well as of geriatric syndromes such as polypharmacy, delirium, dementia, depression, sarcopenia, frailty, falls, immobility, and loss of autonomy are the most important determinants of an older person's biological age. There is great interindividual variation in the presence of such aging features among older adults with CLL. For instance, an observational study in 373 unselected patients with newly diagnosed CLL reported presence of at least one major comorbidity (i.e., chronic artery disease, stroke, cardiac disease, diabetes mellitus, chronic obstructive lung disease, or secondary malignancy) in 46% of the examined subjects. Another 43% had one or more milder comorbidities such as hypertension, joint disease, hyperlipidemia, or peptic ulcer but none of the major comorbidities. The remaining 11% neither had major nor minor concurrent diseases and thus were free from any comorbidity (Thurmes et al. 2008). The prevalence of geriatric syndromes in older adults with CLL has not been studied so far and thus is not well known. However, it can be assumed that these can be found in older patients with CLL at least at similar frequencies than in equally aged community-dwelling populations.

Management of Older Adults with CLL

Diagnosis

There are no data suggesting age-specific differences in the morphological or immunological phenotype of CLL. Independent of age, establishing the diagnosis of CLL therefore should follow general guidelines that have been published – with no further management specifically needed in patients of advanced age (Hallek et al. 2008; Eichhorst et al. 2015; Zelenetz et al. 2016). In brief, diagnosing CLL in an older adult presenting for example with B-symptoms, lymphocytosis, lymphadenopathy, or hepatosplenomegaly requires a blood count including differential, blood smear microscopy, and flow cytometry of the blood.

Prognostication

Advancing age in patients with CLL naturally comes with a growing risk to die from other health problems than from the hematological malignancy. Hypothetically, CLL-specific risk factors such as clinical stage, serum or antigen markers, cytogenetic aberrations, and gene mutations therefore could have differential survival impact in younger versus older individuals. However, recent data suggest that key CLL-specific risk factors such as advanced Rai/Binet stage, elevated serum β2-microglobulin (β2M), unmutated IGHV gene, and del(17p)/TP53mt maintain their prognostic value in older adults with CLL, even if these present with

increased comorbidity and lower performance status: Rai/Binet stage, β2M, IGHV mutational and del(17p)/TP53mt status are integral elements of the CLL International Prognostic Index (CLL-IPI), a newly proposed tool to estimate survival in patients with CLL (International CLL-IPI Working Group 2015). Recently, the CLL-IPI was evaluated in older adults with CLL specifically. In one study of 691 older patients (median age 74 years) with increased comorbidity and previously untreated CLL, CLL-IPI performed well with regard to the prognostication of overall survival as well as progression-free and treatment-free survival (Goede et al. 2016b). CLL-IPI was also found prognostic in another study of 460 subjects with previously treated CLL of whom half at least were older and had increased comorbidity (Soumerai et al. 2016). Among the known risk factors in CLL, so far del(17p)/TP53mt is the only one considered not just prognostic but also predictive for treatment failure.

Next to CLL-specific risk factors, patient-related factors such as comorbidity and geriatric syndromes may determine an older patient's overall prognosis as well as the tolerability and feasibility of the antileukemic therapy. For instance, renal comorbidity as reflected by a reduced creatinine clearance has been shown to increase the risk of hematological toxicity during treatment with purine analogues (Martell et al. 2002). In one study, overall comorbidity burden, as measured by the Cumulative Illness Rating Scale (CIRS), also showed some correlation with tolerability of purine analogue-containing chemotherapy and chemoimmunotherapy (Goede et al. 2012). A growing number of studies demonstrate that patients with CLL and multiple or severe comorbidities survive shorter than those with only mild or without comorbidities (Goede et al. 2012, 2014a; Baumann et al. 2014). The reason for shorter overall survival in comorbid subjects are not just more frequent deaths from coexisting conditions but also from CLL – apparently because therapy is more difficult to administer in these individuals compared to those without comorbidity. One study in older adults with CLL and increased comorbidity found associations between overall survival and the presence of geriatric syndromes such as cognitive decline, reduced gait speed, or poor performance in activities of daily living (Goede et al. 2016a).

In conclusion, prognostication in older adults with CLL is complex. Even in the era of molecularly defined CLL-specific risk factors, assessment of the Rai or Binet stage (Rai et al. 1975; Binet et al. 1977) remains important and of prognostic value. This requires careful palpation of lymph nodes, liver, and spleen, as well as measurement of hemoglobin and platelets. Imaging of cervical, thoracic, abdominal, or pelvic lymph nodes by computer tomography normally will not render treatment decisions and thus is not mandatory in routine practice. Potential benefits of computer tomography must be carefully weighed as many older adults with CLL will present with subclinical chronic kidney insufficiency and hence a risk of contrast media-induced renal failure. The del(17p)/TP53mt status must be assessed prior to treatment in all older adults with CLL, because it will render treatment decisions. Assessment of other molecularly defined CLL-specific risk factors is optional, but some (i.e., β2M, IGVH) are essential for calculation of the CLL-IPI, which appears a valuable prognostic tool not just in younger but also in older adults with CLL. Some recently identified gene mutations in CLL (*ATM, NOTCH1, SF3B1, BIRC3*) (Zent and Burack 2014) as well as other gene mutations such as *KRAS* or *POT1*, which might be particularly prognostic in older adults with CLL in the context of chlorambucil-based chemoimmunotherapy (Herling et al. 2016), remain to be further studied before being routinely used for prognostication in general and in this patient population particularly. Next to the assessment of CLL-specific risk factors, thorough evaluation of comorbidities and geriatric syndromes is needed (Stauder et al. 2017). This requires comprehensive history taking and physical examination as well as laboratory tests (e.g., estimation of the creatinine clearance). Further investigations such as electrocardiography, echocardiography, or bodyplethysmography might be performed if considered appropriate and potentially treatment decision-rendering. A systematic approach to comprehensively assess the comorbidities and

geriatric syndromes in an older adult with CLL is geriatric assessment which sometimes enables physicians to identify health issues that otherwise would have remained undetected (e.g., potentially inadequate medication, mild cognitive impairment, depression, delirium, sarcopenia, risk of falls) (Hamaker et al. 2014b). Such findings could not just be helpful when deciding for the antileukemic treatment regimen but also might drive geriatric interventions to fight geriatric syndromes in a systematic way (Hamaker et al. 2014c). Geriatric assessment therefore can be recommended in older adults with CLL provided that a proper logistical infrastructure exists. Resources can be spared by implementation of geriatric screening or geriatric consultation prior to a more comprehensive assessment (Hamaker et al. 2014a; Schiphorst et al. 2016). Importantly, results of geriatric screening and assessment in older adults with CLL always must be interpreted in context with other findings. Thus, compulsory treatment algorithms based on these diagnostic techniques alone cannot be defined at the present time.

Indication for Treatment

Treatment indications for CLL have been published in general guidelines and are similar for younger and older patients (Hallek et al. 2008; Eichhorst et al. 2015; Zelenetz et al. 2016). In brief, antileukemic therapy is indicated in patients with CLL-driven symptoms or/and advanced disease stage. However, in older adults with CLL, attribution of symptoms to CLL sometimes might be difficult, because these could also be caused by coexisting conditions (e.g., weight loss could be either due to progressive CLL or depression, peptic ulcer, etc.; fatigue could be CLL-related or due to heart failure, lung emphysema, etc.; anemia could be due to subtotal bone marrow infiltration by CLL cells or chronic blood loss, vitamin deficiency, myelodysplasia, etc.). In symptomatic patients with significant comorbidities but early or intermediate disease stage, unspecific symptoms therefore must be carefully dissected and judged before triggering the start of antileukemic treatment.

Choice of Front-Line Treatment

There is a considerable number of therapies available for treating older adults with previously untreated CLL in routine practice, namely chemotherapy alone, chemoimmunotherapy, and kinase inhibitors. Novel treatment combinations and compounds are currently evaluated in ongoing clinical studies, but this section will focus on approved front-line therapies applicable in this patient population outside of trials. Table 1 summarizes the main results of randomized trials which have been performed specifically in older adults with CLL and which are the basis of current treatment recommendations.

Since the introduction of monoclonal antibodies targeted against the CD20 antigen expressed on CLL cells (i.e., rituximab, ofatumumab, obinutuzumab), administration of chemotherapy alone has become an uncommon treatment approach in older adults with CLL. Today, this strategy is reserved only to those patients who do not tolerate an antibody. Available chemotherapeutic drugs for single-agent therapy are chlorambucil, bendamustine, and fludarabine. In a randomized study (CLL5) performed by the German CLL Study Group (GCLLSG), treatment with fludarabine of older adults with CLL did not result in prolongation of overall survival compared to chlorambucil therapy (Eichhorst et al. 2009). A comparison of bendamustine with chlorambucil is only available from a randomized study in younger patients, reporting longer progression-free survival with bendamustine but no overall survival benefit (Knauf et al. 2009). Combined chemotherapy of CLL with fludarabine and cyclophosphamide was investigated in randomized trials, but these did not enroll many older subjects.

Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) is the currently most efficacious treatment of CLL and – as shown by the CLL8 study – life-prolonging compared to combined chemotherapy without rituximab (Hallek et al. 2010; Fischer et al. 2016; Thompson et al. 2016). The FCR regimen therefore represents the current standard of care for younger and fit patients with CLL. FCR is

applicable in carefully selected older subjects who present with excellent fitness and without any comorbidities. However, there is cumulative evidence that in comparison to younger subjects a majority of older patients will tolerate FCR less well, even if fitness is good (Ferrajoli et al. 2005; Hallek et al. 2010; Kovacs et al. 2015). Adverse events, treatment delays, dose reductions, and premature discontinuation of therapy are all more frequently observed in older than younger patients. Dose-attenuated FCR regimens have been suggested (e.g., FCR-lite, Q-lite, FCR3) in order to save treatment toxicity and to improve treatment feasibility. Two randomized phase 2 trials have compared dosed-attenuated FCR with standard dose FCR (Mulligan et al. 2014) and chlorambucil plus rituximab (R-CLB) (Nikitin et al. 2013), respectively (Table 1). Results were encouraging, but since these trials were rather small (less than 50 patients per arm), dose-attenuated FCR regimens have not become a broadly accepted treatment standard in older adults with CLL so far.

A phase 3 study of the GCLLSG (CLL10) mainly enrolled young and fit patients and compared chemoimmunotherapy with bendamustine and rituximab (BR) to FCR (Eichhorst et al. 2016a). This trial demonstrated inferiority of BR to FCR with regard to its primary endpoint progression-free survival (medians: 42 versus 55 months). Importantly, no differences in progression-free survival were observed between study treatments when analyzed solely for the subgroup of patients being at least 65 years or older. Moreover, BR showed significant better tolerability than FCR in this subgroup as well as in the total study population. Rates of grade 3–4 neutropenia (59% versus 84%) and of grade 3–4 infections (27% versus 39%) were lower with BR compared to FCR. A randomized phase 2 study (MABLE) compared BR with R-CLB in older adults with CLL (Michallet et al. 2015) and found BR superior with regard to complete response rates (24% vs. 9%) representing the trial's primary endpoint. Progression-free survival was longer with BR, but there was no difference in overall survival. The rate of grade 3–5 infections was twice as high as with R-CLB (19% vs. 10%). Both studies used BR with the standard dose (i.e., 90 mg/m^2 body surface). To date, there are no solid trial data

Table 1 Randomized clinical trials in older adults with CLL with primary endpoints and main result[a]

Trial	Type	Compared treatments (patient number per arm)	Primary endpoint	Result (medians or rates)	Hazard ratio (95% confidence interval)
Front line					
GCLLSG CLL5	III	F (93) vs. CLB (100)	PFS	19 vs. 18 months	NR
ALLG CLL5	II	FCR5 (38) vs. FCR3 (41) vs. FR (37)	CYC	44% vs. 89% vs. 89%	–
RUSSIA	II	FCR-LITE (48) vs. R-CLB (49)	TOX	45% vs. 35%	–
MABLE	II	BR (121) vs. R-CLB (120)	CRR	24% vs. 9%	–
COMPLEMENT-1	III	O-CLB (221) vs. CLB (226)	PFS	22 vs. 13 months	0.57 (0.45–0.72)
GCLLSG CLL11	III	G-CLB (238) vs. CLB (118) R-CLB (233) vs. CLB (118) G-CLB (333) vs. R-CLB (330)	PFS PFS PFS	30 vs. 11 months 16 vs. 11 months 29 vs. 15 months	0.18 (0.14–0.24) 0.44 (0.34–0.56) 0.40 (0.33–0.50)
RESONATE-2	III	IBRUT (136) vs. CLB (133)	PFS	NR vs. 19 months	0.16 (0.09–0.28)
Further line					
RESONATE	III	IBRUT (195) vs. O (196)	PFS	NR vs. 8 months	0.22 (0.15–0.32)
116	III	IDELA-R (110) vs. R (110)	PFS	NR vs. 6 months	0.15 (0.08–0.28)

[a]Table contains published randomized trials with median age over 65 years

F fludarabine, *C* cyclophosphamide, *R* rituximab, *CLB* chlorambucil, *B* bendamustine, *O* ofatumumab, *G* obinutuzumab (GA101), *IBRUT* ibrutinib, *IDELA* idelalisib, *PFS* progression-free survival, TOX toxicity rate, *CYC* rate of six completed treatment cycles, *CRR* complete response rate, *NR* not reported, *NR* not reached

available for dose-adapted BR schedules (e.g., 70 mg/m^2 body surface) in older adults with CLL. The combination of bendamustine and ofatumumab (BO) also lacks specific evaluation in this patient population. In a nonrandomized phase 2 study conducted in younger patients (Flinn et al. 2016), response rates or BO were close to those observed with BR, and no superiority for BO over BR has been shown so far.

A phase 3 study in older adults with CLL and moderately increased comorbidity (COMPLEMENT-1) compared chemoimmunotherapy of chlorambucil and ofatumumab (O-CLB) with chlorambucil alone (Hillmen et al. 2015). Progression-free survival as the primary endpoint was significantly longer with O-CLB than with chlorambucil (medians: 22 versus 13 months), but there was no overall survival benefit. Grade 3–5 infections and infusion-related reactions (IRR) each were observed in 10% of patients treated with O-CLB. A large phase 3 study conducted by the GCLLSG in older adults with CLL and significantly increased comorbidity (CLL11) compared chemoimmunotherapy with chlorambucil and obinutuzumab (G-CLB) with R-CLB (Goede et al. 2014b). G-CLB was found significantly superior with regard to progression-free survival as the trial's primary endpoint (medians: 29 versus 15 months) and also time to next treatment (medians: 51 versus 38 months). Furthermore, a trend in overall survival benefit for G-CLB was observed (Goede et al. 2015a). Additionally, there was a comparison of G-CLB and R-CLB each with chlorambucil alone in this study. Both chemoimmunotherapies showed overall survival benefit over chemotherapy with chlorambucil (Goede et al. 2015b). Grade 3–5 infections occurred at a rate of 10–15% in all three study arms. Grade 3–4 IRR were more frequent during treatment with G-CLB than with R-CLB (20% vs. 4%).

The kinase inhibitors ibrutinib and idelalisib (in combination with rituximab) initially have been explored in older adults with CLL in small, nonrandomized trials (O'Brien et al. 2014, 2015). Notably, both compounds showed activity in patients with del(17p)/TP53mt which was an indicator of treatment failure in the above mentioned chemoimmunotherapy trials. A phase 3 study (RESONATE-2) compared ibrutinib to chlorambucil in older adults with CLL (Burger et al. 2015), with ibrutinib showing superiority over chlorambucil with regard to the primary endpoint progression-free survival (medians: not reached versus 19 months) as well as overall survival. No patients with del(17p)/TP53mt were enrolled. Diarrhea and fatigue were the most frequent adverse events observed with ibrutinib, while myelotoxicity was mild. It must be noted that ibrutinib could cause specific toxicities. Several studies including RESONATE-2 have reported new onset of atrial fibrillation at rates of 5–10%; particularly in patients with preexisting cardiovascular comorbidity (Byrd et al. 2014; Burger et al. 2015). Ibrutinib inhibits platelet aggregation which could induce bleeding. The risk of ibrutinib-induced hemorrhage (which mostly occurs as skin and less frequently as cerebral or gastrointestinal bleeding) appears increased in patients taking anticoagulants. Ibrutinib is metabolized in the liver via CYP3A4. This could result in drug-drug interactions if medication is taken that is metabolized via the same hepatic enzyme system (e.g., clarithromycin, voriconazole) (Finnes et al. 2015). According to current knowledge, the kinase inhibitor must be taken permanently which may cause adherence problems in older adults with CLL (Maddocks et al. 2015). Idelalisib has not yet been explored in randomized fashion in older adults with previously untreated CLL. Importantly, recent studies of idelalisib in younger patients with untreated CLL reported serious accumulation of autoimmunity-mediated colitis, hepatitis, and pneumonitis (Lampson et al. 2015), as well as infections by pneumocystis jirovecii and cytomegaly virus (FDA Alert 2016).

Based on this evidence, recommendations for the front-line therapy of CLL in older adults have been published by national and international organizations (Eichhorst et al. 2015, 2016b; Zelenetz et al. 2016). Such recommendations are displayed in Table 2. At present, chemoimmunotherapy is a broadly accepted standard of care for older adults with previously untreated CLL lacking del (17p)/TP53mt. Older patients with good fitness

Table 2 Summary of NCCN and ESMO recommendations for front-line treatment of older adults with CLL in need of therapy[a]

NCCN 2016 recommendations				
Suggested fitness categories	Older patient ≥65 years without significant comorbidity		Frail patient with significant comorbidity	
Suggested risk categories	Without del(17p)/ TP53mt	With del(17p)/ TP53mt	Without del(17p)/ TP53mt	With del(17p)/ TP53mt
Suggested treatment regimens	G-CLB IBRUT O-CLB R-CLB BR	IBRUT R-HDMP	G-CLB IBRUT O-CLB R-CLB	IBRUT R-HDMP
ESMO 2015/2016 recommendations				
Suggested fitness categories	Fit patient		Less fit patient	
Suggested risk categories	Without del(17p)/ TP53mt	With del(17p)/ TP53mt	Without del(17p)/ TP53mt	With del(17p)/ TP53mt
Suggested treatment regimens	FCR BR[b]	IBRUT IDELA+R[c]	G-CLB, O-CLB, R-CLB	IBRUT IDELA+R[c]

NCCN National Comprehensive Cancer Network, *ESMO* European Society of Medical Oncology, *G* obinutuzumab (GA101), *CLB* chlorambucil, *IBRUT* ibrutinib, *O* ofatumumab, *R* rituximab, *B* bendamustine, *HDMP* high-dose methylprednisolone, *F* fludarabine, *C* cyclophosphamide, *IDELA* idelalisib

[a]Table displays treatment recommendations as listed in the corresponding NCCN and ESMO publications (see references)

[b]To be considered in fit older patients with previous history of infections

[c]Only if not suitable for ibrutinib

(i.e., no or only mild comorbidities, no geriatric syndromes) are suitable for more intense chemoimmunotherapies (e.g., standard dose BR, standard dose FCR only in very fit patients). Less fit patients (i.e., with significant comorbidity or geriatric syndromes) are candidates for chlorambucil-based chemoimmunotherapy (e.g., G-CLB). Dose-modified BR or FCR is possible, but the level of evidence is considerably lower. The main risks of chemoimmunotherapy in older adults with CLL are infusion-related reactions and infections due to myelosuppression. Therapy usually is stopped after six treatment cycles, and a treatment-free time period of 3–5 years can be expected. Ibrutinib is a newly available treatment option in these patients. Lack of infusion-related reactions and myelotoxicity are key advantages while risk of bleeding, drug-drug interactions, nonadherence, late-onset complications, and potentially nonresponse to chemoimmunotherapy after disease progression are of disadvantage. Chemoimmunotherapy shows unsatisfying treatment results in older adults with CLL and presence of del(17p)/TP53. These patients therefore should be treated upfront with ibrutinib. Idelalisib plus rituximab should only be used if patients are not suitable for ibrutinib and always with proper prophylaxis for pneumocystis jirovecii and cytomegaly virus infection/reactivation.

Choice of Further-Line Treatment

Therapies that can be used in older adults with previously treated CLL in routine practice are chemoimmunotherapy, ibrutinib, or idelalisib (in combination with rituximab) which block BTK and PI3K, respectively and venetoclax which block the antiapoptotic protein BCL2. Ongoing clinical studies explore novel agents (e.g., acalabrutinib, duvelisib, ublituximab) and combinations. The focus of this section will be therapies approved for further-line treatment in older adults with CLL outside of trials, however. Main results of two corresponding randomized trials are shown in Table 1.

The number of randomized trials investigating chemoimmunotherapy in relapsed or refractory CLL is small – with none of those having been conducted specifically in older subjects. Greater

evidence in this patient population exists for kinase inhibitors. A phase 3 study (RESONATE) compared ibrutinib with ofatumumab in heavily pretreated patients of whom a larger proportion was of advanced age (Byrd et al. 2014). Ibrutinib proofed superior to ofatumumab with regard to progression-free survival as the primary endpoint (medians: not reached versus 8 months) and overall survival. Benefits from ibrutinib were observed in all subgroups including patients with del(17p)/TP53mt. Specific adverse events of ibrutinib were bleeding and atrial fibrillation (see section "Choice of Front-Line Treatment"). Another phase 3 study (116) compared idelalisib plus rituximab with rituximab alone in older adults with CLL and significantly increased comorbidity (Furman et al. 2014). Progression-free survival as the trial's primary endpoint was longer with the combination treatment (medians: not reached versus 6 months). Again, benefits were seen across subgroups including patients with del(17p)/TP53mt. Diarrhea was the most frequent toxicity in the idelalisib arm. Autoimmunity-induced hepatitis and pneumonitis were also recorded. In contrast to front-line therapy, long-term study results suggest that idelalisib plus rituximab is a safe treatment of relapsed or refractory CLL. In non-randomized trials, venetoclax demonstrated remarkable activity in relapsed or refractory CLL, even in patients who had del(17p)/TP53mt (Roberts et al. 2016; Stilgenbauer et al. 2016). So far, there are no specific data available for venetoclax monotherapy in older adults with pretreated CLL. An important toxicity of venetoclax is tumor lysis syndrome which needs special consideration in older adults with CLL and preexisting renal comorbidity.

Recommendations for further-line therapy of CLL in older adults made by national and international organizations (Eichhorst et al. 2015, 2016b; Zelenetz et al. 2016) are shown in Table 3. Readministration of chemoimmunotherapy is an option if the CLL has not reoccurred within the first 24–36 months from the start of front-line treatment and still lacks del(17p)/TP53mt. Irrespective of del(17p)/TP53 status, older adults with earlier recurrence of CLL should be treated with ibrutinib or idelalisib plus rituximab. Both kinase inhibitors are administered until disease progression. Ibrutinib and idelalisib

Table 3 Summary of NCCN and ESMO recommendations for further-line treatment of older adults with CLL in need of therapy[a]

NCCN 2016 recommendations				
Suggested fitness categories	Older patient ≥65 years without significant comorbidity		Frail patient with significant comorbidity	
Suggested risk categories	Without del(17p)/TP53mt	With del(17p)/TP53mt	Without del(17p)/TP53mt	With del(17p)/TP53mt
Suggested treatment regimens	IBRUT IDELA + R VEN[b] CIT	IBRUT IDELA + R VEN[b] R-HDMP	IBRUT IDELA + R VEN[b] CIT	IBRUT IDELA + R VEN[b] R-HDMP
ESMO 2015/2016 recommendations				
Suggested fitness categories	Fit patient		Less fit patient	
Suggested risk categories	Without del(17p)/TP53mt	With del(17p)/TP53mt	Without del(17p)/TP53mt	With del(17p)/TP53mt
Suggested treatment regimens	IBRUT or IDELA + R CIT[c]	IBRUT or IDELA + R	IBRUT or IDELA + R CIT[c]	IBRUT or IDELA + R

NCCN National Comprehensive Cancer Network, *ESMO* European Society of Medical Oncology, *IBRUT* ibrutinib, *IDELA* idelalisib, *R* rituximab, *VEN* venetoclax, *CIT* chemoimmunotherapy, *HDMP* high-dose methylprednisolone

[a]Table displays treatment recommendations as listed in the corresponding NCCN and ESMO publications (see references)

[b]To be considered particularly for patients deemed intolerant or refractory to ibrutinib or idelalisib

[c]To be considered in patients with late recurrence of CLL (>24–36 months from the start of initial chemoimmunotherapy)

failure, respectively, may be followed by a switch to the other kinase inhibitor or treatment with venetoclax.

Conclusion

Future research likely will result in further changes of the management of older adults with CLL. New molecularly defined risk factors (e.g., gene mutations) are expected to improve prognostication in general and in this patient population specifically. Fitness evaluation in older adults with CLL is a moving target and will depend on the particular toxicity profiles of treatments becoming available. Geriatric consultation, screening, and assessment likely will stay important; maybe less for the choice of antileukemic therapy, but for the stratification of older adults with CLL towards supportive geriatric interventions. Several ongoing clinical trials in CLL are specifically designed for older patients and explore novel combination treatments (e.g., venetoclax plus CD20 antibody) (Fischer et al. 2015). Together with recommendations and guidelines for older adults with CLL provided by national and international organizations, this chapter will need to be constantly adapted to these ongoing developments.

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Chronic Myelogenous Leukemia and Myeloproliferative Disorders in Older Adults

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Contents

Abstract

Chronic myeloid leukemia (CML) and other myeloproliferative neoplasms are more often diagnosed in people aged above 65. CML is more common in older adults, frequently diagnosed among people aged 65–74. Given the large proportion of older adults with these diseases, it is of interest to pay higher attention in special physiologic and comorbidity

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conditions found in older people. Plenty of data can be obtained from clinical trials in these diseases about tolerance, side effects, and outcome in elderly people when compared with younger people. Comorbid conditions are now being assessed in these chronic myeloproliferative diseases, with a strong correlation with toxicity and survival. Quality of life may also be improved with the new target therapy strategies approved not only in CML but also in primary myelofibrosis patients.

Keywords
Chronic myeloid leukemia · Myeloproliferative neoplasms · Polycythemia · Essential thrombocytosis · Myelofibrosis

Introduction

Chronic myelogenous (also known as *myeloid*) leukemia (CML) is a pluripotent hematopoietic stem cell neoplasm characterized by *BCR-ABL1* fusion gene, which is derived from a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11), also known as the Philadelphia (Ph) chromosome. The resultant hybrid oncogene is transcribed as a chimeric *BCR-ABL* mRNA, which is translated into a functional abnormal protein. *ABL1* encodes a non-receptor tyrosine kinase that phosphorylates substrate proteins via its SH1 domain, affecting crucial cellular activities such as increased proliferation, loss of stromal adhesion, and resistance to apoptosis. The *BCR-ABL1* gene results in two critical events in the disease: it provides a unique biomarker for the diagnosis of the disease and, second, it is susceptible to drug targeting. Tyrosine kinase inhibitors (TKIs) block the ATP-binding pocket of ABL1 kinase domain, inhibiting phosphorylation and resulting in cell death (Apperley 2015).

Other entities different than CML are the myeloproliferative neoplasms (MPNs), previously known as myeloproliferative diseases (MPDs). They are a group of diseases of the bone marrow in which excess cells are produced. The concept of myeloproliferative disease was first proposed in 1951 by the hematologist William Dameshek (Dameshek 1951). In the most recent World Health Organization (WHO) classification of hematologic malignancies, this group of diseases was renamed from "myeloproliferative diseases" to "myeloproliferative neoplasms" (Arber et al. 2016). This reflects the underlying clonal genetic changes that are a salient feature of this group of disease (Tefferi and Vainchenker 2011). The categories of MPNs have not significantly changed since the 2008 fourth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, but discoveries of new mutations and improved understanding of the morphologic features of some entities have impacted the diagnostic criteria for the disease entities. In recent years, new data have suggested the need for revisions to the diagnostic criteria for the *BCR-ABL1*-MPNs (Barbui et al. 2015). New findings have been demonstrated to have diagnostic and/or prognostic importance like *JAK2*, *MPL* mutations, and in particular the *CALR* mutation, providing proof of clonality, diagnostic importance, and influence prognosis or the need to differentiate "true" essential thrombocythemia (ET) from prefibrotic/early primary myelofibrosis (prePMF).

Chronic Myeloid Leukemia

Epidemiology

In the National Cancer Institute "Surveillance, Epidemiology, and End Results Program," the number of new cases of CML in the United States was 1.8 per 100,000 men and women per year, and the number of deaths was 0.3 per 100,000 men and women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths. CML is more common in older adults and among men, with a median age at diagnosis of 64 years old. CML is most frequently diagnosed among people aged 65–74. Forty-nine percent of cases are diagnosed in people over 65, so it is of interest to pay higher attention in special physiologic and comorbidity conditions found in older people (Howlader et al. 2016).

In order to establish the incidence of CML in Europe, a large population-based study (EUTOS study) was conducted in 20 European countries with a sample of 92.5 million adults (Hoffmann et al. 2015). The standardized incidence per 100.000 inhabitants in all countries was 1.10 for males and 0.82 for females. For both sexes, the yearly incidence rose from a minimum of 0.39 new cases in very young adults to a maximum of 1.52 in senior adults of 70 years and more. This study showed important differences when comparing data from "real life" with pivotal treatment studies, with main differences concerning age, with a median of 55 years in the EUTOS population study and 46–51 years for company-sponsored trials.

Presentation

CML is a triphasic disease: most patients are diagnosed in the "chronic phase," in which symptoms can be fairly easily controlled but without effective medical intervention will progress through a period of increasing instability known as "accelerated phase" to terminal transformation to an acute leukemic-like illness or so-called blast crisis (Apperley 2015).

CML patients are usually asymptomatic at diagnosis and are discovered incidentally. Commons symptoms at diagnosis include fatigue, night sweats, and weight loss and are normally due to hypercatabolic symptoms, splenomegaly, anemia, or platelet dysfunction. Hyperleukocytosis has been related in men with priapism. Most patients will present with splenomegaly (50–90%) at diagnosis, and painless hepatomegaly may be present in up to half of the patients. Thrombotic and hemorrhagic complications are not as frequent as in the other MPNs, observed only in less than 5% of patients.

Diagnosis

Once CML is suspected, regardless of the age of the patient, specific test must be performed to confirm the diagnosis (see Table 1). Most cases of CML in chronic phase can be diagnosed from peripheral blood findings combined with detection of t(9;22)(q34.1;q11.2) or, more specifically, BCR-ABL1 by molecular genetic techniques. However, a bone marrow aspirate is essential to ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the phase of disease (Arber et al. 2016). Roughly, 90% of new patients are diagnosed in the chronic phase. The definitions of acceleration and blast crisis are largely dependent on the proportion of blasts in the blood and bone marrow but vary in the two commonly used systems: the World Health Organization (WHO) classification and the European LeukaemiaNet (ELN). The major difference in WHO classification is in blast cells percentage, where for WHO is 15–19% for accelerated phase and $\geq$20% for blast crisis. ELN definitions are those that have been internationally shared and used in almost all recent major studies of CML. Other parameters to distinguish CML phases are basophils, thrombocytopenia, increasing spleen size, extramedullary disease, appearance of other cytogenetic abnormalities, or extra Ph chromosome during treatment or extramedullary disease (Baccarani et al. 2013, 2015).

Table 1 Test to be performed in CML newly diagnosed patients (Adapted from Apperley 2015)

Mandatory diagnostic tests for chronic myeloid leukemia
Blood count with blood film differential. This will typically show a so-called left shift of the myeloid series with the presence of immature myelocytes and metamyelocytes, basophils, and eosinophils. These must be accurately quantified as the results contribute to accurate identification of disease stage and prognostic scoring systems
Blood count with blood film differential. This will typically show a so-called left shift of the myeloid series with the presence of immature myelocytes and metamyelocytes, basophils, and eosinophils. These must be accurately quantified as the results contribute to accurate identification of disease stage and prognostic scoring systems
Cytogenetics and karyotyping by G banding: fluorescent in situ hybridization is not sufficient at diagnosis as it is unable to identify chromosomal abnormalities in addition to the t(9;22) translocation
Reverse transcriptase PCR for BCR-ABL1 mRNA transcripts

Definition of disease is regardless the age, and all patients should be properly diagnosed according to current criteria.

Treatment

The goal of therapy in CML is to achieve a complete cytogenetic response. New treatment strategies with TKIs avoid the use of both chemotherapy and allogeneic transplantation in a clear majority of patients. TKIs are extremely well tolerated and are suitable therapies for older patients, despite frailty status. The choice among the different options would be guided according to patient's comorbidities.

It is crucial to establish the phase of the disease because it will have impact on treatment decisions and prognostic implications. Treatment recommendations are different when accelerated phase and blast crisis are recognized at baseline, prior to any treatment, or during the treatment of chronic phase. Patients presenting in accelerated phase are well responsive and should be treated with TKIs, better with the more potent second-generation TKIs. They are eligible for allogeneic stem cell transplantation (SCT) only if not achieving an optimal response. But this strategy is restricted only to young patients and the rare "fit" older patient with CML.

In contrast, young patients presenting in blast crisis are in high risk of progression, and all of them should be considered eligible for a SCT procedure, except older people. The patients who progress from chronic phase to accelerated phase or blast crisis are less sensitive to any subsequent treatment, and they should be treated with a TKI and considered for SCT only if they are young and fit enough, a strategy not possible to be done in older people.

Over the last decade, with the incorporation to new treatment strategies in CML like TKIs, the expected overall survival of patients with CML has reached the general population at the same age interval (Bower et al. 2016). Therefore, the expected prevalence of the disease is increasing year by year. In the United States, the prevalence of CML is increasing from about 70,000 in 2010, 112,000 in 2020, 144,000 in 2030, 167,000 in 2040, to 181,000 in 2050 when it will reach a near plateau prevalence (Huang et al. 2012). This dramatic improvement in the prevalence of CML will have two major consequences: first, a significant increasing in the budget we will have to spend to treat our CML patients since nowadays expert guidelines recommend maintaining treatment indefinitely; and second, the progressive aging of patients with CML, implying necessarily having to deal with the treatment of leukemia with a multidisciplinary approach within the different pathologies that our geriatric patients will have to deal with. Understanding the relationships between comorbidity, treatment outcomes, and patient's health-related quality of life (HRQOL) is thus essential to robustly inform clinical decision-making (Uemura et al. 2016).

In CML, age was considered a prognostic factor in Sokal score (Sokal et al. 1984) and Hasford score (Hasford et al. 1998). Sokal score which was generated with four variables representing percent blasts, spleen size, platelet count, and age provided a useful representation of risk status in CML population. It was possible to identify a lower-risk group of patients with a 2-year survival of 90%, subsequent risk averaging somewhat less than 20%/year and median survival of 5 year, and an intermediate group and a high-risk group with a 2-year survival of 65%, followed by a death rate of about 35%/year and median survival of 2.5 year (Barbui et al. 2011a). Hasford score, developed in patients treated with interferon alfa, was generated with six covariates: age, spleen size, blast count, platelet count, eosinophil count, and basophil count. Three distinct risk groups were identified, with median survival times of 98 months (40.6%), 65 months (44.7%), or 42 months (14.6%) (Tefferi et al. 2014a). In the era of TKIs, a new risk score has been developed: EUTOS score (Hasford et al. 2011). The strongest predictors for the achievement of complete cytogenetic response at 18 months were spleen size and percentage of basophils. Spleen size is measured in cm under the costal margin, basophils as their percent in peripheral blood. Age was not predictable of outcome in CML patients in the era of TKIs any longer.

Several approaches have been tested in order to minimize toxicities of TKIs and improve the quality of live in CML patients. In clinical trials where elderly patients, with optimal and stable response, were changed to a regimen of intermittent imatinib (1 month on and 1 month off), imatinib-associated side effects were reduced in 50% with no progressions or death due to CML (Russo et al. 2015). The Spanish group of CML has also recently published how decreasing imatinib dose to 300 mg in patients with sustained deep responses can improve tolerability and preserves efficacy (Cervantes et al. 2016). But probably, the most interesting approach in this sense is the probability of discontinuing treatment to get what it has been called as "operational cure" in CML. Several clinical trials (and more ongoing) including more than 2000 patients have shown how around 50% of patients in deep and stable molecular response can safely cease their therapy without relapsing. Furthermore, those who are unsuccessful in their cessation attempt can safely reestablish remission after restarting their TKI therapy. However, there is no evidence enough to recommend treatment strategies out of clinical trials unless there are important side effects. New data from clinical trials ongoing will hopefully allow hematologists to give further recommendations for such important question as how much time of exposure to TKI is needed before stopping treatment or when to restart treatment after losing response (Hughes and Ross 2016). But there are still no data regarding discontinuation strategies in elderly population.

For resistant or intolerant imatinib patients, dasatinib and nilotinib are the current options, with probabilities to obtain complete cytogenetic responses of around 50%. However, after 5 years of treatment, only 70% of patients remained in the study, which means that most of these patients would need to have treatment change in a third-line strategy. It is important to note that nilotinib dose on label in second line is 400 mg BID (300 mg BID in first line). For patients' intolerance or resistance to second-generation TKIs (2GTKIs), current recommendations recommend treatment change to a different 2GTKI (nilotinib, dasatinib, or bosutinib) or ponatinib.

Treatment patterns, overall survival, healthcare resource use, and costs in elderly patients with CML using second-generation tyrosine kinase inhibitors as second-line therapy have been analyzed. Despite similar adherence, dasatinib patients were more likely to start on the recommended dose and to have dose reductions than nilotinib patients. Fewer nilotinib patients discontinued or switched to another TKI than dasatinib patients. Nilotinib patients had longer median OS and lower mortality risk, fewer inpatient admissions, fewer emergency room visits, and fewer outpatient visits than dasatinib patients (Smith et al. 2016). But of notice, more cardiovascular adverse events have been seen in elderly population when compared with younger people. Regarding dasatinib treatment, Charlson comorbidity index and adult comorbidity evaluation-27 (ACE-27) scores might predict treatment compliance and development of pleural effusions in elderly patients with CML when treated with second-line dasatinib (Breccia et al. 2011). Bosutinib has shown in second line after imatinib failure results similar to dasatinib or nilotinib in the same indication with a good safety profile. In third line, after failing to imatinib and nilotinib or dasatinib, probabilities to obtain complete cytogenetic responses are around 25%. Most frequent side effects related to bosutinib are gastrointestinal (diarrhea and hepatotoxicity) which are generally well managed, not being these side effects a common reason for treatment discontinuation (Cortes et al. 2016). Ponatinib is at this moment the most effective treatment for patients resistant to previous 2GTKIs, with probabilities achieving complete cytogenetic responses around 50%. Ponatinib is the only effective drug for patients harboring the T315I mutation. However, the use of ponatinib has been related with 30% probabilities of suffering cardiovascular events. For these reasons, current recommendations are to start with lower dose in cardiovascular high-risk patients (30 or even 15 mg) and decrease dose once complete cytogenetic responses have been achieved. At this moment, this approach is being tested in clinical trials (Fava and Saglio 2016).

Philadelphia-Negative Chronic Myeloproliferative Neoplasms

Polycythemia Vera

Regarding the other MPNs, median age of patients at diagnosis of polycythemia vera (PV) is approximately 60 years (Tefferi et al. 2013). The reported annual incidence of PV increases with advanced age and varies from 0.710 to 2.6 per 100,000 inhabitants in Europe and North America. Most reports indicate a slight male predominance, with the male-female ratio ranging from 1 to 2:1 (Campo et al. 2008).

In 2016, the World Health Organization (WHO) modified the criteria required to be diagnosed of PV. Currently, major criteria are hemoglobin >16.5 g/dL or hematocrit >49% in men/hemoglobin >16 g/dL or hematocrit >48% in women, morphology showing a panmyelosis, and presence of a JAK2 mutation (V167F or exon 12 mutations). There is only one minor criterion: serum erythropoietin (EPO) level below the normal range. In order to be diagnosed of PV, all three major criteria are required or the two first major criteria and the minor criteria. Although recommended in every patient, biopsy may not be required in cases with sustained absolute erythrocytosis (hemoglobin levels >18.5 g/dL or hematocrit >55.5% in men/hemoglobin >16.5 g/dL or hematocrit >49.5% in women) if a JAK2 mutation is detected and EPO level diminished (Arber et al. 2016). Therefore, in an elderly and/or unfit patient who fulfilled these criteria, the bone marrow biopsy could be spared.

A recent study carried out in Mayo Clinic found that life expectancy in patients with PV was inferior to that of an age- and sex-matched control population, with estimated median survivals of 14 years for PV. A survival score, developed with a cohort of 1545 patients, classified patients into three groups. Age greater than 67 years classified patients directly in the high-risk group with a median survival of 10.9 years compared to 27.8 years in the low-risk group. Age greater than 61 years was also found to be an independent prognostic marker for development of leukemia (Barbui et al. 2011a).

Polycythemia is the main alteration in the complete blood count, but leukocytosis with neutrophilia and thrombocytosis may also be present. Patients with PV might also have leukocytosis, splenomegaly, and microvascular symptoms, palpitations, atypical chest pain, paresthesias, erythromelalgia, thrombosis, bleeding, and pruritus (usually after bathing and other constitutional symptoms (e.g., fatigue)). In nearly 20% of patients, an episode of venous or arterial thrombosis is documented in the medical history and may be the first manifestation of PV, even prior to rise in hemoglobin levels (Dameshek 1951). Leukemic or fibrotic transformation rates at 20 years are estimated at 10–20% for PV (Tefferi et al. 2014a). There is no way to cure the disease or prevent the development of leukemia or post-PV myelofibrosis; consequently, the current therapy in PV is aimed at lowering the risk of thrombosis (Tefferi and Barbui 2015). The risk classification system in these disorders is shaped according to thrombosis risk. Low-dose aspirin must be given to every patient diagnosed of PV (Landolfi and Marchioli 1997). In case of major hemorrhagic events, antiaggregant therapy should be discontinued. In case of a first episode of thrombosis, indefinite anticoagulation should be the best approach. Several studies in PV have identified age older than 60 years and previous thrombosis as the main predictors of vascular complications (Marchioli 2005). Hence, cytoreductive therapy should be administered in patients older than 60 years or who have suffered from any arterial or venous thrombotic event (Barbui et al. 2011a). As in younger patients, in elderly patients hematocrit should be kept below 45% (Marchioli et al. 2013). Either hydroxyurea or IFN-α is first-line cytoreductive therapy at any age (Barbui et al. 2011a). Second-line treatment for intolerant or resistant patients include the first-line option not administered or, in case of prior hydroxyurea administration, the JAK2 inhibitor ruxolitinib (Vannucchi et al. 2015). Pipobroman, busulfan, and ^{32}P are other second-line therapies reserved for patients with short life expectancy (Barbui et al. 2011a).

Essential Thrombocythemia

Essential thrombocythemia (ET) is a MPN that involves primarily the megakaryocytic lineage. More than one half of the patients are asymptomatic at the time of diagnosis when a markedly elevated platelet count is discovered at the time of a complete blood count. The remaining patients may present at the clinics with the same symptoms explained in PV. Median age at diagnosis is 67 years, and the female-to-male (F/M) ratio was 2.6:1 (Jensen et al. 2000).

No major changes have been done in the 2016 revision to the WHO classification of myeloid neoplasms, besides the inclusion of new molecular markers. Hence, all four major criteria are required to be diagnosed of ET: a platelet count >450.000/microL; a trephine biopsy morphology showing an increased number of enlarged, mature megakaryocytes with hyperlobulated nuclei and no significant fibrosis; not meeting criteria for other myeloid neoplasm; and the presence of any of the three driver mutations (*JAK2* V617F, *CALR*, or *MPL* found in 50–60%, 19–22%, and 1–3% of patients, respectively) (Pardanani et al. 2006; Kong et al. 2016). In around 15% of patients, no mutation in these genes is detected (i.e., are triple negative). In such cases, clonal marker is required or absence of evidence for reactive thrombocytosis (Dameshek 1951). In general, *JAK2* V617F mutations are found in older patients compared to those who carry a *CALR* mutation, probably due to the association of type-1 *CALR* mutations to younger patients (Tefferi et al. 2014b, c).

Life expectancy is reduced in ET compared to that of an age- and sex-matched control population, although it is higher than in PV patients, with a median survival of 20 years (Tefferi et al. 2014a).

Arterial or venous thrombotic events occur in around 25% of patients, either previous or after ET is diagnosed (Colombi et al. 1991). As described in PV, therapy is aimed at reducing the risk of thrombosis and, in turn, is guided by the thrombotic risk of the patient. Hence, patients older than 60 years or with a previous record of arterial or venous thrombosis might receive cytoreductive treatment. Prophylactic low doses of aspirin should be individualized according to patient's risk. It seems that cases with JAK2 mutation are at higher risk of thrombosis rather than cases with CALR mutation, where the risk is much lower (Barbui et al. 2011b). In case of major hemorrhagic events, antiagregant therapy should be discontinued. Hydroxyurea is the first-line cytoreductive therapy, but tolerance is much worse in older people. Moreover, the incidence of skin lesions like ulcers is higher in older people. Anagrelide is the recommended second-line therapy for ET. In older people, cardiac function should be closely monitored due to secondary tachycardia induced by the inhibition of phosphodiesterase and ulterior myocardiopathy. IFN might be considered an experimental therapy (Barbui et al. 2011a). Although a non-leukemogenic drug is preferred after hydroxyurea treatment, due to an increase of the incidence of leukemia evolution, in case of short life expectancy, pipobroman, busulfan, or ^{32}P could be administered (Barbui et al. 2011a; Najean and Rain 1997).

Primary Myelofibrosis

Primary myelofibrosis (PMF) is a clonal proliferation of a pluripotent hematopoietic stem cell, in which the abnormal cell population releases several cytokines and growth factors in the bone marrow that lead to marrow fibrosis and stroma changes (Barosi 1999). Some patients initially diagnosed of PV or ET eventually develop this disease, denominated post-PV myelofibrosis (post-PV MF) or post-ET myelofibrosis (post-ET MF). PMF is the least frequent among the chronic myeloproliferative diseases. One study reported an estimated incidence of 1.5 per 100,000 per year. PMF occurs mainly in middle-aged and older adults. The median age at presentation is 67 years (Mesa et al. 1999).

In order to be diagnosed of PMF, a patient must also show, at least, one of the following: anemia, leukocytosis, palpable splenomegaly, increased LDH, or leukoerythroblastosis. Around 12% of patients carry a triple-negative mutation status (i.e., negative for *JAK2*, *CALR*, or *MPL* mutations). In order to diagnose these patients, a search for the most frequent accompanying mutations (e.g., ASXL1, EZH2, TET2, IDH1/IDH2,

SRSF2, SF3B1) must be carried out (Dameshek 1951). Unfortunately, mutations in some of these genes have been reported in around 5% of elderly people, associated to clonal premalignant hematopoiesis, which could reduce the reliability of these additional criteria in this group of patients (Xie et al. 2014).

Surveillance is reduced compared to that of an age- and sex-matched control population with a median survival of 6 years (Tefferi et al. 2014a). Several scores, namely, IPSS, DIPSS, and DIPSS plus, have been developed in order to predict for survival. In all of them, age greater than 65 was found to be an adverse prognostic factor (Passamonti et al. 2010; Gangat et al. 2011; Cervantes et al. 2009).

The only curative treatment is allogeneic hematopoietic stem cell transplantation. Regrettably, old adults cannot benefit from this therapeutic option. A few years ago, ruxolitinib, a JAK2 inhibitor, was approved by the FDA for treatment of patients with intermediate-2 or high-risk MF according to IPSS score and also for intermediate-1 risk group by the EMA. Ruxolitinib effectively reduces spleen volume and constitutional symptoms compared to best available therapy. The median duration of spleen response is 3.2 years. Although crossover was allowed between arms, there is a trend to statistically significant differences in overall survival at 5 years. Most frequent adverse events observed with ruxolitinib were thrombocytopenia, anemia, and an increased risk of infections (Harrison et al. 2016).

In order to improve the anemia, usually below 10 g/dl, the therapeutic options available include erythropoiesis-stimulating agents, androgens, immunomodulators, splenectomy, and prednisone. Therapeutic options for symptomatic splenomegaly, apart from ruxolitinib, include cytoreductive drugs, mainly hydroxyurea, splenectomy, and splenic radiation (Cervantes 2014).

Age and Comorbidities

Comorbid health conditions such as heart disease, pulmonary disease, diabetes, and arthritis are commonly present in elderly patients (Extermann 2000). The variety of comorbid conditions and their individual severity, as well as the cumulative impact of these conditions, have the potential to uniquely impact the cancer patient's treatment and prognosis (Yancik et al. 2001; Janssen-Heijnen et al. 2005). In a recent study carried out to demonstrate that comorbid health conditions disproportionately affect elderly cancer patients, 27,506 newly diagnosed cancer patients were analyzed to examine the prevalence and severity of comorbid ailments by age. Hypertension was the most common comorbidity in all patients, diabetes was the second most prevalent comorbidity in middle-aged patients, and previous solid tumors were the second most prevalent condition in patients aged 74 and older. Moreover, the prevalence and severity of comorbid conditions like dementia and congestive heart failure increased with age. A subgroup analysis also demonstrates that with increasing age, the proportion of patients who present with mild comorbidities decreases, while the proportion of patients who present with moderate and severe comorbidities increases (Piccirillo et al. 2008).

In this regard, comorbidity is being assessed in patients with CML. Charlson comorbidity index predicts poor outcome in CML patients treated with tyrosine kinase inhibitor (Uemura et al. 2016). Although the Sokal and Hasford scoring systems are well-known prognostic models specific to CML, it has not been established whether they can effectively predict outcomes in elderly CML patients with comorbidities. The Charlson comorbidity index (CCI) has been explored in studies in CML patients and was found that cases with a CCI score >3 had significantly poorer survival after diagnosis and CCI score was inversely associated to overall survival. It has been demonstrated in prospective clinical trials. In the CML study IV of the German CML Study Group, the influence of comorbidities on remission rate and overall survival in patients with CML was studied. Higher CCI was significantly associated with lower OS probabilities. And even more important, in the multivariate analysis, CCI was the most powerful predictor of OS, which was still valid after removal of its age-related components. Comorbidities have no impact on treatment

success but do have a negative effect on OS, indicating that survival of patients with CML is determined more by comorbidities than by CML itself (Saussele et al. 2015).

In a small study, comorbidities and polypharmacy impact on complete cytogenetic response in CML elderly patients. The CCI and the polypharmacy were correlated to the obtained cytogenetic response. The majority of complete cytogenetic response was obtained by patients who presented a low score of CCI and did not take any other drugs other than TKI (Iurlo et al. 2014).

Of interest is a recent study of the Surveillance, Epidemiology, and End Results cancer registry performed in 1466 patients with CML with a mean age of 78 years treated with imatinib where elderly patients with CML had greater mortality and greater rates of myocardial infarction, stroke, pulmonary embolism, and peripheral arterial disease than did noncancer patients. The event rates were not elevated among the TKI-treated (primary imatinib) patients, suggesting that the vascular events risk in these patients with CML was driven primarily by the underlying factors associated with CML (Lang et al. 2016).

In PMF, there is a study about comorbidities and outcome. Comorbidities were assessed using the adult comorbidity evaluation-27 (ACE-27). In a large cohort of 349 patients, approximately 64% of patients had at least 1 comorbid condition; cardiovascular diseases were the most common up to 63%. Comorbidities had a significant negative impact on survival. Patients with severe comorbidities had twice the risk of death as those with no comorbidities (Newberry et al. 2014).

Age and Polypharmacy in CML Older Patients

The prevalence of polypharmacy increased with age, and from the age of 70 years, two thirds of all drug users were polypharmacy users, defined as taking more than three drugs. Drug use was 50% more prevalent among women than men, but over the age of 70, the sexes did not differ in the prevalence of major polypharmacy. Many different drug combinations were found, and among major polypharmacy users, two thirds had their own unique drug regimen, different from all other drug users. Cardiovascular drugs and analgesics were often involved in polypharmacy among the elderly, while asthma drugs, psychotropic drugs, and antiulcer drugs were predominant among young individuals exposed to polypharmacy. The higher risk for major polypharmacy was substantially increased for individuals treated for cardiovascular diseases, anemia, and respiratory diseases (Bjerrum et al. 1998).

In a specific study of imatinib and polypharmacy in very old patients with CML, the effects on response rate, toxicity, and outcome have been evaluated. Polypharmacy was reported in one third of patients, and drugs more frequently used were antiplatelets, diuretics, proton pump inhibitors, ACE inhibitors, beta blockers, calcium channel blockers, angiotensin II receptor blockers, statins, oral hypoglycemic drugs, and alpha blockers. Comparing patients exposed to polypharmacy to those without, no difference was observed pertaining to the dosage of imatinib, cytogenetic, and molecular responses and hematological and extra-hematological toxicity (Iurlo et al. 2016).

Age and Quality of Life in CML Older Patients

Two thirds of CML patients aged 60 years presented with at least one comorbidity condition at diagnosis. The presence of comorbidity was associated with important impairments in both physical and mental health domains. This negative association with poor health-related quality of life (HRQoL) outcomes was particularly remarkable in patients who reported two or more comorbid conditions. Elderly patients with comorbidities should be more closely monitored due to their poorer HRQoL outcomes, representing a specific population who can benefit the most from supportive care programs (Efficace et al. 2016).

Patients with PMF have significant debilitating symptoms, physical disabilities, and HRQoL. In clinical trials, ruxolitinib treatment has been associated with PMF-associated symptoms improvement from baseline compared with the control group receiving best available therapy (BAT) where symptoms were the same or worsened. Ruxolitinib also resulted in significantly higher response rates in global health status/QoL and Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) summary scores versus BAT at most time points (Harrison et al. 2013).

Real-World Patients Versus Clinical Data Trial

Elderly patients are underestimated in clinical trials, and final results are extrapolated into all patients in real life. Many exclusion criteria of the clinical trials will have a possible selection bias compared with the real life. In a very interesting study, authors evaluated patient characteristics of those that could not be enrolled in nilotinib and dasatinib trials. Up to 13.5% of CML patients should have been excluded by both trials because of polycomorbidities, severe cardiomyopathy, age > 80 with frailty, drug abuse, or other severe concomitant diseases. In addition, some patients should have been excluded in dasatinib trials due to isolated chronic obstructive bronchopulmonary disease, and other patients should have been excluded in nilotinib trials due to isolated diabetes, arrhythmia, and acute myocardial infarction > 6 months before CML diagnosis, chronic pancreatic disease, and peripheral arterial obstructive disease. On the whole, 17.4% of patients would have been excluded by dasatinib trial and 22.7% by nilotinib trial. The patients potentially not eligible for both trials were significantly older and with imatinib had a worse outcome compared with patients potentially eligible. Therefore, an automatic transposition of results available in clinical controlled trials into the frontline real-life management of elderly CML patients should be regarded with caution (Latagliata et al. 2015).

Conclusion

Older patients with CML and other MPNs are at higher risk of suffering from other comorbidities that may impact in the general outcome. The age is by itself an adverse prognosis risk factor in many of these MPNs. The polypharmacy and preexisting medical conditions may influence the follow-up of these patients and should be monitored more closely. Data from clinical trial, where older people are underrepresented, must be taken with caution in order to minimize toxicity and enhance adherence to treatment.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Frailty in Cancer Patients
- ▶ Geriatric Interventions in Oncology
- ▶ Geriatric Screening in Cancer Patients

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Multiple Myeloma in Older Adults

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Abstract

Multiple myeloma (MM) is a plasma cell malignancy of older adults and incidence is expected to increase in the coming years. Despite substantial improvements in patient survival, the disease remains incurable. Early mortality is most common in adults 70 years and older. Novel therapeutics and autologous stem cell transplant (ASCT) have led to improvement in survival; however, transplant eligibility remains a challenge especially in the older adult population. Understanding geriatric assessment evaluations can aid in identifying patients at risk for increased morbidity and mortality in older adults with MM. Novel treatment combinations have improved disease control while balancing efficacy with toxicity for the older adult. Here we explore the diagnostic criteria, staging systems, cytogenetic abnormalities, treatment approach, and geriatric assessment in older adults with MM.

Keywords

Multiple myeloma · Autologous stem cell transplant · Geriatric assessment

Introduction

Multiple myeloma (MM) is a plasma cell malignancy of older adults and accounts for 15% of all hematologic malignancies in the United States (Siegel et al. 2016). The median age of diagnosis is 69 years, and in the next 15 years MM incidence is expected to double (Surveillance Epidemiology, and End Results (SEER) 2017; Smith et al. 2009). Novel therapeutics and routine use of autologous stem cell transplant (ASCT) have led to substantial improvements in patient survival. However, the disease remains incurable (Kumar et al. 2014). MM deaths, overall, are highest in patients aged 75 years and greater, and early mortality is most common in those 70 years and older (Kumar et al. 2014; Warren et al. 2013). MM incidence is more common in men (1.4:1) and African Americans. MM has no clear genetic predisposition, although the risk of developing MM is 3.7-fold higher for a first-degree relative with the disease (Greenberg et al. 2012). MM is a clinical diagnosis, whereby a neoplastic proliferation of plasma cells in the bone marrow results in end organ damage. Older adults diagnosed with MM receive multidrug systemic induction therapy to obtain disease control. Eligible patients may proceed to an ASCT or those who are not eligible complete induction therapy, followed by maintenance therapy or low-dose treatment to sustain disease remission. Here we explore the diagnostic criteria, staging systems, cytogenetic abnormalities, treatment approaches, and geriatric assessment in older adults with MM.

Diagnosis of Multiple Myeloma

Laboratory Testing

Cases of MM were first reported in the late 1800s and coined "Multiple Myeloma" by J. Van Rustizky (1873). Early cases described bone pain with spontaneous fractures, abnormal X-rays, proteinuria, wasting, loss of appetite, and edema. Plasma cells were identified to originate in the bone marrow, and Wright identified these cells to be the cause of multiple myeloma in 1900 (Wright 1900a, b). The advent of bone marrow aspiration and its utilization in patients with anemia and skeletal abnormalities led to increased recognition of this entity (Kyle 2000). End organ damage that defines the clinical entity of MM includes anemia, hypercalcemia, bone disease, and/or renal dysfunction (Table 1) (Rajkumar et al. 2014). Here we discuss these clinical

Table 1 CRAB-E criteria

C	Hyper**C**alcemia	Symptomatic or asymptomatic elevation in serum calcium (>11.5 mg/dL or >2.75 mmol/L)
R	**R**enal failure	Serum creatinine >2 mg/dL (>117 μmol/L) or creatinine clearance <40 mL/min
A	**A**nemia	Normocytic normochromic anemia with hemoglobin <10 mg/dL
B	**B**one lesions	One or more osteolytic lesions noted on imaging
E	Myeloma Defining **E**vents	≥60% clonal bone marrow plasma cell percentage >1 focal lesions (5 mm or more) noted on magnetic resonance imaging (MRI) Involved: Uninvolved serum light chain ratio ≥100

Adapted from: Rajkumar et al. (2014)

abnormalities in the context of the aging adult in the modern era.

Anemia

Identifying anemia due to underlying myeloma requires a degree of clinical suspicion. Anemia is common as one ages, where one in five older adults are identified to have anemia (see ▶ Chap. 19, "Hematopoiesis and Aging"). The most common cause of anemia in older adults is secondary to nutritional deficiencies, chronic renal disease, or inflammation and the remaining one-third have unexplained anemia. A small proportion of "unexplained" anemia is a result of malignancies and bone marrow disorders, including MM. MM related anemia is a myelophthisic process where the plasma cells replace normal hematopoiesis. Anemia is a major clinical manifestation of MM and is present in about 70% of newly diagnosed patients. Causes include marrow replacement or suppression and erythropoietin deficiency from concomitant renal failure (Kyle 2000). The presence of moderate to severe anemia should prompt thorough investigation with a detailed history, complete blood counts, chemistry for serum creatinine, red cell indices, reticulocyte counts, peripheral smear, iron studies including ferritin, and tests for cobalamin to exclude nutritional deficiencies. Chronic renal disease is found in 17% of anemic patients; hence a careful evaluation for myeloma is warranted in a patient with anemia and new or unexplained renal dysfunction (Guralnik et al. 2005; Kyle et al. 2003; Baz et al. 2004). Anemia is a risk factor for adverse outcomes in older adults with cancer. Anemia is associated with decreased survival, functional immobility leading to falls, increased cardiovascular mortality, and decreased chemotherapy tolerance in older adults with cancer (Ferrucci and Balducci 2008).

Renal Dysfunction

Nearly half of patients diagnosed with MM have renal insufficiency (RI) at presentation. RI can be multifactorial secondary to direct tubular injury and fibrosis by toxic monoclonal light chains (cast nephropathy) or other contributing factors such as hypercalcemia, dehydration, hyperuricemia, direct plasma cell infiltration, proximal tubular dysfunction, or amyloid deposition. The International Myeloma Working Group (IMWG) proposed the use of the Modification of Diet in Renal Disease (MDRD) equation for calculation of renal dysfunction in patients with chronic renal disease (Kooman 2009; Levey et al. 2005). A renal biopsy is confirmatory of cast nephropathy or can identify amyloid deposition but is not mandatory in many cases. A 24-h urine collection is essential with urine protein electrophoresis and immunofixation to quantify the amount of monoclonal protein present. RI in myeloma is associated with poor prognosis and significant morbidity, if not reversed (Dimopoulos et al. 2010). Early recognition and treatment can help prevent progression to end-stage renal failure and decrease need for renal replacement therapy. Treatment may include rehydration and prompt chemotherapy initiation. Other measures to decrease paraprotein deposition and cast nephropathy such as plasmapheresis have been used (Leung et al. 2008). Renal function declines with aging, although there is wide variability in

age-related renal loss and/or renal disease (Weinstein and Anderson 2010) Therefore it is of critical importance to differentiate RI secondary to MM from renal dysfunction of other etiologies.

Radiographic Imaging

Bone pain and fractures are hallmarks of MM clinical presentation. Earliest autopsies of patients with MM revealed significant destruction and thinning of the bones (Kyle 2000). Mechanisms of bone involvement include direct invasion, marrow replacement, and dysregulation of bone microenvironment. A complete bone survey with x-rays is recommended for the diagnostic evaluation of lytic bone lesions but could underestimate bony involvement in older adults with osteoporosis (Gleeson et al. 2009). Differentiating benign compression fractures from malignant disease secondary to myeloma can be a challenge, as diffuse myelomatous involvement on MRI has been noted in 29% of those with compression fractures (Kusumoto et al. 1997). If a bone lesion nature is in question (benign vs malignant), a bone biopsy of the suspected lesion is recommended. Moreover, newer imaging modalities including MRI, ^{18}F- FDG PET, CT, and PET/CT scans are more sensitive for detecting MM bone lesions in comparison to skeletal radiography (Regelink et al. 2013). The IMWG criteria has since been revised to allow for osteolytic lesions >5 mm or more diagnosed by MRI, low-dose whole body CT, PET-CT as criteria for end-organ disease. PET-CT is increasingly being incorporated for extramedullary myeloma disease detection, however there is lack of strict reporting criteria for PET-CT, and PET portion alone is not adequate for the diagnosis of multiple myeloma (Cavo et al. 2017).

Hypercalcemia

Hypercalcemia is present in 28% of the patients at the time of diagnosis with nearly half requiring emergent treatment (Kyle et al. 2003). Hypercalcemia is due to bone destruction from osteoclastic activation by tumor cells. It can be asymptomatic or present with wide symptoms ranging from nausea, anorexia, polyuria, polydipsia, constipation, weakness, confusion to stupor. The presenting feature can be challenging in an elderly patient with multiple medical comorbidities. A high serum blood calcium level should be confirmed with an ionized calcium. Calcium binds with IgG monoclonal protein and can result in a spurious increment of measured calcium without hypercalcemia (Annesley et al. 1982). Hypercalcemia impacts overall survival where survival decreased with Ca levels of $\geq$12 mg/ml (Carbone et al. 1967).

Monoclonal Proteins and Light Chains

Myeloma proteins can be classified by immunoglobulin class and light chain identification. Immunoglobulins IgG (52%) and IgA (21%) are most common, followed by light chain disease Kappa (κ) and Lambda (L) (16%), and paraproteins IgD and IgM are rare (2.5%) (Kyle et al. 2003). Characterization of the type of immunoglobulin and presence of light chains is important in assessing chemotherapy response and survival (De Bergsagel et al. 1965). Patients with an M protein burden may also have a higher incidence of bone lesions and hypercalcemia (Report on the first myelomatosis trial 1973). Most patients have serum monoclonal protein with or without urine protein, and 3% of patients have neither, classifying them as nonsecretory myeloma. Identification of monoclonal protein (M protein) in serum and urine is usually done by protein electrophoresis. Immunofixation (IFE) techniques in serum and urine are more sensitive and can identify smaller amounts of monoclonal protein. Quantification of the amount of proteinuria in a 24-h period should be done in the initial evaluation. Quantitative analyses of serum immunoglobulins and serum free light chains are sensitive for screening and are followed for treatment response (Table 2) (Kyle et al. 2003; Kastritis et al. 2014; Drayson et al. 2001).

Table 2 IMWG response criteria

Response category	Response criteria
Stringent complete response	Complete response as defined below plus normal serum free light chain (SFLC) ratio and absence of clonal plasma cells in the bone marrow by immunohistochemistry
Complete response	Negative immunofixatiaon on the serum and urine, disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in the bone marrow
Very good partial response	Serum and urine monoclonal protein (M protein) detectable by immunofixation but not electrophoresis or ≥90% reduction in serum M protein plus urine M protein level <100 mg per 24 h
Partial response	Reduction of serum M protein by ≥50% plus 24 h urinary M protein by >90% or to <200 mg per 24 h[a]
Minimal response	≥25% but ≤49% reduction of serum M protein and reduction in 24 h urine M protein by 50–89% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M protein (absolute increase must be ≥0.5 g/dL) Urine M protein (absolute increase must be ≥200 mg/24 h) In patients with inadequate serum and urine M proteins for response assessment, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) In patients with inadequate serum and urine M proteins and SFLC's, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥10%) Appearance of a new lesion(s), ≥50% increase from nadir in of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

[a]Additional criteria apply Adapted from International Myeloma Working Group Response Criteria for Multiple Myeloma (Kumar et al. 2016)

Beta 2 Microglobulin (β_2M)

Serum β_2M in combination with serum albumin emerged as the single, most important prognosticating factor in the 1980s during the development of the International Staging System (ISS). It was noted to be elevated in advanced disease independent of renal function and could be followed over time. Decreased survival was noted in cases of high β_2M (Cassuto et al. 1978; Norfolk et al. 1980; Bataille et al. 1983). β_2M reflects tumor mass burden and renal function and possibly immune function, but exact biology remains to be explored (Bataille et al. 1986; Jacobson et al. 2003; Durie et al. 2003). The Southwest Oncology Group stratified patients into low, intermediate, and high-risk categories with the inclusion of age and serum albumin similar to ISS (Durie et al. 1990).

Lactate Dehydrogenase (LDH)

Lactate Dehydrogenase is a nonspecific marker of cell turnover found when the enzyme converts pyruvate to lactate in the process of aerobic glycolysis and is increased during hypoxia, tissue injury, and necrosis. It has been shown that higher than normal serum LDH is suggestive of disease aggressiveness with high tumor proliferation rate and the presence of extramedullary disease. High LDH also has been associated with decreased overall survival with both chemotherapy and newer MM agents especially in elderly patients

(Dimopoulos et al. 1991; Terpos et al. 2010; Anagnostopoulos et al. 2005).

Bone Marrow Evaluation and Cytogenetics

Bone marrow biopsy and aspiration is required for evaluation and diagnosis. Bone marrow immunohistochemistry confirms the presence of monoclonal plasma cells and flow cytometry can identify clonal plasma cells. Chromosomal analysis by fluorescence in situ hybridization and conventional karyotyping identify prognostic chromosomal abnormalities. Two main types of cytogenetic abnormalities are trisomies (hyperdiploid) and translocation of the immunoglobulin heavy chain (IgH) gene (nonhyperdiploid). Trisomies include extra copies of chromosomes, mainly odd numbered chromosomes 3, 5, 7, 9, 11, 15, and 17 (Fonseca et al. 2009). Clinically relevant chromosomal abnormalities and their effects on multiple myeloma are listed (Table 3). Gene expression profiling may also add prognostic information but is not widely available (Anderson et al. 2015). Deletion (Kyle et al. 2003) is frequently associated with t(4;14) and del(17p). These abnormalities are associated with decreased event-free survival (EFS) and overall survival (OS), in combination. Translocation t(4;14) and del(17p) along with a high β2M are associated with decreased EFS and OS. Stratification of these cytogenetic abnormalities (CA) is also shown in Table 3 (Avet-Loiseau et al. 2007; Fonseca et al. 2004; Dispenzieri et al. 2007; Kumar et al. 2009).

Staging

Durie-Salmon Staging System (DSS)

Durie and Salmon were the first to classify myeloma into stages based on tumor burden in 1975 (Durie and Salmon 1975). Further characterization of these stages by blood urea concentration, hemoglobin levels, and performance status identified worse prognosis to be associated with higher blood urea concentration, lower hemoglobin, and, understandably, poor performance status (Prognostic features in the third MRC myelomatosis trial 1980). These findings were also reported in the long-term follow-up of the first and second myeloma trials (Merlini et al. 1980; Buckman et al. 1982). The Durie and Salmon staging system incorporated monoclonal protein type and level, calcium, the number of bony lesions, and later divided into substages: substage A with serum creatinine >2 mg/dL, and substage B with ≥ 2 mg/dL, with low and high-risk patients respectively. This staging system did not account for observer bias during evaluation of skeletal metastases. Other classifications adopted other prognostic factors like Sβ2M along with serum albumin, the rate of bone resorption, to overcome observer bias (Bataille et al. 1986; Merlini et al. 1980).

International Staging System (ISS)

The International Staging System was developed incorporating β_2M, renal function, and serum albumin into a three-stage system, which provided the most statistically significant results, and was validated consistently. It was noted that ISS stage I overall survival corresponded to Durie-Salmon stage IA; but interestingly, DSS stage IIA also had similar overall survival at 58 months. All poor-risk DSS substage B patients with a serum creatinine of ≥ 2 mg/dL had worse overall survival which was similar to ISS stage III with Sβ_2M $\geq$ 5.5 mg/L. β_2M in combination with serum albumin emerged as the most important prognosticating factor (Greipp et al. 2005).

Revised-International Staging System (R-ISS)

Cytogenetic abnormalities (CA) detected by FISH play an important role in overall prognosis with standard-risk myeloma having an overall survival (OS) of 50.5 months, and high risk with

Table 3 Chromosomal abnormalities in multiple myeloma

Abnormality	Chromosome	Incidence	Genes	Cytogenetic risk
Trisomies of odd chromosomes (hyperdiploid)	3, 5, 7, 9, 11, 15, 17 (with exception of 1, 13, and 21)	42%	Many	Standard risk (OS: 7–10 yrs)
Chromosome 13 deletion Del(13)	13	48%	Many	Close association with t(4;14)(p16;q32); adverse prognosis only in association with t(4;14) del (17p)
Translocations				
Immunoglobulin heavy chain (IgH)	t(11;14)(q13;q32)	21%	*CCND1* -cyclin D1	Standard risk (OS: 7–10 yrs) K-RAS mutations common
	t(6;14)(p21;q32)	2%	*CCND3* -cyclin D3 gene	
	t(4:14)(p16;q32)	14%	*FGFR-3, MMSET*	Intermediate risk (OS: 5 yrs)
	t(14;16)(q32;q32)	5%	*C-MAF*	High risk (OS:<2–3 yrs)
	t(14;20)(q32;q11)	2%	*MAFB*	
MYC translocation	8	13%	Encodes transcription factor that regulates cell proliferation and apoptosis	Adverse prognosis (median OS: 20.2 months)
Gains and losses				
Gain(1q21)	1	43% 78% in relapsed MM	Amplification of long arm is usually associated with deletion of short arm of chromosome 1 and strongly associated with chromosome 13 deletion	Intermediate risk (med OS: 5 yrs) Increases risk of progression from smoldering myeloma to multiple myeloma; decreased postrelapse survival
Del(1p)	1	18%		High risk (OS: 3 yrs)
Monosomy 17 del(17p13)	17p13– locus for tumor suppressor gene	11%	Loss of heterozygosity of TP53	High risk (OS: 3 yrs)

Adapted from: Fonseca et al. (2009), Avet-Loiseau et al. (2007), Fonseca et al. (2004), Dispenzieri et al. (2007), Kumar et al. (2009)

median OS of 24.5 months (Fonseca et al. 2009). Efforts to improve the ISS, included characterization of CA into low, intermediate, and high-risk groups (Neben et al. 2010; Boyd et al. 2012; Avet-Loiseau et al. 2013). It was noted that very few patients had a nonsignificant cytogenetic analysis that did not impact the prognostication. The Revised-ISS, established in young and elderly patients with newly diagnosed multiple myeloma, identified similar median OS in elderly population (≥65 years of age) (median OS not reached in stage I, 70 months in stage II, and 46 months in stage III); but patients ≥65 years of age constituted only 35% of the population evaluated (Palumbo et al. 2015a). Comparisons among the three staging systems are shown in Table 4.

Treatment Stratification

Treatment for MM is often stratified into transplant eligible and transplant ineligible strategies. This approach historically was based upon age (+/−65y.o.) and presumed tolerance of ASCT. Transplant "eligibility" is an active and important area of myeloma investigation. ASCT is established, in younger populations, to improve survival over nontransplant therapy (Attal et al. 1995; Cavo et al. 2016a) and has PFS advantages

Table 4 Comparison of myeloma staging systems

	DSS 1975		ISS 2005		R-ISS 2015	
Stage	Criteria	OS Median	Criteria	OS Median	Criteria	OS Median
I	Low cell mass ($<0.6 \times 10^{12}$ cells/m^2 BSA) All: 1. Hg >10 g/ml 2. Calcium ≤12 mg/ml 3. Bone lesions: None or solitary plasmacytoma 4. Low M component (a) IgG <5 g/ml (b) IgA <3 g/ml (c) UPEP<4 g/24 hr	A: 69 months B: 22 months	β_2M <3.5 mg/L Serum albumin ≥3.5 g/dL	62 months	Standard risk cytogenetic abnormalities (no high risk) Normal LDH	Not reached
II	Intermediate cell mass ($0.6–1.2 \times 10^{12}$ cells/m^2 BSA) Neither stage I or III	A: 58 months B: 34 months	Not stage I or III	44 months	Not R-ISS stage I or III	83 months
III	High cell mass ($>1.2 \times 10^{12}$ cells/m^2 BSA) Having ≥1: 1. Hg <8.5 g/ml 2. Calcium >12 mg/ml 3. Advanced lytic bone lesions 4. High M component production: (a) IgG >7 g/ml (b) IgA >5 g/ml (c) UPEP >12g/24 hr	A: 45 months B: 24 months	β_2M ≥5.5 mg/L	29 months	High risk cytogenetic abnormalities [(del (17p) and/or t(4;14) and/or t(14;16)] Or High LDH (>upper limit of normal)	43 months

Adapted from: Durie and Salmon (1975), Prognostic features in the third MRC myelomatosis trial (1980), Greipp et al. (2005), Palumbo et al. (2015a)
Substage A (serum creatinine <2 mg/ml), substage B (serum creatinine ≥2 mg/ml)
β_2M <3.5 mg/L but serum albumin <3.5 g/dL or Sβ_2M − 3.5 to <5.5 mg/L irrespective of serum albumin level

over delayed transplant in the novel era (Attal et al. 2015). However, ASCT is feasible and an efficacious component of therapy for older patients with myeloma as well but is underutilized (Wildes et al. 2015a). In the novel area, older adults mobilize sufficient numbers of hematopoietic stem cells and can tolerate transplant with excellent outcomes (Wildes et al. 2015b) leading to the largest growth in myeloma transplant. In contrast, historic reports depict conflicting tolerance, response rates, and survival[48] potentially leading to referral bias. Novel therapeutics and routine use of ASCT have led to substantial improvements in overall response rates and durable remissions for the MM population as a whole (Kumar et al. 2014; Harousseau et al. 2010; Cavo et al. 2010). Nonetheless, applying data from clinical trials based on chronologic age alone has left the clinician with questions on who is and who is not eligible for transplant.

Eligibility for transplant is subjective and variable by transplant institution but is dependent on

age, comorbidities, and underlying health status. Some adults with MM are not candidates for ASCT due to advanced age (≥80), comorbidities, frailty, or personal preference. Studies have shown that patients with advanced comorbidities have inferior outcomes posttransplant (Saad et al. 2014a). Weight loss prior to transplant and lower physical function is associated with a longer transplant length of stay (Rosko et al. 2018). Psychosocial health has also shown to play an important role in ASCT outcomes, where anxiety and depression are associated with inferior outcomes and may play a role in overall survival (Richardson et al. 2018). Optimizing specific factors, such as physical function or nutrition, prior to transplant may aid in the improving health outcomes for older adults. Suggested minimal recommendations for transplant eligibility include an assessment of comorbidities by testing end organ function (e.g., electrocardiogram, ECHO, and pulmonary function testing), psychosocial support (e.g., screens for anxiety, depression, caregiver support, and financial assessment), cognitive health (screen for cognitive impairment), and MM response (e.g., bone marrow testing, skeletal survey, SPEP, FLC, and UPEP). Additional assessments of transplant eligibility that may influence outcomes include nutritional status, physical function (subjective or objective testing), and contributions of polypharmacy; this approach is further outlined in section "Geriatric Assessment in Multiple Myeloma."

Transplant Ineligible Therapy for MM in the Older Adult

Melphalan-Based Therapy

The therapeutic backbone of melphalan and prednisone (MP) was the standard for older adults with MM. A relatively effective drug, oral melphalan was the foundation of therapy for non-ASCT candidates but was avoided in ASCT candidates due to the effect on stem cell mobilization (Alexanian et al. 1969). The addition of novel agents to MP has resulted in improvements in overall survival. Thalidomide was first added to MP (MPT) and confirmed a survival advantage in randomized trials for older adults (Palumbo et al. 2006). Subsequently, with the advent of novel agents, both bortezomib and lenalidomide have been examined in combination with melphalan and are considered a standard frontline therapy for aging adults (Mateos and San Miguel 2013). Older adults with MM are vulnerable to adverse events associated with multidrug combinations, which can lead to dose reductions or cessation of therapy and is associated with poorer outcomes (Palumbo et al. 2015b). Strategies for selecting 2-drug therapy vs. 3-drug therapy is aimed at disease control while balancing for treatment toxicity and accounting for factors related to aging.

Immunomodulatory Drugs (IMiD)-Based Therapy

The addition of thalidomide to MP is associated with improved response rates, depth of response, progression-free survival, and overall survival (OS). However, nonhematological toxicity is increased with the addition of thalidomide to MP (Palumbo et al. 2013). Thalidomide, although efficacious, has fallen in usage due to the advent lenalidomide (Palumbo et al. 2006; Facon et al. 2007a). Lenalidomide is a second generation IMiD developed as a more potent, less toxic analog of thalidomide. Lenalidomide has been studied alone and with combination therapy. Studies show that melphalan, lenalidomide, and prednisone (MPR) with or without lenalidomide maintenance prolongs progression-free survival and OS compared to MP, with a toxicity profile that compares favorably with MPT (Zweegman et al. 2016; Gay et al. 2010). Two-drug options are also favorable; continuous treatment with Rd. (lenalidomide and dexamethasone), in comparison with MPT, is associated with a survival advantage and fewer toxicities (Benboubker et al. 2014). When pairing therapy with dexamethasone, older adults with MM do not benefit from higher dosages of dexamethasone and weekly dexamethasone is recommended over high-dose dexamethasone (40 mg once weekly over 40 mg 4 days on/5 days off) as the latter results in inferior progression-free and overall

survival (Rajkumar et al. 2010). Lenalidomide is associated with mild myelosuppression as part of its adverse event profile, whereas thalidomide is associated with more peripheral neuropathy, fatigue, and constipation (Gay et al. 2010). Recent studies suggest that three-drug regimens may be superior to two-drug regimens in terms of disease response and survival (Durie et al. 2017). Others are investigating dosage attenuation of standard regimens (VCD-lite and RVD-lite) in older adults to attenuate toxicity while maintaining efficacy (O'Donnell et al. 2015).

Bortezomib-Based Therapy

Bortezomib is a proteasome inhibitor and is also a standard frontline therapy in older adults. Twice weekly bortezomib in addition to MP (VMP) improves overall survival compared to MP but is associated with peripheral neuropathy (Mateos et al. 2013). Bortezomib alone (VD) and in combination (VTD, VMP) has been evaluated in older adults ineligible for transplant and have shown that response rates, PFS and OS were similar, yet toxicities were more common with VTD (Niesvizky et al. 2015). Bortezomib, Lenalidomide, and dexamethasone (VRD) induction therapy in comparison to Rd. alone has been shown to have survival advantages for newly diagnosed MM patients and with the exception of peripheral neuropathy, had balanced side effect profiles (Durie et al. 2017). Bortezomib is the preferred agent in those with renal failure and results in prompt disease control and potential for renal recovery. Complete renal response (CRrenal) with resolution of RI to normal creatinine and glomerular filtration rate is more frequent with newer treatment regimens containing bortezomib (71%) than with conventional chemotherapy (41%) or with immunomodulatory therapy (45%) (Dimopoulos et al. 2010). Other combination regimens that substitute conventional melphalan for Cytoxan (VCD, CyBorD) have also been evaluated and show excellent responses compared to Rd. or CRD and are well tolerated (Jimenez-Zepeda et al. 2015; Kumar et al. 2010). Peripheral neuropathy is a significant concern for aging adults with myeloma, several studies have demonstrated that once weekly administration and subcutaneous administration of bortezomib reduces toxicity by roughly 30% while preserving efficacy (Mateos et al. 2010a; Mateos et al. 2010b; Bringhen et al. 2010).

Next Generation Therapy

Balancing efficacy and managing toxicity is a challenge for older adults with myeloma. Recent studies suggest that three-drug regimens may be superior to two-drug regimens (SWOG S0777), in terms of disease response and survival (Durie et al. 2017). Others are investigating dosage attenuation of standard regimens (VCD-lite and RVD-lite) in frail older adults to attenuate toxicity while maintaining efficacy (O'Donnell et al. 2015). Studies such as these may help to better define the optimal induction regimens for seniors who will not undergo ASCT. Therapy selection for older adults is evolving, and questions remain on how to sequence newer agents such as the monoclonal antibodies – daratumumab and elotuzumab. Daratumumab is a CD38 targeted antibody that causes myeloma cell death through a variety of immune-mediated mechanisms and is under active investigation as a frontline agent [NCT02541383, NCT02252172, NCT02874742, NCT02195479, NCT02951819]. Elotuzumab is a first-in-class humanized immunostimulatory monoclonal antibody targeted against signaling lymphocytic activation molecule F7 (SLAMF7, also called CS1) and is approved for relapsed disease, in combination with lenalidomide and dexamethasone (Lonial et al. 2015; Wong et al. 2015). Studies are ongoing to explore how monoclonal antibodies can best be incorporated into MM therapies across the board.

Autologous Stem Cell Transplant in Older Adult with MM

Disparities in OS for older MM patients are multifactorial; under-utilization of ASCT in this population has been a significant contributing factor (Al-Hamadani et al. 2014). Recently, ASCT utilization has improved, and

consequently, overall survival for older adults has also improved. Large registry studies from the European Group for Blood and Marrow Transplantation (EBMT) have shown the proportion of ASCT recipients ≥65 years old increased from 3% (1991–1995) to 18.8% (2006–2010). Over these same time periods, the percentage of patients aged 65–69, alive at 2 years, increased from 55% to 83%, with comparable trends seen for patients aged ≥70 years (Auner et al. 2015a; Sánchez-Ortega et al. 2016). A similar analysis was conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR), where 11,430 patients receiving ASCT reported similar 1-year non-relapse mortality for patients above and below age 70. Increasing age, however, was associated with worse overall survival yet MM-specific mortality rates were similar across age groups (Sharma et al. 2014).

High-dose melphalan followed by ASCT improves overall survival and PFS among fit patients <65 years old compared with delayed transplantation (Palumbo et al. 2014; Cavo et al. 2016b; Attal et al. 1996). Under-utilization for transplant may be a result of conflicting data in older adult ASCT studies. The largest older adult ASCT study was the Intergroupe Francophone du Myélome (IFM) 99–06 study, where 447 patients were randomized to either receive MP, MPT, or tandem ASCTs using a reduced dose of melphalan at 100 mg/m2 (MEL100). Early death was reported in 7% of patients in the MP group, 2% in the MPT group, and 9% in the MEL100 group. MPT was associated with a significant OS benefit compared with both MP and MEL100 (Facon et al. 2007b).

In contrast to these results, more recent prospective evaluations, registry studies, and multiple single-center retrospective analyses have yielded more favorable results in older adult ASCT (Wildes et al. 2015a; Sánchez-Ortega et al. 2016; Sharma et al. 2014; Garderet et al. 2016; Gertz et al. 2007; Siegel et al. 1999; Kumar et al. 2008; Merz et al. 2014). The Mayo Clinic evaluated outcomes of ASCT patients above and below 65 years of age. Older patients were more likely to receive a reduced dose of melphalan (30% vs. 5%), similar overall response rate (97% vs. 98%), similar time to progression (29 months vs. 18 months), and no differences in OS (not reached vs. 53 months) (Kumar et al. 2008). Likewise, the German Myeloma Study group reported on 202 patients aged ≥60 who underwent ASCT where 97% of patients received MEL200, with 21% receiving tandem transplants, and there was no significant difference in mortality by day 100, and age was not a risk factor for adverse outcome (Merz et al. 2014). The feasibility of MEL200 in selected elderly patients was further supported by retrospective studies, where advancing age was not predicative of worse PFS post-ASCT (Bashir et al. 2012; Huang et al. 2017). The optimal dose strategy of high dose melphalan in older adults undergoing ASCT is unclear. Many studies have reported MEL200 without significant differences in treatment toxicity compared to younger patients; furthermore, higher dosages of melphalan may partially explain improved outcomes, compared to other studies using lower dosages of melphalan (Auner et al. 2015b). Nonetheless, melphalan 140 mg/m^2 is commonly used in older adults in an effort to preemptively reduce risk of transplant toxicity (Sharma et al. 2014; Huang et al. 2017).

Risk Stratification

Geriatric Assessment in Multiple Myeloma

As the MM population ages, a rigorous approach assessing the underlying health status aims to balance therapeutic efficacy while minimizing adverse events. A valuable tool to identify and resolve occult health factors is a Geriatric Assessment (GA) (see ▶ Chap. 25, "Comprehensive Geriatric Assessment (CGA) for Cancer Patients"). A GA is a global evaluation of the health of older adults, comprising a multidimensional evaluation of functional status, fall history, social support, cognitive and psychologic status, sensory loss, nutritional status, and comorbidities. Emerging data suggests that use of a Geriatric Assessment (GA) aids in the clinical

Table 5 Geriatric evaluation for older patients

Domains	Common geriatric tools	Assessment and intervention(s)
Comorbidity	Hematopoietic cell transplantation-comorbidity index (HCT-CI) Geriatric syndromes	Remote cancer Urinary problems Visual or hearing impairment Cardiac dysfunction Prior renal impairment Osteoporosis Falls
Function	Instrumental activities of daily living (IADL) Timed up and go (TUG) Short physical performance battery (SPPB) Grip strength 4-meter walk Brief fatigue inventory (BFI)	Evaluation of active and passive range of motion in all extremities. Examination during weight transfer, sit to stand times, gait, posture, timed up and go, and transfers. Recommendations to promote movement, reduce pain, restore function, and prevent disability. Education on prevention of fall risk.
Social support and function	Medical outcomes study-social support survey (MOS-SSS)	Evaluation of social support and caregiver dynamics Assessment of home safety, coping abilities to deal with health status, and spiritual/cultural/religious support Evaluation of socioeconomic status and appropriate recommendations for insurance coverage, employment status, appointment transportation, lodging for appointments, prescription pick-up location, and copay costs
Cognition	Blessed memory orientation and concentration (BOMC) Mini-mental state examination (MMSE) Montreal cognitive assessment (MoCA)	Characterization of mild, moderate, or severe cognitive impairment. Evaluation for decision making capacity, risk for delirium, and life expectancy
Psychological	Geriatric depression scale (GDS) Mental health inventory (MHI) Hospital anxiety and depression scale (HADS)	Evaluation of psychological distress including depression and anxiety, quality of life expectations, and social engagement
Nutritional status	Weight loss Body mass index Mini nutritional assessment (MNA)	Evaluation of weight loss, current diet/intake, oral supplements, appetite, and any barriers to oral intake Recommendations based on each patient's caloric needs and protein intake in the form of counseling, educational material, and supportive contact
Polypharmacy	>5 medications Beers criteria	Inappropriate medication use Review of medications (prescription and nonprescription) with side effects, purpose, interactions, high risk therapeutic classes

Adapted from: Rosko and Artz (2017)

decision-making for patients with MM. Each of these evaluations aims to identify occult factors, unique to aging, that contribute to adverse events in myeloma treatment. Table 5 depicts a set of tools often employed in a cancer specific GA. GA tools are established metrics to accurately assess the risk of morbidity and mortality in cancer populations (Pal et al. 2010; Rodin and Mohile 2007). GAs have been shown to predict mortality and toxicity, independent of performance status and age in solid tumors (Hamaker et al. 2014). Given multiple treatment options for MM and concerns for frailty and tolerance in older adults, a GA is a valuable tool. The International Myeloma Working Group (IMWG) GA based on age, comorbidities, and physical function (by ADL/IADL) can predict mortality in the nontransplant eligible MM population. Furthermore, IMWG GA scores were predictive of death independent of treatment,

cytogenetics, or stage in the MM population, and were recently validated in an older real-world MM population (Palumbo et al. 2015b; Engelhardt et al. 2016). Patient comorbidities also play a role in evaluating the risk of treatment toxicity. Formal systems such as the hematopoietic cell transplantation comorbidity index (HCT-CI) is a transplant-specific modification of the Charlson comorbidity index that has been shown to correlate with OS and readmission rates but not with nonrelapse mortality (Sorror et al. 2007; Jaglowski et al. 2014; Saad et al. 2014b). Although no GA instrument has been prospectively validated in MM to delegate therapy decisions about ASCT or otherwise, these instruments are promising. MM is a disease of the elderly; with the aging of the population, risk assessment tools will become increasingly important to allocate treatment according to patient tolerability.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Hematopoiesis and Aging

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Low-Grade Lymphomas (Other than CLL/SLL) in Older Patients

35

Irene Defrancesco, Marco Frigeni, and Luca Arcaini

Contents

Abstract

The incidence of non-Hodgkin lymphomas has been progressively increasing over the last decades, especially in the elderly. Taken with an aging population, this scenario represents a growing health problem with significant implications for the care of older patients. In fact, because of comorbidities and organ dysfunctions, elderly patients are at an increased risk of therapy-related toxicity. In the setting of indolent lymphomas, even in advanced stages, there is no benefit in terms of outcome in administering early therapy. On the contrary, a "watch and wait" approach represents the standard of care, until specific treatment is indicated. In this case, an accurate evaluation could be made by the comprehensive geriatric assessment (CGA) based on age, comorbidities, and functional disabilities of daily living, which is an important tool to discriminate between fit, unfit, and frail patients.

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CGA is useful to determine the patient chance of tolerating and responding to therapy, making a whole evaluation of older patients, beyond chronological age itself. The therapeutic goal for elderly patients is to find a balance between effective therapy and related toxicity; therefore, therapy regimens used for younger patients may not be always appropriate for the elderly. When treatment is indicated and feasible, the use of rituximab in combination with chemotherapy is the standard of care in first-line treatment. Furthermore, there is a remarkable number of emerging new drugs which represent valid therapeutic options in relapsed/refractory setting and may allow a chemo-free treatment; therefore, continued participation in clinical trials which include also elderly patients should be recommended.

Keywords
Indolent lymphoma · Elderly · Geriatric oncology · Follicular lymphoma · Marginal zone lymphoma · Waldenström's macroglobulinemia

Introduction

The incidence of non-Hodgkin lymphomas (NHL) has been increasing by 1–2% annually over the past two decades in all age groups, mostly in the elderly. Among low-grade lymphomas accounting for approximately 40% of all NHL, the median age at diagnosis is 65 years with higher prevalence in males than females. This scenario, taken with an aging population, has significant implications for the care of older patients. Indolent lymphomas typically have a slow clinical course which does not always require treatment, even in advanced stages in whom a "watch and wait" (W&W) policy (close clinical monitoring) is applicable until therapy becomes indicated to control symptoms. In this case, several factors should be considered before starting a therapy in the elderly, such as comorbidities. It is essential to discuss and if necessary to adapt treatment strategies for this growing population of older patients, considering their biological characteristics and goals of treatment. Emerging new drugs show a favorable toxicity profile which makes them very attractive for older patients. In fact, these agents offer the opportunity to prevent chemotherapy-related myelotoxicity which still represents an obstacle to intensely treat elderly patients.

The comprehensive geriatric assessment (CGA) and the impact of aging on the care of older adults will be reviewed in this chapter, as well as disease incidence, diagnosis, and treatment approaches for low-grade lymphomas, particularly marginal zone lymphoma (MZL), follicular lymphoma (FL), and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (LPL/WM).

Indolent Lymphomas in Older Patients: The Impact of Age

According to the latest WHO classification of lymphoid neoplasm, indolent lymphomas are categorized in several entities (Table 1, WHO 16).

An analysis conducted by the Non-Hodgkin's Lymphoma Classification Project showed among indolent lymphomas (other than CLL) that follicular lymphoma (FL) was the most frequent, followed by marginal zone lymphoma (MZL) in older patients

Table 1 WHO classification 2016, indolent lymphomas (Swerdlow et al. 2016)

Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis[a]
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable[a]
Splenic diffuse red pulp small B-cell lymphoma[a]
Hairy cell leukemia variant[a]
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma[a]
Follicular lymphoma
In situ follicular neoplasia[a]
Duodenal-type follicular lymphoma[a]
Pediatric-type follicular lymphoma

[a]Provisional entity.

(>70 years). The same analysis showed complete remission rate (CRR) decreases with age, from 68% in young patient to 45% in the elderly (The Non-Hodgkin's Lymphoma Classification Project 1997). This difference is consistent with the results of another study (Bai et al. 2003) which showed in older patients affected by indolent NHL, the overall survival (OS) decreases with increasing age and outcome and CRR worsen compared to younger patients. This could be also due to differences in disease biology by age group: elderly patients are more likely to have a diffuse disease and a more frequent extranodal presentation (Cutter et al. 2002). It is widely recognized that age greater than 60 years is an independent pretreatment adverse prognostic factor for NHL. In order to define not arbitrarily older patients, NCCN "Older Adult Oncology" (2017) divided them into three groups:

- "Young" old patients are 65–75 years of age.
- "Old" old patients are 76–85 years of age.
- "Oldest" old patients are older than 85 years of age.

Chronological age has been mainly influencing clinicians for the therapeutic decisions: in fact many elderly patients are often left untreated, and fewer of those treated received adequate intention to treat regimen (Bairey et al. 2006). Clinicians might be inclined to prescribe less toxic and lower-dose drugs, and this attitude increases the chances of failure (Caimi et al. 2010). Poorer tolerability and feasibility of standard treatments consequently determine a lower therapeutic efficacy and less disease control.

However, chronological age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications (NCCN "Older Adult Oncology" 2017).

The Comprehensive Geriatric Assessment: A Useful Tool for Evaluating Elderly Patients

Little is still known about the prevalence of comorbidities and polypharmacy in older patients with NHL, as well as the impact on tolerability and feasibility of diagnostic and therapeutic procedures (Goede 2017). This could be related to the fact that highly aged patients are usually underrepresented in the majority of clinical trials.

An adequate clinical evaluation of older patients is a very complex issue, and it should be widely noted that chronological age itself is not enough to categorize these patients and to guide their management. The concept of *fitness status evaluation* has recently emerged as a more appropriate indicator of fitness and tolerability to chemotherapy compared to chronological age.

In evaluating newly diagnosed elderly patients, age-related factors should be considered (Table 2, Ninan and Morrison 2009).

Aging means organ and tissue functions physiologically decrease (Berkman et al. 1994) conditioning a reduced tolerability to chemotherapy. In addition, comorbidities inevitably result in pharmacokinetic and pharmacodynamic changes which could interfere with absorption, distribution, metabolism, and clearance of drugs; therefore, adverse effects could be exaggerated, and treatment efficacy could be diminished. Indeed, older patients develop major toxicities (myelotoxicity, cardiotoxicity, neurotoxicity, nephrotoxicity) more frequently than younger. Next to physiological aging, the typical polypharmacy of older patients could facilitate geriatric syndromes (Goede 2017). Moreover, it is also likely that tumor biology in the elderly is more aggressive since they manifest immune system dysfunction with a decreased both humoral- and cellular-mediated immune response (Extermann et al. 1998) (see also ▶ Chap. 10, "The Biologic Interconnections Between Aging and Lymphoma" in this book).

Table 2 Factors to be considered for the care of older patients

Poor performance status
Comorbidities
Polypharmacy and interactions with immunochemotherapeutic agents
Age-related organ damage or dysfunction
Age-related alterations in pharmacokinetics and pharmacodynamics
Alterations in immunity
Differences in disease biology by age group

In view of these considerations, a careful and complete evaluation of elderly patients affected by NHL is a central issue for a better management of this population. In fact, the assessment of patient's vulnerability is indispensable in order to offer a tailored dose-intensity therapy, depending on lymphoma-related and patient-related factors. In fact, older population is considerably heterogeneous with regard to biological age and comorbidities, so the aim of the therapy may range from curative intent to palliation. When a treatment is indicated, achieving a prolonged life expectancy with minimal toxicities should be the aim of clinicians, ensuring a good quality of life.

A whole evaluation of the elderly discriminating between fit, unfit, and frail patients could be made by using the comprehensive geriatric assessment (CGA) based on age, comorbidities, and functional disabilities of daily living (Table 3) (see also ▶ Chap. 25, "Comprehensive Geriatric Assessment (CGA) for Cancer Patients" in this book).

The multidimensional assessment of the "fitness geriatric status" includes determination of performance status (Karnofsky or ECOG), functional status (ADL, activities of daily living; Katz's scale or IADL, instrumental activities of daily living; Lawton's scale), comorbidities and their optimal control (Charlson Comorbidity Index or Cumulative Illness Rating *Scale* CIRS), cognitive state (MMSE, Mini-Mental State Examination), evaluation of nutritional status and family and social support (Geriatric Depression Scale (GDS)), and, last but not least, assessment of drugs taken for other comorbidities and possible interactions with antineoplastic treatment offered (Extermann and Hurria 2007) (see also ▶ Chaps. 21, "Drug Interactions in Aging and Cancer" and ▶ 22, "Comorbidity in Aging and Cancer" in this book). Therefore, the multidimensional geriatric assessment seems to be more functional and effective in guiding therapeutic choices compared to clinical evaluation alone.

CGA could be a useful tool to detect conditions which might interfere with treatment and to estimate expected therapy-related toxicities, providing a more accurate evaluation of residual functions than chronological age alone.

Table 3 Comprehensive geriatric assessment score. (From Tucci et al. 2015)

Scale	Fit	Unfit	Frail
Adl	6	5[a]	≤4[a]
Iadl	8	7–6[a]	≤5[a]
Cirs	0 score = 3–4 <5 score = 2	0 score = 3–4 5–8 score = 2	1 score = 3–4 >8 score = 2
Age	–	≥80 FIT	≥80 UNFIT

[a]Residual functions

Of note, to date, CGA advantages have not yet been studied in low-grade lymphomas unlike aggressive lymphomas which can benefit from well-done studies in the elderly (Tucci et al. 2009, 2015) (see also ▶ Chap. 36, "Diffuse Large B-Cell Lymphomas in Older Adults" on this book). However it would be useful to include CGA in clinical trials even in indolent lymphomas, to assess whether a less intensive treatment could be beneficial for older patients.

Diagnostic and Therapeutic Management of Elderly Patients with Low-Grade Lymphomas

The clinical onset of indolent lymphomas is usually subtle. In predominantly nodal forms, lymph node enlargement, often widespread, may be the presenting feature. Coexistence of systemic symptoms (fever, sweats, and weight loss) is uncommon; sometimes mild malaise, fatigue, or a feeling of an abdominal mass (due to retroperitoneal lymphoadenopathies or massive splenomegaly) could be the first symptoms referred by the patient. In indolent primitive extranodal lymphomas, such as MALT lymphomas, clinical picture generally depends on the involved site.

Except for MALT lymphomas, other indolent lymphomas are frequently diagnosed in advanced stage. Bone marrow infiltration is common, as well as presence in the peripheral blood, especially in splenic marginal zone lymphoma (80–90%) and, to a lesser degree, in other lymphoproliferative indolent diseases.

The clinical management of low-grade lymphomas has been elaborated in expert guidelines

(Zucca et al. 2013; Zelenetz et al. 2014; Buske et al. 2013; Dreyling et al. 2013, 2016) which discuss recommended diagnostic procedures and treatment options also in the elderly.

Diagnosis always requires histological examination on excision biopsy of involved site or, if it is difficult to obtain (e.g., abdominal bulky disease), a "core biopsy" is recommended. It is essential to require histological confirmation by a skilled expert pathologist.

NHL staging is based on a careful history and physical examination to assess the patient's general conditions (performance status according to ECOG scale), pathological presence of lymph nodes, and/or hepatosplenomegaly. Laboratory tests include blood counts with differential, indexes of systemic inflammation (ESR, fibrinogen, ferritin, alpha2-globulin, C-reactive protein), liver and kidney function, dosage of serum LDH and beta2-microglobulinemia levels (which are included in several prognostic indexes), serum immunoglobulins, and immunofixation. All patients have to be screened for hepatitis virus (HBV, HCV) and HIV which, in addition to their potential pathogenetic role, may affect treatment decisions. In the case of gastric MALT lymphoma, it is also required to test for *H. pylori* by histological and/or laboratory evaluation. Diagnostic imaging should include computed tomography (CT) scans of the neck, chest, abdomen, and other sites as appropriate. As indicated by the Lugano classification (Cheson et al. 2014), FDG-PET is now recommended at diagnosis in all patients with FDG-avid lymphomas (all histologies except small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and marginal zone lymphoma) (Barrington et al. 2014). Staging is completed in all patients with bone marrow biopsy and aspiration for flow cytometry and cytogenetic and molecular studies. Low-grade lymphomas are often diagnosed in advanced stage and leukemic; therefore, peripheral blood should be evaluated. Staging should be conducted in accordance with international guidelines, using the Ann Arbor system modified by the Lugano classification (Table 4; Cheson et al. 2014).

Table 4 Revised staging system for primary nodal lymphomas: the Lugano classification (Cheson et al. 2014)

Stage	Nodal	Extranodal
Limited		
I	One node or an adjacent group of nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	I or II by nodal extent with limited contiguous extranodal involvement
II Bulky	II as above with bulky disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm or nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extra-lymphatic involvement	Not applicable

For older adults eligible for chemotherapy, particularly anthracycline-containing regimens, it would be essential to obtain an accurate evaluation of cardiac function: it is well known anthracyclines cause short- and long-term cardiotoxicity and the risk for congestive heart failure is cumulative dose-related (Rahman et al. 2007).

As these procedures are associated with little morbidity, they are recommended for all patients regardless of age (Morrison 2007).

The therapeutic goal for elderly patients is to find a balance between effective therapy and related toxicity (Bairey et al. 2006); the best ideal therapy should also be brief and feasible in outpatient setting, guaranteeing a good quality of life. Considering the natural history of indolent lymphomas, it is justified to undertake a W&W approach even in advanced stages, since the probability for these patients of not requiring any treatment is up to 40% for those who are diagnosed at age $>$ 70 years (Ardeshna et al. 2003). W&W approach is the most suitable, especially for the elderly, without any toxicity or cost, since no survival benefit was shown with early treatment, including with rituximab (Ardeshna et al. 2010). In patients aged $>$90 years diagnosed with

indolent lymphomas, outcome is not influenced by treatment which therefore should be reserved only to symptomatic patients in order to relieve symptoms (Trebouet et al. 2013). In the presence of high tumor burden criteria or B symptoms or any other symptoms related to lymphoma (active disease defining criteria, Table 5), specific treatment indications arise.

Management of older patients remains particularly delicate due to their underlying fragility. Fit elderly patients should receive chemoimmunotherapy regimen as first-line treatment, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), or R-CVP (as R-CHOP without doxorubicin) or R-bendamustine (BR). The addition of rituximab to chemotherapy has dramatically improved OS and PFS (Hiddemann and Kneba 2005; Schulz et al. 2007). Since BR is effective and has less toxic side effects (Rummel et al. 2005), it can be considered as the preferred regimen in older fit patients and partially in unfit patients (StiL trial, Rummel et al. 2013, and BRIGHT trial, Flinn et al. 2014). BR is shown to be not inferior to R-CHOP in terms of PFS: in the overall study population, the median PFS was significantly longer after BR compared to R-CHOP (not reached versus 40.9 months with median follow-up of 45 months); within the subset of MZL, progression-free survival (PFS) was not different between the two treatments. BR was better tolerated than R-CHOP (lower rates of hematologic and extra-hematologic toxicities) but with more erythematous skin reactions (Rummel et al. 2013). These studies have made BR an attractive alternative option compared to R-CHOP in older or cardiopathic patients. However, data on tolerability and feasibility of BR or other schemes in "oldest" old patients (>85 years) with multiple or severe comorbidities are still lacking; thus, great caution should be used in this highly vulnerable group of patients when BR or any treatment scheme is offered.

In older patients who are candidates for combination therapy, international guidelines recommend primary prophylaxis of febrile neutropenia with G-CSF as this can reduce infectious complications which are frequent in this population.

Table 5 Available criteria for defining active disease. (Based on Chen et al. 2012)

GELF criteria	BNLI criteria
High tumor burden defined by at least one of the following: Involvement of >3 nodal sites, each with diameter > 3 cm Any nodal or extranodal (except spleen) tumor mass with a diameter of 7 cm Symptomatic splenomegaly Cytopenias (leukocytes $<1.0 \times 10^9$/L and/or platelets $<100 \times 10^9$/L) Leukemia ($>5.0 \times 10^9$/L malignant cells) Pleural effusion or peritoneal ascites B symptoms Elevated LDH or beta2-microglobulin level	Rapid generalized disease progression in the preceding 3 months B symptoms or pruritus Involvement of vital organs Renal or liver involvement Bone lesions Bone marrow infiltration (leukocytes $<1.0 \times 10^9$/L, platelets $<100 \times 10^9$/L and/or hemoglobin <10 g/dl)

In frail patient group, chemoimmunotherapy is not feasible; oral alkylating drugs (chlorambucil or cyclophosphamide) are usually able to control symptoms of disease in the most of cases. The combination rituximab plus chlorambucil is well tolerated by many frail patients, and this regimen improved CRR up to 89% (Martinelli et al. 2003). Fludarabine was demonstrated to be more efficacious than chlorambucil but with a greater hematological and renal toxicity (Leblond et al. 2013). Also low dose of steroid, low-dose irradiation, and best supportive care may be appropriate with the aim to relieve disease symptoms (Table 6).

There are a remarkable number of emerging new drugs for relapsed/refractory patients (such as lenalidomide, idelalisib, or ibrutinib) which may allow a chemo-free treatment. It is likely that these agents will be part of available treatment options, especially for vulnerable naive or treated patients.

Marginal Zone Lymphoma (MZL)

Approximately 50% of newly diagnosed patients have an older age, with median age at presentation around 65–70 years (Goede 2017). MZL is not a

Table 6 Different treatment options according to patient fitness. (Modified from Viardot and Buske, Springer, 2015)

Fitness	Aim of therapy	Treatment options
Fit	Curative intent	BR or R-CHOP[a]
Unfit	Control of symptoms	R-CVP, BR, R-FC[b], R-CBL, radioimmunotherapy, rituximab single agent
Frail	Control of symptoms	Chlorambucil, cyclophosphamide (orally), low-dose bendamustine, rituximab single-agent low-dose RT, low-dose steroid, supportive care

[a]Avoid anthracyclines in patients with cardiac dysfunction
[b]Avoid fludarabine in patients with renal impairment

single entity but a group of three different lymphomas (splenic MZL, nodal MZL, and extranodal MZL of mucosa-associated lymphoid tissue [MALT]), which differ from each other in biological and clinical features, diagnostic work-up, and therapeutic strategies.

Among MZL, extranodal MZL of MALT (EMZL/MALT lymphoma) is the most common (5–8% of all lymphomas), while splenic MZL (SMZL) and nodal MZL (NMZL) are less frequent (each of them accounting for <2% of all lymphomas) (Goede 2017).

Etiology of EMZL/MALT lymphoma may be driven by chronic antigen stimulation which could explain why MZL develop in the elderly in the majority of cases. Additional oncogenic events are essential for lymphoma growth and progression, until it becomes frankly malignant and eventually independent of antigenic drive (Suarez et al. 2006; Zucca and Bertoni 2016). Gastric MALT lymphoma (representing the most common EMZL) has a close association with infection by *Helicobacter pylori* (HP). Eradication of HP by a combination of antibiotic therapy and proton pump inhibitor should be the initial therapy for localized HP-positive gastric MALT lymphomas, resulting in lymphoma regression and long-term clinical control in most patients (Ferreri et al. 2012b; Dreyling et al. 2013). Other infectious agents has been associated to MZLs: Campylobacter jejuni may have a causal role for intestinal MALT lymphoma as well as Chlamydia spp. infection has been well documented in MZL of ocular adnexa, which is effectively treated with antibiotic therapy (Ferreri et al. 2012a).

According to other models of lymphomagenesis, chronic stimulation by HCV can promote development of MZL. This hypothesis is supported by the effectiveness of antiviral therapy in lymphoma eradication. A meta-analysis reports a significantly higher prevalence of HCV in NHL patients compared with controls, both in endemic areas for HCV and in those with low prevalence of this infection (Matsuo et al. 2004). MALT lymphoma in HCV-infected patients may regress after HCV eradication (Arcaini et al. 2007). Since antiviral treatment has a favorable impact on outcome of HCV-infected patients with indolent NHL, it should be offered as fist-line therapy in patients who have not the urge of an immediately cytoreductive treatment (Dreyling et al. 2013; Tarella et al. 2015).

Eradication treatment can be safely administered in older patients since it is considered uncomplicated or at least a low-risk regimen. Nevertheless, treatment efficacy might be compromised by nonadherence to therapy in the elderly because of their considerable polypharmacy or cognitive impairment (Goede 2017).

There are several clinical and biological factors defining outcome in MZL patients. However, for older patients, prognosis is influenced also by the increasing risk of death independent of MZL (especially cardiovascular causes). Therefore, prognostic factors and scores are likely to be unrepresentative in very old (>80 years) compared to moderately old (65–75 years) or young (< 60 years) patients (Goede 2017).

Immunochemotherapy represents the optimal option for fit and eligible patients with advanced-stage MZL. For frail elderly patients, a palliative care is represented by cytoreductive therapy with alkylating agents which have a benign toxicity profile, causing only mild to moderate myelosuppression.

Splenic Marginal Zone Lymphoma

SMZL diagnosis is often incidental. A frequent presenting feature of SMZL is peripheral lymphocytosis in asymptomatic patients. More rarely,

patients can be symptomatic for splenomegaly or cytopenias. In a minority of cases (approximately 20%), autoimmune manifestations can precede or accompany SMZL (autoimmune hemolytic anemia, autoimmune thrombocytopenia, acquired von Willebrand disease). These autoimmune disorders require specific treatment, in addition to lymphoma's therapy.

In the most of cases, SMZL has an indolent course not requiring therapy for a long time. A few patients (about 30%) might have a worse outcome, including transformation to more aggressive lymphoma (5–10%) (Arcaini et al. 2006; Olszewski and Castillo 2013; Conconi et al. 2015).

HCV infection in SMZL patients has been proposed as a model of infection-driven lymphoma genesis (Saadoun et al. 2005). The causal role of HCV is strongly supported by regression of lymphoma after eradicating HCV infection (Arcaini et al. 2014) with interferon-based antiviral treatment but also with new IFN-free regimens (Direct-Acting Antiviral, DAA) (Arcaini et al. 2015).

Definitive diagnosis of SMZL requires splenectomy and spleen histology; if not available, the diagnosis can be made on bone marrow histology, with cell morphology and flow cytometry in peripheral and marrow blood (Arcaini et al. 2016).

It does not exist for SMZL a specific validated prognostic index because of the paucity of patients and prospective trials in this rare disease. The Italian Lymphoma Intergroup (now Fondazione Italiana Linfomi, FIL) had already proposed a system of scoring for prognostic assessment of SMZL patients: it includes hemoglobin level $<$ 12 g/dl, elevated serum lactate dehydrogenase (LDH) level, and albumin level $<$ 3.5 g/dl. Patients can be divided into three risk groups: low risk (no adverse factors), intermediate risk (one adverse factor), and high risk (two or three adverse factors) (Arcaini et al. 2006). In a following international study, hemoglobin, platelet count, high LDH level, and extrahilar lymphadenopathy were identified as independent prognostic factors, dividing patients into three risk groups again: low risk (no adverse factor), intermediate risk (1–2 adverse factors), and high risk (3–4 adverse factors) (Montalban et al. 2012, 2014). These scores have been validated in an independent series of SMZL patients (Kalpadakis et al. 2014).

Consensus guidelines (Dreyling et al. 2013; Zelenetz et al. 2014) recommend treatment only in the presence of symptoms or progressive disease; otherwise, asymptomatic patients are candidates for a W&W strategy.

As first-line therapy, splenectomy should be offered in order to eliminate a significant amount of disease: in fact, the splenic sequestration is removed with consequent improvement of peripheral cytopenias; this also relieves symptomatic abdominal discomfort. Splenectomy allows the patient to remain free from treatment for many years (Thieblemont et al. 2002). This procedure should be contraindicated in cases with disseminated disease. Also in this case, CGA is useful to identify older patients with preexisting cognitive impairment who are at an increased risk to develop delirium after abdominal surgery (Ganai et al. 2007). Therefore, pros and cons of splenectomy should be carefully evaluated in this patient group, and preexisting comorbidities or geriatric syndromes have to be considered before offering a surgical procedure (Kavic et al. 2005).

A valid and less traumatic alternative to splenectomy is represented by rituximab single agent (Else et al. 2012) which should be offered in older patients with comorbidities or with contraindications to surgical procedure. Rituximab is minimally myelosuppressive, and therefore even very old patients can safely benefit.

In case of disseminated disease, combination regimen is considered as the standard.

Extranodal Marginal Zone Lymphoma

MALT lymphoma is the commonest MZL type, accounting for 5–8% of all B-cell lymphomas (Olszewski and Castillo 2013). The most frequently affected organ is the stomach; other non-gastric site (virtually all tissues) can be involved: salivary glands, orbits and conjunctiva, thyroid, lung, and other gastrointestinal (GI) sites.

Generally MALT lymphoma shows more often an indolent course; histological transformation is

less frequent than follicular lymphoma (below 10% in most series), also occurring as a late event, and independent of dissemination (Sagaert et al. 2006; Zucca and Bertoni 2016).

MALT lymphoma usually remains in a localized stage (often multifocal within the involved organ) for a long period of time. Non-gastric MALT lymphomas have overall a poorer prognosis than gastric localizations, although they generally maintain a low tendency to spread outside of the MALT-type sites. Nodal spread is a risk factor for the evolution into a more aggressive lymphoma.

Staging is based on CT scan and bone marrow biopsy (marrow infiltration occurring in 20% of cases). In primary gastric lymphoma, to run an eco-endoscopic examination which would allow an accurate assessment of infiltration degree in gastric wall is recommended. This procedure can also detect any involvement of adjacent lymph nodes (usually underestimated by other investigations) which constitutes a risk factor for the spread of lymphoma (Zucca et al. 2003).

In localized MALT lymphoma, radiation therapy may be the favored choice, also for infected patients who do not achieve a lymphoma regression following eradication therapy (Dreyling et al. 2013). Radiotherapy is not free from side effects: local toxicity is possible, but in the majority of older patients, radiotherapy is well tolerated in a similar way of younger patients (Goede 2017).

For patients with disseminated disease, there is still no clear consensus about the treatment: careful observation could be an adequate initial approach. When treatment is required, rituximab plus chemotherapy may represent the most appropriate choice, as in the other indolent NHL (Dreyling et al. 2013).

Nodal Marginal Zone Lymphoma

NMZL is a rare disease accounting for <2% of all NHL. The median age at diagnosis is lower than the other types of MZL ranging from 50 to 65 years. In the most of cases, NMZL is disseminated with nodal (usually non-bulky) and peripheral involvement. Bone marrow infiltration is present in about one third of patients, while leukemic and cytopenias are rare (Thieblemont et al. 2016). Clinical outcome is generally inferior to the other MZL. Treatment is based on the same principles used for follicular lymphoma. For localized disease, radiotherapy is the standard; in cases of low tumor burden, a watchful waiting approach is indicated, while disseminated disease requires immunochemotherapy as appropriate option.

Follicular Lymphoma

Follicular lymphoma (FL) is the commonest subtype of low-grade lymphomas, accounting for approximately 25–30% of all newly diagnosed NHL (Harris et al. 1994). The median age at diagnosis is slightly higher than 50 years which is slightly lower compared to that of other indolent lymphomas. Incidence is higher in patients older than 75 years (Smith et al. 2011).

As reported by recent international guidelines (Zelenetz et al. 2014; Dreyling et al. 2016), FL is an indolent but incurable disease which is likely to shift into an aggressive phenotype in about 15–20% of cases. Morphologically, FL is divided into three grades: 1, 2, and 3A grades behave in a more indolent manner, while grade 3B behaves more clinically aggressive, whose recommended therapy is similar to that of diffuse large B-cell lymphoma. Staging is completed in FL by whole-body FDG-PET, which sometimes upstages disease showing extranodal or occult localization. FDG-PET does not have high sensitivity for detection of bone marrow infiltration; therefore, bone marrow biopsy and aspiration for flow cytometry is always indicated. If needed, it could be added molecular studies to detect the presence (or persistence after therapy) of cells with bcl2-IgH rearrangement or t(14;18) using RQ-PCR or cytogenetic analysis, respectively.

Prognosis of FL remains heterogeneous. Once again, age over 60 years is a predictor of decreased survival. The Follicular Lymphoma International Prognostic Index (FLIPI), established in 2004 (Solal-Céligny et al. 2004), divides patients into three risk groups according to five parameters (age greater than 60 years, Ann Arbor stage III or IV, elevated serum LDH level, hemoglobin <12 g/dl, >4 nodal sites involved).

However, FLIPI was made in pre-rituximab era on retrospective data. More recently, in the rituximab era, a revised FLIPI-2 was introduced (Federico et al. 2009). This score includes five parameters: age greater than 60 years was confirmed as prognostic factor together with hemoglobin value less than 12 g/dl; increased level of beta2-microglobulin, diameter of largest lymph node, and bone marrow involvement were introduced as new prognostic factors.

Treatment of follicular lymphoma depends mainly on disease stage, and it is not guided by FLIPI and FLIPI-2. For localized stages (I–II, without bulky disease, accounting for 15–20%), treatment of choice is involved-field radiation therapy (IFRT) alone (24 Gy is indicated to obtain a curative intent; 2x2 Gy has mainly a palliative effect). IFRT allows to achieve long-term disease-free survival in about 45% of patients (Peterson et al. 2004). However, patients with low life expectancy, with severe comorbidities, or with contraindications to radiotherapy are candidates for a "W&W" policy or rituximab single agent.

For advanced stages (III, IV, or II with bulky disease), with high tumor burden or with symptoms, rituximab plus chemotherapy is considered the standard. Anyway, the choice of chemotherapy regimen should be made taking into account several factors, including age, comorbidities, and patient's will (Castellino et al. 2017). Frail elderly patients may be treated with alkylating agents for palliative intent, as in other indolent lymphomas.

Patients responding to first-line combination treatment are candidates for maintenance therapy with rituximab, which was shown to improve progression-free survival (PFS) compared to observation strategy (75% vs. 58% after 3 years) (Seymour et al. 2013; Taverna et al. 2013). Rituximab maintenance improves duration of response both in first line and in relapse setting (Salles et al. 2011), regardless of induction therapy scheme. Rituximab maintenance is able to maintain response with minimal toxicity and preserve quality of life.

The efficacy of rituximab maintenance in older patients with advanced follicular lymphoma responding to brief first-line chemoimmunotherapy has been evaluated in a clinical trial designed by Fondazione Italiana Linfomi (FIL) (Vitolo et al. 2013). This trial compared rituximab maintenance to no further treatment in elderly patients with advanced FL who had responded to a brief first-line treatment (four courses of R-FND) followed by 4 weekly doses of rituximab consolidation. This therapy scheme achieved excellent results with high complete response rate (CRR) and PFS, supporting the feasibility of this anthracycline-containing regimen in patients older than 60 years and also in those with comorbidities. No differences between the two arms were detected by OS.

Another treatment option is radioimmunotherapy with 90Y-ibritumomab tiuxetan (Zevalin), an anti-CD20 antibody conjugated with a radionuclide, recommended as consolidation therapy (Morschhauser et al. 2008). Despite its prolonged myelotoxicity which requires close monitoring especially between 4 and 8 weeks after treatment, Zevalin would remain a valid alternative option in patients not eligible for high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) such as elderly patients (Castellino et al. 2017).

At relapse a new biopsy is indicated, in order to exclude histological shift into more aggressive lymphoma. For elderly patients, options are a further period of "W&W" if disease relapses with low tumor burden and/or the patient is asymptomatic, second-line immunochemotherapy if feasible and lymphoma has high tumor burden, or palliative care if the patient is not a candidate for curative treatment. Rituximab should be added to salvage therapy if the duration of remission after first-line treatment has been longer than 6–12 months (Dreyling et al. 2016). In rituximab-refractory cases, obinutuzumab (an anti-CD20 antibody of second generation) plus bendamustine or CHOP demonstrated improved PFS compared to chemotherapy alone (GADOLIN trial, Sehn et al. 2016, GAUDI' trial, Radford et al. 2013).

Novel drugs are available in monotherapy or in association with chemotherapy; idelalisib (PI3K inhibitor) could be used in double refractory FL based on a phase II study (Gopal et al. 2014).

Lenalidomide single agent or in association with chemotherapy or rituximab showed high activity in FL and other indolent NHL (Fowler et al. 2014).

Lymphoplasmacytic Lymphoma and Waldenström's Macroglobulinemia

Lymphoplasmacytic lymphoma (LPL) is a rare lymphoproliferative disorder which occurs more frequently in older adults and is characterized in most of cases by the presence of a serum paraprotein associated with bone marrow infiltration by lymphoplasmacytic cells. LPL associated with serum IgM paraprotein is called Waldenström's macroglobulinemia (WM).

According to international guidelines (Buske et al. 2013), LPL/WM constitutes less than 5% of all NHL. It generally has an indolent clinical course responding to treatment, although over time, it may become refractory to chemotherapy and transform into an aggressive form. Spread to nodal and/or hepatosplenic sites is present in about a quarter of patients (15–20%), while extranodal involvement and leukemic phase are uncommon (Treon 2015). Patients could have signs and/or symptoms attributable to tumor infiltration such as cytopenias and/or to monoclonal paraprotein (hyperviscosity, cryoglobulinemia, cold agglutinin disease, neuropathy, amyloidosis).

Hyperviscosity is a central feature in WM patients, due to large size of IgM molecules and their high levels which make peripheral blood more viscous, with consequent slower transit time through capillaries (Gertz and Kyle 1995). Hyperviscosity syndrome is a clinical indication for immediate plasma exchange, regardless of IgM entity. Most commonly symptoms are represented by bleeding, less frequently by dizziness, headache, vertigo, hearing loss, paresthesias, or diplopia. Neurological deficits are not specific, ranging from confusion to dementia-like syndrome, making them difficult to recognize especially in the elderly. Neurological symptoms could also be the sign of central nervous system infiltration by the disease (Bing-Neel syndrome).

As for other indolent lymphomas, "W&W" policy is the standard approach to LPL in patients without symptoms. LPL/WM has a long natural history, and affected patients are often elderly with coexisting medical problems. The mainstay of therapy is based again on rituximab-chemotherapy combination or on the use of bortezomib (Viardot and Buske 2015). Another approach in older patients is the DRC regimen, which consists of dexamethasone, oral cyclophosphamide, and rituximab: this scheme was shown to be highly effective in treatment-naïve WM patients, with low toxicity (Dimopoulos et al. 2007). Rituximab single agent is effective, but time to response is slow and can cause a critical increase in IgM serum levels triggering hyperviscosity syndrome which requires urgent plasmapheresis (Treon et al. 2004).

New drugs acting on the BCR signaling pathway have been tested in WM since MYD88 mutations represent the most studied pathogenetic event in the majority of MW cases (Treon et al. 2012): both ibrutinib (Btk inhibitor) and idelalisib (PI3k inhibitor) are effective in patients with WM. Ibrutinib, administered as monotherapy (420 mg/die) in 63 previously treated WM patients, resulted in an overall response rate (ORR) higher than 73% and PFS at 2 years of 70%. Ibrutinib has shown to be effective in 100% of MYD88-mutated patients with a benign and manageable toxicity profile (Treon et al. 2015; Dimopoulos et al. 2017). Experiences with idelalisib in the relapsed setting are lower, but results seem to be hopeful (ORR 80%, median PFS of 22 months in a study of Gopal et al. 2014).

Conclusions

The incidence of NHL has been progressively increasing, especially in older adults, together with a steady increase of median age population. The treatment of elderly patients affected by low-grade lymphomas still remains a challenge which could be faced with integrating multidisciplinary care.

Chronological age by itself is not sufficient to guide treatment in these patients. CGA could be a useful tool in order to improve assessment of patient's vulnerability and to guide the choice of the most appropriate treatment for each individual patient. In fit older patient, regimens commonly used for younger patients are feasible. However, curative intent is not generally applicable for the most of elderly patients with NHL. For this remaining population, it would be necessary to guarantee high quality of care and a good quality of life with minimal treatment-related toxicity. In this challenging clinical setting, novel drugs are promising to obtain patient-targeted treatment, with a better tolerability and potentially a better effectiveness. In the near future, new drugs might provide for an oral chemo-free treatment, especially for vulnerable treated patients. Therefore, continued participation in clinical trials which include elderly patients should be recommended.

Cross-References

- Comorbidity in Aging and Cancer
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Diffuse Large B-Cell Lymphomas in Older Adults
- Drug interactions in Aging and Cancer
- The Biologic Interconnections Between Aging and Lymphoma

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Diffuse Large B-Cell Lymphomas in Older Adults

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Contents

Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in the elderly and is increasing in incidence. Although significant therapeutic advances have recently been made in the care of older DLBCL patients, based upon results of randomized clinical trials, many older patients are not eligible for such trials due to comorbidities and functional decline. Pretreatment evaluation of older patients to ascertain potential tolerance to therapy is especially important in therapeutic decisions for this population. Evaluation by performance status alone is insufficient, especially in the elderly, and consideration of the impact of comorbidities and functional/social decline needs to be included in such assessment. In this chapter, we will review approaches to therapy of the older patients with DLBCL, including initial treatment, role of maintenance therapy, use of combined modality therapy

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for limited stage disease, and strategies for the relapsed/refractory older patient. We will also address the issues of prognosis, comorbidities, geriatric assessment, supportive care measures in older patients with DLBCL, and recommendations for assessment and allied care.

Keywords
Diffuse large B-cell lymphoma · Non-Hodgkin lymphoma · Elderly · Therapy · Prognosis · Geriatric assessment

Introduction

Non-Hodgkin's lymphoma (NHL) is common in the elderly, with median age at diagnosis of 67 years. The incidence of this malignancy has been increasing, especially in patients >60 years of age (Thieblemont and Coiffier 2007; Howlader et al. 2012; Smith et al. 2011). Diffuse large B-cell NHL (DLBCL) is the most common NHL subtype in the elderly, with prognosis being poorer than in younger patients (Thieblemont and Coiffier 2007). Although significant therapeutic advances have been made in the past two decades for older DLBCL patients, standard therapies are complicated by comorbidities and preexistent alterations in functional status. In this chapter, we will review prognosis, impact of comorbidities, role of geriatric assessment, approaches to therapy in the treatment-naive and salvage settings, and supportive care measures for older DLBCL patients.

Demographics and Staging in Older DLBCL Patients

More elderly than younger patients are diagnosed with DLBCL (Thieblemont and Coiffier 2007). Incidence rates increase with older age, being approximately 30/100,000 per year in patients >65–70 years of age (Howlader et al. 2012; Smith et al. 2011). Median age at DLBCL diagnosis is between 70 and 75 years; approximately half the cases occur in patients ≥65 years of age, and 40% in those older than 70 years (Smith et al. 2011; Sarkozy and Coiffier 2013). The incidence is higher in men than women, approaching 2:1 in the elderly. Age at diagnosis has been shown to be a major prognostic factor in registry studies (Howlader et al. 2012; Monnereau et al. 2013; Sant et al. 2008; Marcos-Gragera et al. 2011). Net survival (NS) is survival that would be observed if cancer was the only possible cause of death and represents an indicator in population studies. In one series, 5-year NS was 47% (95% CI: 45–49), with a 40-fold decrease in 5- and 10-year NS in males >75 years of age (Monnereau et al. 2013). Among the oldest males (i.e., 65–75, versus >75 years), 5-year NS dropped from 45% (95% CI: 40–50) to 26% (95% CI: 22–31).

Histologic classification of NHL has evolved from the International Working Formulation (IWF) in 1982, to the 1994 REAL (Revised European American Lymphoma) schema, followed by the 2001 World Health Organization (WHO) classification (updated in 2008), which includes morphologic, immunophenotypic, genetic, and clinical aspects (The Non-Hodgkin's Lymphoma Pathologic Classification Project 1982; Harris et al. 1994; Jaffe 2009). Diagnostic material should be submitted for histologic, immunophenotypic, immunohistochemical, cytogenetic, and molecular analysis. Recommendations for initial evaluation, staging, and response assessment of NHL have recently been updated (Cheson et al. 2014). Although division into limited (I–II) and advanced (III–IV) stage disease remains, suffixes A and B for symptoms will no longer be used. Staging evaluation should include physical examination, complete blood count with differential, lactic dehydrogenase (LDH), hepatitis B/C serologies, CT scans of chest, abdomen, and other sites as appropriate and functional imaging with PET scan, which is more sensitive in extranodal disease sites. For elderly patients in whom scans are not feasible, CXR and abdominal ultrasound may be substituted. Bone marrow biopsy is no longer indicated for routine staging. Cerebrospinal fluid cytology may be assessed in patients at high risk of central nervous system involvement. Baseline determination of cardiac ejection fraction is necessary prior to anthracycline-based therapy.

Prognostic Factors

DLBCL is a heterogeneous disease with regard to prognosis, clinical features, and treatment outcome, related to a variety of molecular pathways and pathogenic mechanisms involved in oncogenesis. Clinical risk factors as well as biomarkers may be utilized to refine prognostication (Table 1). Adverse disease subtypes as immunoblastic morphology, activated B-cell (ABC) subtype, and Epstein Barr virus-positive DLBCL are overrepresented in elderly patients (Pfreundschuh 2010; Hofscheier et al. 2011).

Clinical Prognostic Models The International Prognostic Model (IPI) was derived and validated in the pre-rituximab era from patients receiving anthracycline-based chemotherapy (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993). Adverse prognostic factors identified included age > 60 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, stage III/IV disease, more than one extranodal disease site, and elevated lactate dehydrogenase (LDH). Four prognostic risk groups were defined (low, low intermediate, high intermediate, high) with 5-year survival rates of 73%, 51%, 43%, and 26%, respectively. The age-adjusted IPI has been used in elderly patients. The utility of the IPI in the rituximab /R-CHOP era was examined in several series (Sehn et al. 2007; Ziepert et al. 2010; Advani et al. 2010). In a British Columbia registry series (median age 61 years) with a revised-IPI (R-IPI) scoring system, three prognostic groups (very good, good, poor, risk) were identified, with 4-year survival rates of 94%, 79%, and 55%, respectively (Sehn et al. 2007). In another analysis of 1062 patients receiving rituximab-based chemotherapy in three prospective trials, the IPI retained significance for event-free (EFS), progression-free (PFS), and overall survival (OS) (Ziepert et al. 2010). The addition of rituximab significantly improved outcome within each IPI subgroup. The Elderly-International Prognostic Model (E-IPI), utilizing an age cutoff of 70 years, classified more patients as low risk as compared to prior prognostic classifications and found significant differences in FFS and OS in low-intermediate, as compared with low, risk patients (Advani et al. 2010). In a more recent report with a 70 year age cutoff, among factors as albumin, lymphocyte count, gender, IgG level, bulky disease, hemoglobin, and B-symptoms, only albumin was prognostic (Gang et al. 2015). This group proposed a modified prognostic index (DLBCL-PI) including age (70 years), PS, LDH, and albumin eliminating extranodal disease site(s) as a factor. For patients <70 years of age, the DLBCL-PI included PS, LDH, albumin, and more than one extranodal disease site, excluding stage. An accompanying editorial concluded that an age cutoff of 70 years is most appropriate at present (Mikhaeel 2015). Lastly, in a prospective cohort study, pretreatment quality of life was predictive of survival in R-CHOP-treated patients (Jung et al. 2012).

Table 1 Prognostic factors for outcome in older DLBCL patients

Clinical factors (age-adjusted International Prognostic Index)
Performance status
Advanced stage disease
>1 extranodal disease site
Elevated LDH
Histologic features
Immunoblastic morphology
Epstein Barr virus-positive variants
Gene expression profile
Germinal center B-cell, activated B-cell subtypes
Stromal-1, stromal-2 signatures
Markers of:
Apoptosis (BCL2, survivin, Fas)
Cell cycle regulation (p53)
Cellular proliferation (Ki-67)
B-cell differentiation (BCL6, FOXP1)
Angiogenesis (HIF-1α, VEGFR2)

Biomarkers, Gene Expression, and Immunohistochemical Prognostic Factors Lymphoma biomarkers most extensively studied include genes and protein products involved in apoptosis (BCL2, survivin, Fas), cell-cycle regulation (p53), cellular proliferation (Ki-67), B-cell differentiation (BCL6, FOXP1), and angiogenesis (HIF-1α and VEGFR2) (Wilson et al. 2007; Mounier et al. 2003; Adida et al. 2000; Hara et al. 2009; Xu-Monette et al. 2012; Miller et al. 1994;

Jerkeman et al. 2004; Winter et al. 2006; Barrans et al. 2004; Evens et al. 2010; Gratzinger et al. 2010). MYC gene rearrangements and MYC protein overexpression are associated with inferior outcome, as are the "double-hit lymphomas" involving aberrations of MYC and/or BCL2 and BCL6 (Savage et al. 2009; Horn et al. 2013; Vaidya and Witzig 2014).

Gene expression studies have identified the germinal center B-cell (GCB) and activated B-cell (ABC) DLBCL subtypes (Alizadeh et al. 2000; Rosenwald et al. 2002; Lenz et al. 2008a). In patients >80 years of age, 60–70% of DLBCL are of the ABC subtype (Lenz et al. 2008b; Mareschal et al. 2011; Fontan et al. 2012). Patients with the GCB compared to ABC subtype have a significantly better prognosis (5-year survival of 76% versus 16%) with anthracycline-based therapy. Another study identified three molecular signatures (germinal center B-cell [GCB], stromal-1, stromal-2 signatures) with tumor microenvironment correlation (Lenz et al. 2008b). The stromal-1 signature, characterized by genes associated with connective tissue growth factor and monocyte/macrophage lineage, correlated with significantly better prognosis compared to the stromal-2 signature, which was associated with genes involved in angiogenesis. Immunohistochemical (IHC) studies on paraffin-embedded tissue are more readily available and have been utilized as surrogates for gene expression (Choi et al. 2009; Copie-Bergman et al. 2009). However, there is no consensus of the optimal prognostic IHC panel in rituximab-treated patients.

Comorbidities in Elderly Patients

Comorbid conditions in the elderly are common, being present in >60% of patients older than 70 years (Janssen-Heijnen et al. 2005). With older age, hematopoietic reserve may be limited, with therapy-related myelotoxicity being more common. Drug pharmacokinetics and pharmacodynamics may also be altered in older patients. Delivery of therapy can be impacted, as well as disease outcome (Janssen-Heijnen et al. 2005). Subsequent dose reductions can result in lower dose intensity and a higher rate of treatment failure (Gomez et al. 1998). Assessment of end-organ dysfunction is critical to guide physicians in cancer therapy dosing. When the comorbidity index of the National Institute of Aging/National Cancer Institute was applied in a Netherlands population study of aggressive lymphoma patients, it was found that high-impact comorbidity doubled the risk of death, independent of the IPI (Janssen-Heijnen et al. 2005; Yancik et al. 1998). The Cumulative Illness Rating Scale (CIRS) has been employed in the EORTC trials to assess comorbidity, being part of the functional definition of frailty. Charlson et al. determined that number and severity of comorbid illnesses can predict survival in general medical patients admitted to an inpatient unit (Charlson et al. 1987). In a study of older cancer patients, it was found that functional status and comorbidity were independent, necessitating separate assessment for each (Extermann et al. 1998). Measures as Karnofsky score (KPS) and PS may not address geriatric issues as polypharmacy, social support, ability to use the telephone, and depression, which can predict survival in older patients. Currently available functional scales include self-reported measures as ability to complete activities of daily living (ADL) and instrumental (I-)ADL, as well as performance-based tests as get up and go and gait speed. Polypharmacy, with issues of potential drug interactions and compliance, is common in elderly patients with comorbidities. Comorbidities may also preclude clinical trial enrollment of elderly patients. In one study of older NHL patients, there were no significant differences in baseline demographics and lymphoma characteristics among patients aged 60–74 and those >75 years, except for PS (Lim et al. 2008). In multivariate analysis, lymphoma histology, PS, and stage were predictive for survival in patients <75 years of age. Among patients age ≥ 75 years, only PS was prognostic for survival. Thus PS, comorbidity, and functional status need to be independently assessed.

The impact of comorbidity in treatment planning and prognosis was examined in a retrospective review of 140 DLBCL patients >70 years of age (Sonnen et al. 2002). Treatment outcomes

were related to IPI risk stratification. The most common comorbidities were peripheral neuropathy and cardiovascular and diabetic complications. Lymphoma was the cause of death in 76% of patients. The Eindhoven Cancer Registry was examined to determine severity of comorbidity among older patients (median, 64 years) in the Netherlands (Janssen-Heijnen et al. 2005). In aggressive NHL patients, comorbidities were present in 48% of those <60 years of age and 78% of older patients. The likelihood of receiving chemotherapy for patients >60 years of age was only a third that of younger patients ($p = 0.05$). Among patients with cardiovascular comorbidity, the likelihood of receiving chemotherapy was only 40% compared to those without such comorbidity ($p = 0.04$). Likewise, receipt of CHOP-like chemotherapy was 40% for those >60 years of age compared with younger patients, after adjustment for gender, stage, and severity of comorbidity. Dose reductions were not more common in the elderly and did not occur more frequently among patients with high impact comorbidity. Hematologic toxicity was the most common reason for dose reduction. There was no difference in spectrum and incidence of toxicity comparing older and younger patients. Severity of comorbidity had no significant impact on toxicity occurrence, except for patients with cardiovascular comorbidity. In aggressive NHL, 3-year crude survival was 62% for patients age 40–60 years, and 41% for those >60 years. Survival decreased significantly with increasing IPI risk score and was significantly lower for patients with high-impact comorbidity.

With regard to cardiovascular comorbidity, certain agents as the anthracyclines have potential cardiotoxicities, including QT prolongation, myocardial ischemia, and congestive heart failure (CHF) (Aapro et al. 2011). In a Surveillance, Epidemiology, and End Results (SEER) Medicare database study, any doxorubicin use was associated with a 29% risk of CHF (Hershman et al. 2008). CHF risk increased with number of doxorubicin claims, increasing age, prior heart disease, comorbidities, diabetes, and hypertension. Patients with prior heart disease were less likely to receive doxorubicin. Those with hypertension and diabetes had 58% and 27% greater risks of developing CHF. Advanced age was predictive both for withholding doxorubicin and subsequent CHF. Those >80 years had more than twice the CHF risk as patients 65–70 years of age. In a recent publication, treatment-naïve DLBCL patients (median age 65 years) were randomized to initial therapy with R-CHOP or the same regimen with non-pegylated liposomal (NPL) doxorubicin substituted for doxorubicin (Fridrik et al. 2016). In patients with normal cardiac function, six cycles of R-CHOP had low rates of cardiotoxicity, and NPL-doxorubicin did not reduce cardiotoxicity. Screening evaluation of patients to receive cardiotoxic drugs should include assessment of risk factors as hypertension, atherosclerotic cardiovascular disease, diabetes, CHF, prior exposure to cardiotoxic drugs or thoracic radiation, and baseline electrocardiogram and either echocardiogram or MUGA scan (Eschenhagen et al. 2011). Cumulative upper doses of anthracyclines should not be exceeded (i.e., 400–450 mg/m^2 for doxorubicin; 140 mg/m^2 for mitoxantrone), and cardiac function should be serially monitored. The utility of troponins or brain natriuretic peptide for prediction and monitoring of cardiotoxicity is not clear. Potential cardiotoxicity of novel targeted agents should also be considered. In another single institution analysis of patients ≥80 years of age, 87% had at least one comorbidity, with cardiovascular disease being most common (Thieblemont et al. 2008). Stratification of patients by Charlson comorbidity index (CCI) was 0 (13.7%), 1–2 (36.6%), 3–4 (33.7%), and >4 (15.1%). Anthracycline-based therapy was administered in 32% of aggressive lymphoma patients. Lymphoma was the predominant cause of death (57.5%), with comorbidity accounting for 13.7%.

Renal dysfunction is common in the elderly and impacts choice of therapeutic agents (Nabhan et al. 2012). Recommendations for chemotherapy dosing of older patients with renal insufficiency have been published as an International Society of Geriatric Oncology (SIOG) task force guideline (Lichtman et al. 2007; Launay-Vacher et al. 2007). Additional study is needed to determine which of the available creatinine clearance

formulae (modification of diet in renal disease (MDRD), Cockcroft-Gault) is most accurate in older patients (Marx et al. 2004). Evaluation of renal function in extreme obesity or cachexia is often not valid. Most drugs utilized for DLBCL therapy as cyclophosphamide, vincristine, doxorubicin, and bendamustine have limited renal elimination, thus dose adjustments are not necessary. Nephrotoxicity of platinum derivatives limits their usage. Appropriate hydration is warranted.

Chemotherapy-induced peripheral neuropathy (CIPN) is a potential toxicity of several drugs utilized for DLBCL therapy, as platinum derivatives, taxanes, vinca alkaloids, and lenalidomide. Monitoring of neuropathy and hearing loss are recommended. There are no age-specific guidelines for dose reduction of these agents in the elderly/frail. The occurrence of CIPN is influenced by cumulative dose, co-administration of neurotoxic drugs, and presence of predisposing factors as diabetes or alcohol abuse. No agents have proven effectiveness in prevention of CIPN (Argyriou et al. 2012).

Dementia is also a significant issue in oncology care (Lichtman 2006; Extermann 2005). Cognitively impaired patients have markedly reduced survival compared to nonimpaired patients (Wolfson et al. 2001). In a SEER colon cancer database review, patients with dementia are significantly less likely to have undergone histologic diagnosis, be offered surgical resection, or adjuvant chemotherapy. The risk of toxicities that can cause delirium, as diarrhea, dehydration, or fever, is higher in impaired patients. Elective surgery is markedly preferred to emergency surgery in such patients, with improved outcome including markedly decreased mortality (Kemeny 2004).

Comprehensive Geriatric Assessment and Measures of Frailty

A multidimensional approach to geriatric assessment, incorporating functional capacities, comorbidities, cognitive function, social support, emotional status/depression, nutritional status, and polypharmacy, is important to assess biological-physiologic age, which is more important than chronological age in choosing treatment regimens and predicting tolerance to therapies. Measures as KPS/PS, ADL, and IADL are limited in scope and ability to assess multiple domains, subjective, and not good predictors in the elderly. The comprehensive geriatric assessment (CGA) is a fundamental tool in care of geriatric patients, with components of including functional assessment, comorbidities, nutritional status, cognitive function, psychological state, social support, and medication review (Table 2). Incorporation of the CGA into oncology practice has been limited by logistic and resource constraints. Hurria et al. has developed a CGA that is self-administered and feasible in the outpatient setting, with assessment across multiple domains (Hurria et al. 2011). This tool is currently being validated in both a larger prospective study and the oncology cooperative group setting. In utilizing components of CGA to better assess PS, Siegel et al. selected three functional tests validated in older populations and readily applicable in clinic, specifically "timed up and go," hand grip, and "Tinetti gait and balance test," to improve functional status assessment (Siegel et al. 2006). Screening tools, as the vulnerable elders survey (VES-13), to identify those at-risk individuals in need of more formal CGA, require prospective oncologic validation. A SIOG task force concluded that although CGA should be utilized for elderly oncology patients, a specific CGA tool cannot be recommended given available data (Extermann et al. 2005).

Table 2 Components of a comprehensive geriatric assessment

Performance status
Assessment of activities of daily living (ADL), instrumental ADL (IADL)
Comorbidities
Functional assessment
Fitness/frailty
Nutritional status
Cognitive function
Psychological state
Social support
Polypharmacy

An abbreviated geriatric assessment has been used in some NHL series. Winkelmann et al. evaluated 143 patients, median age 63 years (29% ≥70 years), and found that comorbidity and dependence in IADL were associated with overall survival, irrespective of lymphoma subtype or therapy (Winkelmann et al. 2011). Tucci et al. evaluated patients age ≥ 65 years with CGA prior to therapy, with following treatment decisions for aggressive or palliative therapy made solely by clinical judgment (Tucci et al. 2009). As CGA was able to differentiate fit versus unfit patients better than clinical judgment, they concluded that CGA is an appropriate measure to identify patients that can receive anthracycline-based therapy. In another series, doses of rituximab-based combination chemotherapy in elderly patients were adjusted based upon a modified CGA, reflecting comorbidities and activities of daily living (ADL) and instrumental IADL scores (Spina et al. 2012). More recent reports in DLBCL patients at least 70 years of age, in which measures as ADL, IADL, mini mental state examination, mini nutritional assessment, and cumulative illness rating scale were employed, found that underperformance in geriatric assessment was associated with increased mortality rates (Aaldriks et al. 2015; Tucci et al. 2015; Goede and Schulz 2015). Some, but not all, mortality was lymphoma-related, complicating these findings. Such algorithms should ideally reflect treatment feasibility and adherence, as well as the mortality endpoint, for more useful application in prospective treatment decisions.

Although there is no single definition of frailty, suggested criteria include age > 85 years, dependence in ADL, exhaustion, slow gait speed, decreased hand grip, unintentional weight loss, and decreased physical activity. These patients may have an increased incidence and severity of therapy-related toxicities, shortened survival, and may be candidates for supportive care. However, further delineation of frailty is needed, such that patients who still have remaining functional reserve are not withheld from active treatment (Balducci 2007, 2009; Balducci and Beghe 2000; Fried et al. 2001). Data has been reported from an elderly DLBCL series in which CGA identified 99 frail patients who received a variety of treatment regimens (Merli et al. 2014). Age-adjusted IPI of 2–3 and respiratory comorbidity were the only factors predictive for OS, with 5-year OS of 28%. Outcome in frail patients was poorer with rituximab-containing therapy than in fit patients.

Supportive Care Issues in the Elderly

The occurrence of chemotherapy-related toxicities has been reported from series specifically in older adults (Hurria et al. 2011; Extermann et al. 2012). A 53% incidence of grade 3–5 toxicities was reported in a series of 500 patients (mean age 73 years) receiving solid tumor chemotherapy, with pretreatment assessment including CGA, disease, laboratory, therapy-related parameters, and sociodemographics (Hurria et al. 2011). Using these pretreatment variables, a three-tiered risk-scoring system predictive of toxicity occurrence was developed. From a series of 518 patients ≥70 years planned to receive chemotherapy, a CRASH (chemotherapy risk assessment scale for high-age patients) score was prospectively developed (Extermann et al. 2012). These multidimensional risk assessment tools are useful in pretreatment evaluation of older patients, to guide dose adjustment and supportive care measures.

Older patients are at greater risk of febrile neutropenia (FN) and FN hospitalization, with its resultant increased morbidity, mortality, length of stay, and cost (Kuderer et al. 2006; Chrischilles et al. 2005). Risk is greatest in early chemotherapy cycles, with consideration of supportive care measures being warranted (Lyman et al. 2011; Balducci and Repetto 2004). Treatment outcomes may also be impacted upon by subsequent dose reductions (Lyman et al. 2011; Lyman and Delgado 2003). In one study, 17% of patients had at least one FN hospitalization, and more than 50% such hospitalizations occurred in cycles 1 or 2 of therapy. Increased risk of FN hospitalization was associated with the following baseline characteristics: age ≥ 65 years, serum albumin ≤3.5 g/dL, planned average relative dose

intensity ≥80%, baseline absolute neutrophil count (ANC) <1500/mm3, and presence of hepatic disease. Lack of early myeloid growth factor usage in Cycles 1 and 2 was also associated with a trend for increased risk of FN hospitalization. A composite risk score delineated patients at greater risk of FN hospitalization, including age > 65 years, hepatic dysfunction, renal insufficiency, and receipt of prior chemotherapy.

An Oncology Practice Pattern Study reviewed records of predominantly community-based intermediate-grade lymphoma patients receiving initial CHOP chemotherapy, and identified in multivariate analysis the following factors associated with time to first FN event: age ≥ 65 years, cardiovascular disease, renal disease, baseline hemoglobin <12 g/dl, >80% planned average relative dose intensity (ARDI), and no prophylactic myeloid growth factor use. (Lyman et al. 2003). Among patients having an FN event, half had initial occurrences by day 14 of cycle 1 of therapy. In a following study of treatment-naive elderly patients randomized to CHOP or R-CHOP therapy on the US intergroup trial, one or more FN episodes occurred in 41% of patients, with FN most often in cycle 1 (38% of events) (Morrison et al. 2017). In multivariate analysis, risk factors for FN included age > 65 years and anemia (hemoglobin <12 g/dl). Another large observational study of 1113 DLBCL receiving R-CHOP-14 OR -21 therapy reported higher FN rates in those patients ≥65 years of age, and poor adherence to FN guidelines in high risk patients (Lugtenburg et al. 2012). Models as these can be prospectively used to identify patients at greatest risk of FN and for whom prophylactic myeloid growth factor usage is best utilized.

Guidelines for myeloid growth factor usage have been developed. The European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend that adverse FN risk factors, including age ≥ 65 years, be assessed prior to each treatment cycle (Aapro et al. 2006). When using regimens associated with ≥20% FN risk or dose-dense regimens, prophylactic myeloid growth factor use is recommended. When using regimens associated with 10–20% FN risk, particular attention should be given to patient-related factors that may increase such risk. Also, if reductions in dose intensity are associated with poorer prognosis, primary myeloid growth factor prophylaxis may be used to maintain full-dose therapy. According to the American Society of Clinical Oncology (ASCO) guidelines, myeloid growth factor use is likewise recommended when the FN risk is ≥20% and no other comparably effective regimen not requiring myeloid growth factor support is available (Smith et al. 2006). Primary prophylaxis is recommended in high risk patients based on age, medical history, disease variables, and therapy-related myelotoxicity. Prophylactic myeloid growth factors for DLBCL patients aged ≥65 years receiving curative regimens as R-CHOP should be utilized to reduce FN and infection incidence.

There are no specific recommendations for the use of erythrocyte stimulating agents (ESA) in older patients. Both ASCO and American Society of Hematology recommend that for patients receiving myelosuppressive chemotherapy with a hemoglobin <10 g/dL, there should be a discussion of potential harms (i.e., thromboembolic complications, shorter survival) and benefits (i.e., fewer transfusions) of ESA, with comparison to potential harms (i.e., infection, immune-mediated reactions), and benefits (i.e., rapid hemoglobin rise) of red cell transfusions (Rizzo et al. 2010a, b). ESA should be given at the lowest possible dose and discontinued after 6–8 weeks of use in nonresponders. Patients not actively receiving chemotherapy should not receive ESA, except those with low-risk myelodysplastic syndromes. They should be used with caution with treatment agents associated with an increased risk of thromboembolism.

Initial Therapy of DLBCL in the Elderly

For decades, cyclophosphamide, adriamycin, vincristine prednisone (CHOP) chemotherapy was the standard treatment for DLBCL, with complete response (CR) rates of 50% in patients age 65–75 years, and 40% in those >75 years (McKelvey et al. 1976; O'Reilly et al. 1997; Connors and O'Reilly 1997). Median remission

duration was 16 months; 50–60% of younger, and 25–30% of older, patients achieved cure. CHOP therapy became standard based on a randomized trial comparison to other regimens (m-BACOD, Pro-MACE-CytaBOM, MACOP-B), with no significant difference in efficacy (CR rate, progression-free [PFS] and overall survival [OS]), but a more favorable toxicity profile (Fisher et al. 1993). Outcome of older patients receiving full dose anthracycline-based chemotherapy was similar to younger patients. However, more toxicities and deaths from intercurrent illnesses were found in some reports (Ballester et al. 1993; Armitage and Potter 1984; Vose et al. 1988; Solal-Celigny et al. 1987; Tirelli et al. 1988; O'Connell et al. 1986). The feasibility of delivering full dose CHOP therapy to elderly patients with myeloid growth factor support was demonstrated (Campbell et al. 1999; Sonneveld et al. 1999; Jacobson et al. 2000). Subsequent trials examined the role of anthracyclines, etoposide, and alternative CHOP dosing for older patients, demonstrating the importance of anthracyclines and greater toxicity with etoposide. (Meyer et al. 1995; Sonneveld et al. 1995; Bastion et al. 1997; Tirelli et al. 1998; Pfreundschuh et al. 2004) (Table 3). These included randomization to CHOP-14 versus CHOP-21 (CR, 70% vs. 60%, respectively), as well as CHOEP-14 (CHOP plus etoposide) or CHOEP-21 (CR, 72% vs. 76%, respectively).

In the past decade, initial rituximab(R)-CHOP therapy for older DLBCL patients, as well as younger with favorable prognostic characteristics, was established as standard-of-care (Table 4) (Coiffier et al. 2002, 2010; Habermann et al. 2006; Feugier et al. 2005; Vose et al. 2001; Sehn et al. 2005; Morrison et al. 2010). In the GELA (Groupe d'Etude des Lymphomes de l'Adulte) trial, treatment-naïve DLBCL patients, age 60–80 years, were randomized to R-CHOP (rituximab on day 1 each cycle) or CHOP therapy, with CR rates of 76% and 63% (p=0.005), 10-year PFS of 36.5% and 20%, and 10-year OS of 43.5% and 27.6%, respectively (Coiffier et al. 2002, 2010; Feugier et al. 2005). Eight cycles of R-CHOP/CHOP therapy were administered to 80% and 72% of patients, respectively. Deaths due to other causes, secondary malignancies, and late relapses were comparable among the two groups. The benefit of R-CHOP (two doses of rituximab prior to cycle 1, and a single dose prior to cycles 3, 5, and 7) was also demonstrated in the US intergroup trial (Habermann et al. 2006). Responding patients (CR, partial response [PR]) had a secondary randomization to maintenance rituximab (weekly for 4 weeks, repeated every 6 months for 2 years) or observation. Overall

Table 3 Randomized trials in older patients: pre-rituximab era

Reference	Therapy (*n*)	Age (median)	PS	CR (%)	Survival	
Meyer et al. (1995)	*n*=38	Age ≥65 years (71)	PS 2,3–50%		2-year PFS	2-year OS
	CHOP			68%	57%	74%
	CHOP			74%	46%	51%
Sonneveld et al. (1995)	*n*=148	Age ≥60 years (71)	PS 2,3–18%		3-year DFS	3-year OS
	CHOP			49%	17%	42%
	CNOP			31%	13%	26%
Bastion et al. (1997)	*n*=453	Age ≥69 years (75)	PS ≥2–31%		5-year OS	
		Range, 69–90 years			(Median, 13 months)	
	CVP			33%	19%	
	CVP+pirarubicin			48%	27%	
Tirelli et al. (1998)	*n*=120	Age ≥70 years (75)	PS 2,3–42%		2-year PFS	2-year OS
		Range, 70–93 years				
	CHOP			45%	55%	65%
	VMP			27%	25%	30%

PS=performance status; CR=complete response; OS=overall survival

Table 4 First-line therapy for DLBCL in older patients: phase III R-CHOP trials

Reference	Therapy (*n*)	Median age, years (range)	% patients ECOG PS-2	Efficacy		
				R-CHOP	CHOP	p-Value
Coiffier et al. (2002), Feugier et al. (2005), and Coiffier et al. (2010)	CHOP vs R-CHOP (21-day cycle) (*n*=399)	69 (60–80)	20%	CR rate		
				76%	63%	0.005
				10-year PFS		
				37%	20%	<0.0001
				10-year OS		
				44%	28%	<0.0001
Pfreundschuh et al. (2008)	CHOP vs R-CHOP (14-day cycles); 6 vs 8 cycles (*n*=1222)	68 (61–80)	14%	CR rate (6 cycles)		
				78%	68%	0.007
				3-year PFS		
				73%	57%	0.0001
				3-year OS		
				78%	68%	0.018
Habermann et al. (2006) and Morrison et al. (2010)	CHOP vs R-CHOP (21-day cycle); responders randomized to maintenance rituximab vs observation (*n*=632)	69 (60–92) 8% ≥80 years of age	15%	Overall response rate		
				77%	76%	NS
				9-year FFS		
				35%	25%	0.008
				9-year OS		
				44%	37%	0.11
Pfreundschuh et al. (2014a)	Dose-intensified rituximab + R-CHOP-14 (6 cycles) (n=189)	68 (61–80)	11%	CR 85% 3-year EFS 71% 3-year OS 84%		
Delarue et al. (2013)	R-CHOP-21 vs. R-CHOP-14 (8 cycles) (*n*=602)	70 (60–80)	22%	R-CHOP-21	R-CHOP-14	p-value
				Overall response rate (CR rate)		
				86% (74%)	87% (71%)	NS
				3-year EFS		
				60%	56%	NS
				3-year PFS		
				62%	60%	NS
				3-year OS		
				72%	69%	NS

(*continued*)

Table 4 (continued)

Reference	Therapy (*n*)	Median age, years (range)	% patients ECOG PS-2	Efficacy		
				R-CHOP	CHOP	p-Value
Cunningham et al. (2013)	R-CHOP-21 vs. R-CHOP-14 (8 cycles) (*n*=1080)	61 (19–88)	13%	R-CHOP-21	R-CHOP-14	p-value
				Overall response rate (CR rate)		
				88% (63%)	91% (58%)	NS
				2-year PFS		
				75%	75%	NS
				2-year OS		
				81%	83%	NS

PS=performance status; CR=complete response; EFS=event-free survival; FFS = failure-free survival; PFS = progression-free survival; OS = overall survival

response rate (ORR) to induction therapy was comparable (R-CHOP, 77%; CHOP, 76%). With median follow-up of 9.4 years, the 9-year failure-free survival (FFS) was 35% (R-CHOP) and 25% (CHOP) ($p = 0.008$) (Morrison et al. 2010). Maintenance rituximab led to prolonged FFS following CHOP ($p = 0.003$), but any benefit was abrogated with R-CHOP induction ($p = 0.79$). Maintenance rituximab had no significant impact on OS (9-year OS: R-CHOP, 44%; CHOP, 37%, $p = 0.11$). With CHOP induction, median time to treatment failure (TTF) was 9.5 years with maintenance rituximab and 2.0 years with observation ($p = 0.003$). However with R-CHOP induction, median TTF was comparable with maintenance rituximab or observation (8.5 and 7.5 years, respectively, $p = 0.79$). At least six cycles of induction therapy were administered to 79% of patients.

In the RICOVER-60 trial, patients age 61–80 years were randomized to six or eight cycles of R-CHOP-14 or CHOP-14, with CR rates after six cycles of 78% and 68%, respectively (Pfreundschuh et al. 2008). Three-year event-free survival (EFS) was 67% and 47%, respectively. Benefits were also seen in PFS (73% versus 57%, $p = 0.0001$) and OS (78% versus 68%, $p = 0.0181$, respectively). Median relative doses of myelosuppressive agents received was ≥95%. Outcome was no better with eight, versus six, cycles of therapy. When CHOP-14 patients were divided into high-risk (age > 75 years and performance status [PS] >3) and standard-risk (age 60–75 years and PS < 3, or age < 60 years) subgroups, hospitalizations were more common in the high-risk group (88% vs. 68%), mainly due to infection, malnutrition, and declining PS (Tholstrup et al. 2007). The issue of central nervous system (CNS) relapse was also examined in the RICOVER-60 trial (Boehme et al. 2009). CNS prophylaxis (intrathecal methotrexate, days 1 and 5, of cycles 1 and 2) was given to patients with marrow, testicular, and upper neck/head involvement. Risk factors for CNS disease were involvement of >1 extranodal site and B-symptoms. However, with the addition of rituximab, the relative rate of CNS disease was reduced, and intrathecal prophylaxis was not beneficial except for those with testicular involvement. In the subsequent SMARTE-R-CHOP-14 trial, two doses of rituximab were administered prior to six cycles of R-CHOP (Pfreundschuh et al. 2014a). Overall, no outcome advantage was seen as compared to the RICOVER-60 results. However, in the poor prognosis patients, 3-year EFS and OS were prolonged with the added rituximab (67% versus 54%, and 80% versus 67%, respectively).

Although dose dense therapy appeared advantageous, a prospective comparison of R-CHOP-21 and R-CHOP-14 was necessary to confirm any potential benefit (Delarue et al. 2013; Cunningham et al. 2013). The GELA trial included patients aged 60–80 years with at least one other adverse prognostic factor (Delarue et al. 2013). With median follow-up of 56 months, neither 3-year PFS (R-CHOP14, 60%; R-CHOP21, 62%, $p = 0.04$) nor 3-year OS (69% and 72%,

respectively, $p = 0.7487$) differed by treatment; toxicity profile was comparable. In another trial of patients of age 18–88 years (56% >60 years), no efficacy differences were seen (2-year OS 83% with R-CHOP-14, 81% with R-CHOP-21), but grade 3/4 thrombocytopenia, febrile neutropenia, and infection were more common with R-CHOP-14 (Cunningham et al. 2013).

Risk factors for early death in older patients receiving rituximab-based regimens have been examined in SEER-Medicare databases (Olszewski et al. 2016). Among 5530 patients of median age 76 years, of whom 94% received anthracycline-based regimens, at 30 days the cumulative incidence of death was 2.2%, and the incidence of hospitalization was 23.5%. The most common causes of death were lymphoma (72%), cardiac disease (9%), and septicemia (3%). Risk factors for early death were age $\geq$ 75 years, B-symptoms, chronic kidney disease, poor functional status, prior use of walking aids or wheelchairs, and prior hospitalization or upper endoscopy. Use of myeloid growth factor support decreased early deaths in those at highest risk.

Subsequent trials have attempted to improve on the outcome achieved with R-CHOP. In a phase II trial of 64 patients (median age 68 years) treated with R-CHOP plus bevacizumab, there was no improvement in PFS, and grade $\geq$ 3 toxicities, including cardiac and gastrointestinal perforations, occurred in 81% of patients (Stopek et al. 2012). The addition of bortezomib to R-CHOP therapy has been examined in several phase II trials (Ruan et al. 2010; Offner et al. 2015). In one, with 40 DLBCL patients of median age 56 (range, 20–87) years, CR rate was 75%, with 2-year PFS and OS of 64% and 70%, respectively (Ruan et al. 2010). Outcome was similar in non-germinal center (GCB) and GCB subtypes. Another trial in which bortezomib was substituted for vincristine (VR-CAP) and compared to R-CHOP in 164 patients (median age, 59 years, with 32% >65 years) with non-GCN DLBCL, found no differences in CR rate, PFS, OS, and grade $\geq$ 3 adverse events (Offner et al. 2015). Lenalidomide plus R-CHOP therapy (R2CHOP) has also been examined (Nowakowski et al. 2014; Vitolo et al. 2014). In one study in which 64 patients, median age 65 (range, 22–87) years, received lenalidomide, 25 mg daily on days 1–10 with R-CHOP, overall response rate (ORR) was 98% (CR, 80%), with 2-year EFS and OS of 59% and 78%, respectively (Nowakowski et al. 2014). There was no difference in EFS and OS on the basis of non-GCB and GCB phenotype. A second trial was confined to 49 patients age 60–80 years, with 15 mg of lenalidomide given daily on days 1–14 with R-CHOP, with an ORR of 92% (86% CR) and a tolerable toxicity profile (Vitolo et al. 2014). Preliminary data on the combination of daily ibrutinib plus R-CHOP in a phase 1b study has been reported (Younes et al. 2014). Of the 18 DLBCL patients, all responded with CR rates in those of GCB and non-GCB subtypes of 71% and 100%, respectively.

The addition of etoposide to R-CHOP (dose-adjusted [DA]-EPOCH-R) has been studied in several phase II and III trials (Wilson et al. 2012; Garcia-Suarez et al. 2013; Purroy et al. 2015; Wilson et al. 2016). From a series of 69 patients, median age 58 (range, 23–83) years, 84% achieved a CR, and with median follow-up of 62 months, TTP and OS were 81% and 84%, respectively (Wilson et al. 2012). However, TTP and OS were more favorable in those with GCB versus non-GCB phenotype (100% and 94% versus 67% and 58%, $p = 0.008$, respectively). The regimen was well-tolerated with no significant non-hematologic grade 4 toxicities. A 2-week DA-R-EPOCH-14-like regimen was studied in 20 patients of median age 55 (range, 19–70) years, and compared to a similar population receiving the regimen every 3 weeks (Garcia-Suarez et al. 2013). Toxicity was manageable, and 3-year PFS was better with the 2-week regimen (95% versus 74%, $p = 0.08$). Another phase II trial of DA-EPOCH-R including 68 DLBCL patients found that patients with BCL2 rearrangement had a poorer outcome than those of ABC or GCB subtypes without this rearrangement (Purroy et al. 2015). Lastly, results of the large phase III intergroup trial comparing therapy with R-CHOP versus DA-EPOCH were recently reported (Wilson et al. 2016). Outcomes were similar, with 3- and 5-year EFS of 79% and

66% with DA-EPOCH-R, and 81% and 69% with R-CHOP. Three-year OS was 85% in both arms. However, grade 3/4 hematologic toxicities, febrile neutropenia, and sensory/motor neuropathy were more frequent with DA-EPOCH-R.

Alternative approaches to R-CHOP-21 for more frail and/or elderly patients have been examined, primarily in phase II trials (Table 5) (Visani et al. 2008; Corrazelli et al. 2011; Peyrade et al. 2011, 2017; Hasselblom et al. 2012; Merli et al. 2012; Musolino et al. 2011; Hainsworth et al. 2010; Zinzani et al. 2010; Fields et al. 2014; Monfardini et al. 2005; Soubeyran et al. 2011; Murawski et al. 2014; Weidmann et al. 2011; Walter et al. 2012). Dose-attenuated regimens as R-miniCHOP, DA-POCH-R, epirubicin, cyclophosphamide, vinblastine, prednione, rituximab (R-miniCEOP), and ofatumumab plus reduced dose CHOP have been both safe and efficacious in older patients (Peyrade et al. 2011, 2017; Hasselblom et al. 2012; Merli et al. 2012; Musolino et al. 2011). Other alternative regimens studied have included liposomal doxorubicin; induction R-CNOP or R-CVP for three cycles followed by maintenance rituximab in responders; four cycles of R-CHOP followed by ^{90}Y-ibritumomab tiuxetan; substitution of gemcitabine for anthracyline in a R-CHOP-like regimen; vinorelbine plus prednisone; and COP (Visani et al. 2008; Corrazelli et al. 2011; Hainsworth et al. 2010; Zinzani et al. 2010; Fields et al. 2014; Monfardini et al. 2005; Soubeyran et al. 2011). Use of dose-dense rituximab in patients aged 60–80 years did not result in an improved outcome compared with R-CHOP and had increased infectious toxicities, limiting its utility (Murawski et al. 2014). Bendamustine-rituximab (BR) has been examined in small series (Weidmann et al. 2011; Walter et al. 2012; Park et al. 2016). An ORR of 69% (CR 54%) to BR with favorable toxicity profile was demonstrated in very elderly patients (Weidmann et al. 2011). Another retrospective study examined BR as an alternative to R-CHOP in unfit DLBCL patients (Walter et al. 2012). In a recent publication in patients of median age 80 years with 52% having a PS of $\geq$2, although ORR was 78% (CR 52%), survival was short (median PFS and OS of 5.4 and 10.2 months, respectively (Park et al. 2016).

Initial "prephase treatment" with prednisone for 7 days, given alone or with 1 mg of vincristine, may be considered for DLBCL patients of all ages, but especially for the more frail elderly (Pfreundschuh 2010). An alternative prephase option is oral cyclophosphamide (400 mg on days 1, 3, 5). Use of such treatment decreases first cycle depth and duration of neutropenia, tumor lysis, and therapy-associated deaths with R-CHOP-based therapy. The benefit of prephase treatment should be weighed against preexisting comorbidities as diabetes.

In summary, six cycles of R-CHOP-21 therapy should be offered to fit older patients, with appropriate supportive care measures, as it has been demonstrated in large phase III trials that the majority of elderly patients are able to receive full-dose therapy. The use of geriatric assessment tools will be important in evaluating older/frail patients and choosing appropriate therapies. For very elderly (>80 years) patients or those unfit for R-CHOP-21, regimens with alternative agents or dose reductions demonstrate efficacy and tolerability. Such treatment, with appropriate supportive measures and close toxicity monitoring, can be more than palliative and add meaningful quality and quantity of life.

Treatment Approaches for Limited Stage Disease or Bulky Disease

Approximately 25–30% of DLBCL patients present with limited stage disease, defined as stage I or nonbulky stage II (<10 cm in greatest diameter) disease (Armitage and Weisenburger 1998). Despite treatment with involved field radiation therapy (IFRT) with CR rates approaching 90%, 5-year disease-free survival (DFS) for stage I and II disease was 50% and 20%, respectively, with relapses common outside the radiation field and in extranodal sites (Kaminski et al. 1986; Vaughan Hudson et al. 1994; Chen et al. 1979; Reddy et al. 1977; Spicer et al. 2004). Presently, sole use of IFRT may be considered for patients unfit for chemotherapy.

Trials in the pre-rituximab era included a Southwest Oncology Group (SWOG) trial in

Table 5 First-line therapy for DLBCL in older patients: alternative regimens from phase II/III trials

Reference	Therapy (*n*)	Median, age, years (range)	% pts. ECOG-PS ≥2	Efficacy	Reasons for non-CHOP therapy
Visani et al. (2008)	R-COMP-21 (20)	73 (61–82)	45%	ORR 90% CR 65%	Cardiac issues Frailty
Corrazelli et al. (2011)	R-COMP-14 (41)	73 (62–82)	32%	ORR 73% CR 68% 4-year DFS 72% 4-year OS 67%	Cardiac issues Frailty
Peyrade et al. (2011)	R-mini-CHOP-21 (150)	83 (80–95)	34%	ORR 73% CR 62% 2-year PFS 47% (median, 21 months) 2-year-OS 59% (median, 29 months)	Age ≥80 years
Hasselblom et al. (2012)	Moderately reduced R-CHOP (40)	85 (80–91)	50%	3-year PFS 41% 3-year OS 41%	Age ≥80 years
Merli et al. (2012)	R-mini-CEOP (114)	73 (64–84)	16%	ORR 81% CR 68% 5-year EFS 46% 5-year OS 63%	Age >60 years
Peyrade et al. (2017)	Ofatumumab+dose-reduced CHOP (120)	83 (80–95)	29%	ORR 68% CR 56% 2-year PFS 57% 2-year OS 65%	Age ≥80 years
Musolino et al. (2011)	DA-POCH-R (23)	77 (70–90)	74%	ORR 90% CR 57% 3-year EFS 54% 3-year OS 56%	Age ≥70 years Poor prognosis disease
Hainsworth et al. (2010)	R-CNOP or R-CVP, with maintenance rituximab (51)	78 (61–90)	37%	2-year PFS 71% 4-year PFS 56% 2-year OS 72% 4-year OS 67%	Age >60 years Poor PS
Fields et al. (2014)	R-GCVP (62)	77 (52–90)	50%	ORR 61% CR 39% 2-year PFS 50% 2-year OS 56%	Cardiac comorbidities
Weidmann et al. (2011)	BR (14)	85 (85–90)	29%	ORR 69% CR 54% Median PFS 8 months Median OS 8 months	Advanced age Pt request for less aggressive therapy; not eligible for R-CHOP
Walter et al. (2012)	BR (15)	79 (68–92)	33%	ORR 61% CR 38% Median PFS 6 months Median OS 9 months	Poor PS Cardiac co-morbidities Pt request
Park et al. (2016)	BR (23)	80 (Median)	52%	ORR 78% CR 52% Median PFS 5.4 months Median OS 10.2 months	Advanced age Cardiac issues

PS = performance status; ORR = response rate; CR = complete response; DFS=disease-free survival; EFS = event-free survival; PFS = progression-free-survival; OS = overall survival

which 400 patients (median age 59 years) with stage I (68%), IE, or nonbulky stage II/IIE disease were randomized to eight cycles of CHOP or three cycles of CHOP followed by IFRT (Miller et al. 1998). In 5-year follow-up, the combined modality arm was more favorable than CHOP alone (5-year PFS 77% and 64%, $p = 0.03$; 5-year OS 82% and 72%, $p = 0.02$, respectively). However, the curves overlapped for PFS at 7 year follow-up, and for OS at 9 years, due to lymphoma relapses in the combined modality group (Miller et al. 2001). With adverse risk factors of stage II disease, elevated LDH, PS 2, and age > 60 years, 5-year OS was 95%, 77%, and 50%, for 0, 1–2, or 3 risk factors, respectively ($p = 0.01$). Five-year OS in bulky stage II disease patients (49%) was similar to that of advanced stage patients, supporting similar treatment approaches. Now with median follow-up of 17.7 years, there are no differences in PFS and OS with either approach, nor in the cumulative incidence of second malignancies (Stephens et al. 2016). Stage II/IIE disease replaced advanced stage disease in the Miller modification of the IPI (Miller 2004). In a retrospective review of 308 patients (median age 64 years) with stage I (61%) or nonbulky IIA disease who received three cycles of anthracycline-based therapy followed by IFRT, similar outcomes were seen using the Miller-modified IPI, with 5- and 10-year PFS of 94%/89% (no risk factors), 79%/73% (1–2 factors), and 60%/50% (3–4 factors); corresponding OS was 97%/89% (no factors), 77%/56% (1–2 factors), and 58%/48% (3–4 factors) (Shenkier et al. 2002).

The impact of IFRT consolidation following chemotherapy has been examined (Horning et al. 2004; Shikama et al. 2006; Reyes et al. 2005; Bonnet et al. 2007). In an ECOG trial, eight cycles of CHOP was followed by observation (n = 179) or consolidative IFRT (n = 173) achieving a CR (n = 219; 61%) or PR (n = 98; 28%)]; all PR patients received IFRT (Horning et al. 2004). Although 31% of PR patients converted to CR following IFRT, this did not impact relapse rate or OS. Comparing CR patients with CHOP and observation versus CHOP followed by IFRT, 6-year DFS was 56% and 73% ($p = 0.05$), and 5-year OS was 73% and 73% ($p = 0.24$), respectively, with no difference in 10- or 15-year OS. In another series of patients age > 70 years with stage IA/contiguous IIA nonbulky disease, three cycles of reduced dose CHOP followed by IFRT resulted in 3-year PFS and OS of 83% (Shikama et al. 2006). In a GELA trial, good risk patients (60–80 years of age, 95% with age-adjusted IPI of 0, 65% stage I, 35% stage II) received four cycles of CHOP followed by IFRT or observation, with no differences in toxicities or 5-year EFS and OS (64% and 61%, $p = 0.6$; 68% and 72%, $p > 0.05$, respectively) (Bonnet et al. 2007). Relapse patterns also varied between CHOP alone (47% exclusively initial disease site; 16% local and distant sites; 37% exclusively distant) and CHOP followed by IFRT (21%, 13%, and 66%, respectively).

Trials in the rituximab era sought to improve on survival with CHOP for three cycles followed by IFRT. In a phase II SWOG trial in which 60 patients (median age 69 years, 57% stage I disease, stage-modified IPI 1 in 70%) with ≥1 adverse risk factor received CHOP ×3 + IFRT, plus four doses of rituximab, 2- and 4-year PFS and OS were 93% and 88%, 95%, and 92%, respectively, at median follow-up of 5.3 years (Persky et al. 2008). Now with median follow-up of 12 years, 5 and 10 year OS are 82% and 67%, respectively, with a persistent pattern of relapse despite the addition of rituximab (Stephens et al. 2016). More recently, a series of 874 limited stage DLBCL patients at least 66 years of age identified through Surveillance, Epidemiology, and End Results (SEER) data who received three to four cycles of R-CHOP followed by IFRT (n = 359) or six to eight cycles of R-CHOP alone (n = 515) was examined (Odejide et al. 2015). Those receiving R-CHOP followed by IFRT had a lower likelihood of receiving second line therapy and of febrile neutropenia occurrence, compared to R-CHOP alone. However, OS was comparable in both groups, suggesting that R-CHOP + IFRT may be better tolerated in the elderly than a full course of R-CHOP.

The role of radioimmunotherapy with conjugated antiCD20 antibodies was examined in several studies (Miller et al. 2008; Witzig et al. 2015; Friedberg et al. 2014). In one, 44 patients (median age 61 years, 48% stage I disease; stage-modified IPI of 1 (66%), 2 (25%), 3 (9%)] received CHOP

×3, followed by IFRT and yttrium-90 ibritumomab tiuxetan (zevalin) consolidation (Miller et al. 2008). With a 2-year median follow-up, 2-year PFS and OS were 92% and 95%, respectively. In an ECOG study, four to six cycles of R-CHOP was followed by ibritumomab tiuxetan consolidation, and by IFRT if residual disease was present (Witzig et al. 2015). A CR was achieved by 89% of patients without the need for IFRT; 5 year PFS and OS were 78% and 94%, respectively. The impact of iodine-131 tositumomab consolidation following six cycles of R-CHOP, two cycles of CHOP, followed by I^{131} tositumomab consolidation was examined in patients with advanced or bulky stage II DLBCL patients in a SWG trial (Friedberg et al. 2014). With median follow-up of 3.9 years, 2-year PFS and OS were 69% and 77%, respectively. However, benefit from such consolidation is limited by early disease progression, deaths, and declining PS from induction therapy.

IFRT should be considered for improved local control and EFS for patients with bulky disease (≥10 cm) with equivocal positron emission tomography (PET) scan findings after chemotherapy (Pfreundschuh et al. 2006, 2011; Marcheselli et al. 2011; Held et al. 2014; Dorth et al. 2012; Phan et al. 2010; Ballonoff et al. 2008). The role of IFRT to bulky disease sites in elderly patients (age 61–80 years) was examined in the RICOVER-60 trial (Dorth et al. 2012). Patients receiving six cycles of R-CHOP, followed by two additional rituximab doses, then IFRT to sites of initial bulky (≥7.5 cm) disease and extralymphatic involvement, were compared with those who received such therapy without IFRT. EFS was superior with IFRT ($p = 0.005$), with trends toward superior PFS and OS, thus abrogating bulky disease as a risk factor. In the ongoing OPTIMAL >60 trial involving older DLBCL patients, the role of IFRT is being examined in those with a negative PET scan after induction therapy. In a retrospective review of 469 patients (40% limited, 60% advanced, stage disease) who received IFRT versus observation following R-CHOP, 5-year PFS (90% versus 75%) and OS (91% versus 83%) were superior with IFRT (Phan et al. 2010). In limited stage patients, corresponding 5-year PFS and OS were 82% and 92% versus 68% and 73%, respectively.

The role of PET scans was examined in limited stage patients, following three cycles of R-CHOP therapy (Sehn et al. 2008). Those who were PET-negative (74%) received a fourth cycle of R-CHOP; PET+ patients (26%) received IFRT. With median follow-up of 17 months, one PET-negative patient relapsed, and 2-year PFS and OS was 97%. In the PET-positive patients, 3 of 17 relapsed (all outside the radiation field), with 2-year PFS and OS of 83% and 76%, respectively. An ongoing trial is examining the role of IFRT in patients with PET-negative disease. The role of IFRT compared with involved node RT (INRT; radiation to pre-chemotherapy involved nodes with margins ≤5 cm) was studied in 288 limited stage (stage I/II, no B symptoms, bulk <10 cm) patients, of whom 56% were >60 years of age, 55% with extranodal disease, and 15% had received rituximab (Campbell et al. 2012). With median follow-up of 117 (IFRT) and 89 (INRT) months, there was no difference in TTP, PFS, or OS. The most common site of failure was distant relapse. Thus, reducing the radiation field size resulted in low marginal recurrence risk with no impact on outcome.

In summary, IFRT improves local disease control, with no excess therapy-related myelodysplasia. Second malignancy risk in the radiation field is 11–15%, but decreases with older age (Armitage et al. 2003; Mudie et al. 2006; Tward et al. 2006; Hemminki et al. 2008). Although the role for IFRT in advanced stage disease remains controversial, recent data suggests that it may benefit older patients with bulky disease.

Maintenance Therapy

Based upon data in indolent NHL, the potential role of maintenance therapy in DLBCL has been examined. Maintenance interferon alfa 2b therapy was studied in 223 DLBCL patients, half >65 years of age, with high- (80%) or high-intermediate (20%) IPI risk disease, who after attaining a CR with CHOP-bleomycin induction

were randomized to maintenance interferon (5 million units, three times weekly for a year) or observation (Aviles et al. 2001). With median follow-up of 45 months, no advantage to maintenance interferon was found. The estimated 5-year EFS and OS with maintenance therapy were 71% and 54%, respectively, compared with 69% and 54% with observation ($p = 0.2$). In another trial, 169 DLBCL patients with high-intermediate or high-risk IPI disease who achieved a CR to induction therapy were randomized to maintenance interferon alfa 2b, cyclophosphamide, and prednisone or to observation (Avilés et al. 2004). Again, no 5-year EFS and OS survival advantage was found (71% and 84% with maintenance, 63% and 83% with observation, respectively, $p = 0.2$).

The utility of maintenance rituximab was examined in the US intergroup trial, with 632 patients ≥60 years of age randomized to CHOP or R-CHOP induction therapy (Habermann et al. 2006; Morrison et al. 2010). The 451 responding patients (CR/PR) were then randomized to maintenance rituximab (weekly for 4 weeks, every 6 months, for 2 years) or observation. With median follow-up from induction and maintenance randomizations of 9.4 and 9.0 years, respectively, 9 year FFS and OS were 35% and 44% with R-CHOP, and 25% and 37% with CHOP, respectively (Morrison et al. 2010). Overall, maintenance rituximab resulted in prolonged FFS ($p = 0.014$), but not OS. Specifically, maintenance rituximab prolonged FFS after CHOP ($p = 0.003$), but not after R-CHOP induction, and had no impact on OS. Median time to failure (TTF) for CHOP plus maintenance rituximab and CHOP-observation was 9.5 and 2.0 years, respectively. With R-CHOP induction, median TTF was similar with maintenance rituximab or observation (8.5 and 7.5 years, respectively). PFS was improved in all IPI subgroups in 228 patients receiving R-CHOP induction followed by maintenance rituximab (monthly for a year, then every 3 months for the second year) (Huang et al. 2012). In another study, maintenance rituximab (weekly for 4 weeks, every 6 months for 2 years) was given to 51 elderly (median age 78 years) patients with no disease progression following three cycles of induction R-CNOP or R-CVP therapy (Hainsworth et al. 2010). With 4-year median follow-up, 2-year PFS and OS were 71% and 72%, respectively.

However, more recent data has suggested a potential role for maintenance rituximab in select patient subsets. In a phase III multicenter study, 683 patients (662 DLBCL, 21 follicular NHL grade 3B) achieving a CR with induction R-CHOP-like therapy were then randomized to maintenance rituximab (one dose every 2 months for 2 years) or observation (Jaeger et al. 2015). Overall, no advantage in EFS, PFS, and OS was seen with maintenance rituximab. However, in subgroup analysis, both EFS and PFS were superior in male patients rituximab maintenance receiving maintenance rituximab compared to observation (84.1% versus 74.4%, and 89.0% versus 77.6%, respectively). Those men with a low IPI index receiving rituximab maintenance had the best outcome. In another multicenter trial in which patients with CD20-positive B-cell NHL (152 with DLBCL) were randomized to maintenance rituximab (one dose every 3 months for 2 years) versus observation, 5-year relapse-free survival (RFS) was comparable in those with DLBCL (Witzens-Harig et al. 2015). However, men with DLBCL receiving rituximab maintenance had superior RFS and OS compared with observation (88% versus 74%, $p = 0.05$; 100% versus 88%, $p = 0.03$, respectively). The use of weekly rituximab "consolidation" (weekly for four doses) in responding patients following four cycles of R-CHOP induction was examined in 51 DLBCL patients >70 years of age (Jung et al. 2014). With median follow-up of 20.3 months, 2-year PFS and OS were 63.9% and 68.7%, respectively. In comparison to historical controls receiving six cycles of R-CHOP, such treatment was considered a reasonable compromise between safety and efficacy in this elderly population. The report that men >60 years of age have more rapid rituximab clearance than women does not explain these gender-based differences (Pfreundschuh et al. 2014b; Lunning and Armitage 2015).

In summary, although there is presently no proven role for rituximab maintenance in DLBCL induction therapy responders, recent

reports raise controversy on this issue (Lunning and Armitage 2015). There may be select subgroups, as the very elderly/frail not receiving full-dose induction therapy, or males with IPI <1, in which maintenance rituximab may confer benefit.

Management of Relapsed/Refractory DLBCL in the Elderly

Although significant advances have been made in DLBCL therapy, 30–40% of patients will have relapse or have refractory disease (Coiffier et al. 2002). These patients may be divided into three subgroups (Hamlin et al. 2003; Friedberg 2011). Primary refractory disease, with an approximate 10% incidence, is defined as <50% reduction in lesions or new lesions during induction therapy. These patients have a poor outcome, with reponses to salvage regimens uncommon. A second subgroup will achieve a PR with >50% reduction in measurable disease, but with persistent disease following induction. The third subgroup will relapse following an initial CR with induction therapy, with most relapses occurring within 2 years following induction treatment. Outcome is poor in those relapsing within a year of initial therapy. Relapsed DLBCL in the elderly is increasingly associated with non-germinal center (ABC phenotype) biology, with inferior outcomes (Feugier et al. 2005; Gisselbrecht et al. 2010; Thieblemont et al. 2011; Mareschal et al. 2011; Hans et al. 2004; Jais et al. 2008; Copie-Bergman et al. 2009). The second-line age-adjusted IPI (lactate dehydrogenase [LDH], stage, PS) may be utilized to predict outcome at relapse (Hamlin et al. 2003). In the elderly relapsed/refractory patient, treatment goals should focus not only on response but also disease control, symptom palliation, and quality of life, as durable remissions are uncommon. A minority may be suitable for high-dose salvage therapy followed by autologous stem cell rescue (HDT/ASCR) consolidation.

Patients Not Eligible for Transplant Approaches. For patients who are not transplant candidates, including most >70 years of age, induction therapy is the only curative option. In a recent meta-analysis, most salvage therapy studies have been single arm trials with small patient numbers (<50 patients), in which median OS ranged from 4–13 months (Colosia et al. 2014). At present, no standard salvage regimen has been established, with options including clinical trials (if available), single agent or combination therapies, or best supportive care, with decisions dependent on comorbidities, functional status, and goals of the given patient. Single agent rituximab has only modest activity, especially in those relapsing within 6 months of prior rituximab but may be considered in combination salvage regimens. In a GELA trial, relapsed patients had 2-year OS of 26% with median OS <9 months (Feugier et al. 2005). Those who relapsed late and had no prior rituximab had improved outcome with rituximab-containing salvage regimens, with a 2-year survival of 58%, versus 24% without rituximab ($p = 0.00067$). Toxicity concerns may limit use of R-ICE or R-DHAP in the salvage setting. However in a recent report, 32 patients (median age 75.6 years) with relapsed/refractory DLBCL who received dose-reduced ICE+/- rituximab in the salvage setting had an ORR of 53% (CR 41%) and median PFS and OS of 3.9 and 17 months, respectively, with good tolerability (Sarif et al. 2016). Other well-tolerated combination salvage regimens include CEPP(B), gemcitabine-based therapy (R-Gem-Ox), bendamustine, and CVP +/- rituximab (Rigacci et al. 2012; Horn et al. 2012; Chao et al. 1990; El Gnaoui et al. 2007; Corazzelli et al. 2009; Rodriguez et al. 2007; Yao et al. 2013; Weidmann et al. 2002; Vacirca 2009; Ohmachi et al. 2013; Coleman et al. 2008; Niitsu and Umeda 1997; Witzig et al. 2011; Zinzani et al. 2011; Witzig et al. 2009; Wiernik et al. 2008; Wang et al. 2013). In a small phase II trial of single agent bendamustine salvage therapy, ORR was 44% (CR, 17%) (Weidmann et al. 2002). The addition of rituximab to bendamustine (BR) resulted in a 51% ORR (CR, 15%) (Vacirca 2009). In another BR trial, ORR in patients ≥65 years of age was 62% (CR, 38%) (Ohmachi et al. 2013). Several oral regimens utilize single agent etoposide given continuously, and low dose "metronomic therapy" with prednisone, etoposide, procarbazine,

cyclophosphamide (PEP-C) (Coleman et al. 2008; Niitsu and Umeda 1997). Salvage single agent lenalidomide resulted in a 33% ORR and median response duration of 10 months (Witzig et al. 2009, 2011; Zinzani et al. 2011; Wiernik et al. 2008; Wang et al. 2013). Lenalidomide-rituximab therapy lead to an ORR 28% (CR, 22%) with median PFS and OS of 2.8 and 10.2 months, respectively, although grade 3/4 hematologic toxicities were common (Wang et al. 2013). Palliative radiation therapy to sites of symptomatic disease may also be considered. Treatment and supportive/palliative care guidelines for such elderly patients have been developed by organizations as NCCN, American Society of Clinical Oncology (ASCO), and International Society of Geriatric Oncology (SIOG) (Table 6) (Morrison et al. 2015a, b).

Transplant-Eligible Patients. There is limited data regarding HDT/ASCR in older patients. Feasibility of this approach is determined by functional as well as chronologic age, including assessment of comorbidities, activities of daily living (ADL), instrumental-ADL (IADL), and psychosocial support aspects. These aspects, as well as comprehensive geriatric assessment (CGA), are useful to predict overall risk of this treatment approach, as well as relapse risk, transplant-related mortality (TRM), and non-relapse mortality (NRM), which are higher in older patients (Guglielmi et al. 1998; Wildes et al. 2008; Charlson et al. 1994; Sorror et al. 2005; Raimondi et al. 2012; Hurria et al. 2011; Extermann and Hurria 2007; Deeg and Sandmaier 2010). A CIMBTR registry review of older (>55 years) aggressive lymphoma transplant

Table 6 Representative guidelines for care of the older lymphoma patient

Organization	Guideline	Website
ASCO	ASCO 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline	http://www.asco.org/quality-guidelines/asco-2006-update-recommendations-use-white-blood-cell-growth-factors-evidence
ASCO	ASCO provisional clinical opinion: The integration of palliative care into standard oncology care	http://www.asco.org/quality-guidelines/asco-provisional-clinical-opinion-integration-palliative-care-standard-oncology
ASCO	ASCO-ASH clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer	http://www.asco.org/quality-guidelines/asco-ash-clinical-practice-guideline-update-use-epoetin-and-darbepoetin-adult
NCCN	Senior adult oncology	http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf
NCCN	Palliative care	http://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf
NCCN	Cancer-related fatigue	http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf
NCCN	Distress management	http://www.nccn.org/professionals/physician_gls/pdf/distress.pdf
SIOG	Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper	http://siog.org/index.php?option=com_content&view=article&id=139&Itemid=92
SIOG	International Society of Geriatric Oncology chemotherapy taskforce: Chemotherapy toxicity in the elderly	http://siog.org/index.php?option=com_content&view=article&id=145&Itemid=92
SIOG	International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency	http://siog.org/index.php?option=com_content&view=article&id=147&Itemid=92
SIOG	Use of comprehensive geriatric assessment in older cancer patients: Recommendations from the task force on CGA of the International Society of Geriatric Oncology	http://siog.org/index.php?option=com_content&view=article&id=151&Itemid=92

patients reported a 5-year TRM rate was 15% and relapse rate was 66%, with DFS of 19% and OS of 30% (Lazarus et al. 2008). In a EBMTR review of 463 DLBCL patients ≥60 years of age at transplant, TRM was 1.6 times that of younger patients (Jantunen et al. 2008). Similar CIMBTR registry data found TRM to be 1.86 times that of younger patients (Lazarus et al. 2008). A 35% NRM was found in patients ≥70 year of age, compared to 8% in patients age 65–69 years. In a more recent single institution report in which 202 NHL patients (37% with DLBCL) of median age 65 (range, 60–74) years underwent HDT/ASCR, with median follow-up of 3.6 years, 3-year PFS and OS were 60% and 73%, respectively, with a 4% TRM rate (Dahi et al. 2014).

The impact of posttransplant rituximab, as compared with observation, has been reported in several randomized trials (Haioun et al. 2009; Gisselbrecht et al. 2012). Poor risk DLBCL patients, all <60 years of age, who received high-dose consolidative therapy followed by autologous transplant, were then randomized to four weekly doses of rituximab versus observation (Haioun et al. 2009). With median 4 year follow-up, there was a trend toward improved EFS in those receiving rituximab. In the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, 242 patients were randomized to rituximab, given every 2 months for 1 year, or observation following transplant (Gisselbrecht et al. 2012). The 4-year EFS following transplant was comparable (52% and 53%, respectively). In the rituximab group, EFS was more favorable in women (63%) than in men (46%). Based upon these findings, this group did not recommend posttransplant rituximab in such patients.

In those older patients considered candidates for HDT/ASCR, there is no clear standard second-line therapy. Rituximab is often included in such regimens (Kewalramani et al. 2004; Vellenga et al. 2008). In the CORAL study, comparable response rates (ORR 63%) were achieved with R-ICE or R-DHAP (Gisselbrecht et al. 2010). Cisplatin-related nephrotoxicity and neurotoxicity with ifosfamide, both of which are age-dependent, are potential limitations with these regimens. Phase II trials have examined the utility of gemcitabine or oxaliplatin-based regimens (Gopal et al. 2010; Lignon et al. 2010; Rigacci et al. 2010). However with second line regimens, if the disease is not chemosensitive, outcomes are poor and consideration for clinical trials or supportive care is appropriate (Elstrom et al. 2010). In several small series of patients >70 years of age undergoing HDT/ASCR, long-term disease control (>1 year) was achieved in 48–59% (Elstrom et al. 2012; Andorsky et al. 2011). In the CORAL study, in which patients were with median age 55 (range, 19–65) years, 3-year PFS and OS were 37% and 49%, respectively (Thieblemont et al. 2011). Most relapses occurred following rituximab-based induction therapy, and within 1 year of prior therapy, with a 3-year PFS of only 23%, similar to EBMT registry data (Mounier et al. 2012).

Therapy of DLBCL in the Elderly – Conclusions

Despite treatment advances for older DLBCL patients based upon prospective randomized trials in the era of rituximab-based therapies, many patients are not eligible for such trials based on underlying comorbidities and functional deficits related to aging. Alternative regimens may be considered for those unable to tolerate R-CHOP due to comorbidities or frailty. There is presently no clear-cut role for maintenance therapy of DLBCL. In the relapse setting, only select elderly patients will be candidates for high dose treatment approaches, and treatment should be given with palliative intent in those who are not transplant candidates. Measures for more formal assessment of older patients are being developed, to include more facets than PS alone. Although potentially curative therapies should be offered to older patients when possible, pretreatment evaluation should include some formalized assessment and consideration not only of comorbidities but also of functional, social, and psychological constraints, such that safety and tolerability of a given regimen can be determined. Supportive care measures are of particular importance in the elderly. With the evolution of new novel agents, it is anticipated that continued advances will be made in the care of older DLBCL patients.

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The Evolving Role of Transplant for Older Adults

37

Andrew S. Artz and Rebecca L. Olin

Contents

Abstract

In recent years, the number and percentage of both allogeneic and autologous transplants being performed in older patients has increased. These trends can be attributed to the aging of the population in general, but also improved transplant methodology making transplant safer and better tolerated. Uptake of allogeneic transplant, which is most commonly performed for acute myelogenous leukemia and myelodysplastic syndrome, has also been affected by the development of non-myeloablative conditioning regimens. Autologous transplants, most commonly performed for multiple myeloma and non-Hodgkin lymphoma, continue to play an important role in the care of the older patient, and in particular, for multiple myeloma, evidence exists to support the safety of melphalan-based autologous transplant well over the age of 70. The current challenge in the transplant field is to

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understand which factors affect transplant outcomes, including disease-related and patient-related factors. While chronologic age plays a role in decision-making, physiologic fitness is likely more important. Increasing data exists to support the use of functional assessments, alone or as part of a comprehensive geriatric assessment. As well, any decision to proceed to transplant must consider the relative merits of nontransplant therapies.

Keywords
Transplantation · Stem cell · Allogeneic · Autologous

Introduction

The absolute number and relative percentage of hematopoietic stem cell transplants (HCT) performed for older patients have consistently increased over the years (Pasquini and Wang 2015; Hahn et al. 2013). In the 1990s, fewer than 10% of transplants were performed for older patients (≥50 years for allogeneic, ≥60 years for autologous). By contrast, in the more recent 2007–2013 era, 44% of autologous transplant recipients and 22% of allogeneic transplant recipients were at least 60 years of age. Moreover, the entire rise in the absolute numbers of HCT can be accounted for by patients 60 years or older.

Patients in their eighth decade of life now represent the area of fastest growth of allogeneic and autologous grafts and can have reasonable outcomes (Muffly et al. 2016; Auner et al. 2015). In a European registry of over 50,000 autologous transplants for multiple myeloma, patients aged 70 years and older represented 3% of transplants from 2006 to 2010 compared to only 1.1% one decade before (Auner et al. 2015). Similarly, Muffly reported in abstract form that 3.3% of allogeneic HCT reported to CIBMTR in 2012–2013 derived from this age group versus only 0.4% the decade before (Muffly et al. 2016).

Many factors underlie greater HCT utilization in older patients (Artz and Ershler 2010) (Table 1).

Table 1 Trends promoting hematopoietic cell transplant (HCT) for older adults

Characteristic	Example
Reduced intensity conditioning[a]	Fewer acute regimen-related toxicities
Peripheral blood stem cells	Reduces time to neutrophil engraftment Easier collection of hematopoietic cells for patients and older donors
Supportive care	
Infectious disease	Better infectious disease monitoring (e.g., CMV detection) and better treatments for opportunistic infections
Growth factors	Facilitate stem cell collection and reduce neutropenia phase post-HCT
Immunosuppression[a]	More tolerable immunosuppression reducing toxicity
Human leukocyte antigen (HLA) matching[a]	Better HLA matching reduces post-HCT complications
Donor registries[a]	Merging of registry databases electronically facilitates unrelated donor identification. Cord blood banks provide resource for unrelated cord blood
Patient health	Older adults have fewer disabilities and longer life expectancy allowing more intensive treatment
Societal attitudes	Patient and physician attitudes have shifted to expect life-prolonging treatment for older adults
Availability	More transplant centers and insurance coverage for older adults

[a]Restricted to Allogeneic HCT (Adapted from Artz and Ershler 2010)

Of note, while reduced intensity or non-myeloablative conditioning has been widely credited for the rise in allogeneic transplants, the parallel rise in autologous transplant (as myeloablative preparative regimens remain the rule) for older adults argues that other factors are at play. Improvements in supportive care, including infectious disease monitoring, prophylaxis, and treatment, have all played a key role in

expanding the use of both allogeneic and autologous transplants. Societal attitudes toward treatment of older adults are also changing. For allogeneic transplant, better HLA matching for unrelated donors has improved outcomes and availability of unrelated donors, contributing to this being the leading donor source in older patients. Finally, the demography of aging reveals an expanding number of older persons nationwide, who suffer a disproportionate burden of the incidence and mortality related to most hematologic malignancies.

Despite rising use of HCT for hematologic malignancies in older adults, only a small fraction of older patients with transplant-eligible diseases actually receive a transplant. Estimates of the percentage of older patients diagnosed with acute myeloid leukemia (AML) who ultimately undergo allogeneic transplant range from 0.8% to 6% (Ustun et al. 2013; Oran and Weisdorf 2012). Similarly, Yao estimated the utilization rate for unrelated allografts for all hematologic malignancies at 44%, 29%, and 8% among patients aged 20–44, 45–64, and 65–74 years, respectively, even after adjusting for lower rates of transplant eligibility in older adults due to comorbidities and induction mortality (Yao et al. 2013). Prospective studies of transplant in older adults and more widespread dissemination of transplant feasibility promise to further escalate utilization.

Allogeneic Transplantation

What Is the Effect of Increasing Age on Allogeneic Hematopoietic Stem Cell Transplant (alloHCT) Outcomes?

Older age historically prohibited transplant and modern evidence do still support worse outcomes in older versus younger transplant recipients. However, this gap may be narrowing. Depending on the approach used to answer this question, the question of whether increasing age affects transplant outcome is controversial and data are mixed.

In large registry studies or large database studies covering the entire age spectrum of adults, older age is consistently associated with worse transplant outcomes. The Center for International Blood and Marrow Transplant Research (CIBMTR) data demonstrates better one-year overall survival for alloHCT recipients <50 years versus ≥ 50 years, though the difference is 10% or less depending on whether the donor used is related or unrelated (Pasquini and Wang 2015). An analysis of 1853 patients aged 0.1–75 years and transplanted from 2000 to 2006 showed that risk of death not due to disease (a.k.a., nonrelapse mortality or NRM) still increases with older age. Using age groups of 20 year increments with the 0–19-year-old group as a reference point, NRM worsened over age 40 (Sorror et al. 2014).

On the other hand, smaller retrospective studies have evaluated the effect of recipient age, restricted to an older patient population, and found no difference of older age on alloHCT outcomes (Koreth et al. 2010; Sorror et al. 2011; Chevallier et al. 2012; McClune et al. 2010; Lim et al. 2010; McClune et al. 2014) (Table 2). The explanation for this discrepancy may lie in patient selection bias (older patients may be more closely scrutinized for transplant clearance) and small-moderate sample sizes of these retrospective studies. We believe for older adults consider fit for transplant, one should generally not exclude based on age alone, at least up to around age 75 years.

On a patient level, older adults have substantially worse nontransplant outcomes due to worse disease and/or greater nontreatment deaths. Studies of age differences within transplant cohorts do not inform the risks or benefits of the procedure for older patients.

Consideration of Treatment Alternatives: Transplant Versus Nontransplant Therapy

A decision to pursue allogeneic transplant for any patient must always be balanced against nontransplant alternatives and outcomes. Prospective studies comparing transplant to nontransplant

Table 2 Studies evaluating effect of age on allogeneic transplant outcomes

Study	Population	NRM	GVHD	OS
Koreth et al. (2010)	N = 158, aged 60–71, mixed indications	No effect	Lower risk of cGVHD in age > 65 vs 60–65	No effect
Sorror et al. (2011)	N = 372, aged 60–75, mixed indications	No effect	No effect	No effect
Chevallier et al. (2012)	N = 600, aged 60–71, mixed indications	No effect	No effect	No effect
McClune et al. (2010)	N = 1080, aged 40–79, AML CR1 or MDS	No effect	Borderline higher risk of cGVHD in age > 65	No effect
McClune et al. (2014)	N = 1248, aged 40–75, NHL	Worse NRM for age ≥ 55	No effect	Worse OS in age ≥ 55
Lim et al. (2010)	N = 1333, aged 50–74, MDS	No effect	NR	No effect

cGVHD chronic graft versus host disease, *NHL* Non-Hodgkin lymphoma, *MDS* myelodysplastic syndrome, *NRM* nonrelapse mortality, *OS* overall survival, *NR* not reported
Adapted from Artz and Olin (2016)

approaches have generally been restricted to younger patients (Koreth et al. 2009). Data regarding the efficacy of allogeneic transplant in an older population have largely been derived from retrospective analyses and one prospective donor versus no donor comparison. Allogeneic transplant for acute myeloid leukemia is perhaps the best studied and the most common disease in older adults for which allogeneic transplant is entertained.

Estey et al. studied consecutive AML patients >50 years of age seen at MD Anderson Cancer Center, and performed a case-control study comparing the outcomes of transplanted patients versus those who received chemotherapy (Estey et al. 2007). The analysis demonstrated longer relapse-free survival in the transplanted patients, with limitations including selection bias and small sample size. Farag et al. compared the outcomes of patients aged 60–70 with AML in first remission receiving RIC transplants reported to the CIBMTR with outcomes of patients receiving induction and consolidation chemotherapy on cooperative group trials (n = 94 versus 96, respectively) (Farag et al. 2011). Allogeneic transplant was associated with a lower risk of relapse, higher NRM, longer leukemia-free survival, but only a nonsignificant increase in overall survival. Kurosawa et al. reported a retrospective study of patients aged 50–70 with AML in first remission, using Japanese national registry data, comparing transplanted versus nontransplanted patients (n = 152 versus 884, respectively) (Kurosawa et al. 2011). Transplant was associated with lower relapse risk and longer relapse-free and overall survival. In subgroup analysis, transplant was associated with improved overall survival among patients with an eligible sibling donor, but not among patients with only an unrelated donor. Finally, Versluis et al. reported results from older patients enrolled in four successive prospective HOVON-SAKK acute myeloid leukemia trials. In multivariate analysis of 640 patients aged ≥ 60 years who achieved CR1, receipt of allogeneic transplant in CR1 was associated with improved 5-year overall survival versus nontransplant approaches, especially in intermediate and poor risk groups (mirroring results from the US meta-analysis study (Koreth et al. 2009) in younger patients) (Versluis et al. 2015).

One prospective multicenter study of allogeneic transplant in older AML patients was conducted from 2004 to 2011 through the Alliance cooperative group and the BMT CTN (CALGB 100103/BMT CTN 0502) (Devine et al. 2012). AML patients in first remission aged 60–74 underwent sibling or unrelated reduced intensity conditioning (RIC) transplant. The trial enrolled 123 patients with a median age of 64. At 2 years, DFS and OS were 39% and 46%, respectively, with TRM 14%. Acute severe

GVHD at 100 days was 3% and chronic GVHD at 2 years was 26% (similar to a large study of nonmyeloablative transplant reported by Sorror and colleagues in patients 60 years and older (Sorror et al. 2011)).

A prospective donor versus no donor comparison (a.k.a. "biologic randomization") for older patients with AML has been presented in abstract form by Niederwieser et al. (Niederwieser et al. 2014). As part of the OSHO AML 2004 trial, patients in CR1 underwent randomization based on donor availability (matched related and unrelated donors preferred, though mismatched unrelated donors allowed for high risk disease). In an analysis of 315 patients aged 60–74 years, receipt of a reduced intensity allogeneic transplant improved leukemia-free survival relative to consolidation chemotherapy (32% vs. 13% at 8 years, $p < 0.0005$), reduced incidence of relapse (40% vs. 79%, $p < 0.0001$), but produced higher NRM (28% vs. 9%, $p < 0.0001$). The improvement in overall survival after allogeneic transplant was not statistically significant (35% vs. 24% at 8 years, $p = 0.18$). In a subsequent analysis, benefit of allogeneic transplant was seen in European Leukemia Net (ELN) Intermediate-1, Intermediate-2, and High risk groups (Niederwieser et al. 2016).

These studies demonstrate that RIC allogeneic transplant in the older patient population is feasible and outcomes are encouraging; this study provides a benchmark for outcomes against which other nontransplant AML therapies can be measured.

For older patients with myelodysplastic syndrome (MDS), decision analysis has been a particularly informative approach in understanding the role of allogeneic transplant. Koreth et al. used Markov modeling to compare reduced intensity transplant versus nontransplant strategies for patients aged 60–70 (Koreth et al. 2013). For patients with low/intermediate-1 risk MDS, nontransplant therapies remain the favored approach, but for patients with intermediate-2/high risk MDS, allogeneic transplant improves both life expectancy and quality-adjusted life expectancy.

Regardless of disease type, a consideration of treatment alternatives should always include clinical trial options. In the current era of somatic mutation profiling and targeted therapies, nontransplant alternatives (as well as posttransplant maintenance options) have proliferated, at least in clinical trials. Immunotherapy represents another particularly exciting approach, generally restricted to clinical trials at present.

Assessing Candidacy for alloHCT: Disease-Specific Factors

Once a decision is made that a patient's disease type and risk should prompt preliminary consideration of alloHCT, the next step is to determine whether or not that patient is a transplant candidate. Evaluation of disease control, donor options, and social support should always occur regardless of patient age. However, older age requires a more nuanced approach to disease-specific factors, as well as patient-specific factors discussed in section "Assessing Candidacy for alloHT: Patient-Specific Factors" (Fig. 1).

Disease Prognosis

Poor disease-free survival without transplant will generally spur consideration of transplantation. Unfortunately, in older AML patients, even traditionally "good risk" prognostic factors appear to be trumped by older patient age; for example, patients with AML aged 60 and older fare considerably worse after standard induction and consolidation relative to younger patients for the same cytogenetic and molecular markers (Buchner et al. 2009; Grimwade et al. 2001; Prebet et al. 2009). Therefore, consideration of allogeneic transplant is usually warranted in older patients, and could be entertained even in AML with "good risk" prognostic markers.

Disease Control

Disease relapse remains the most common cause of transplant failure, and poorly controlled disease precludes alloHCT in a large number, if not the majority, of older patients. The tendency to de-escalate initial therapy due to older age may produce lower response rates. However, in older patients who will be receiving a reduced intensity

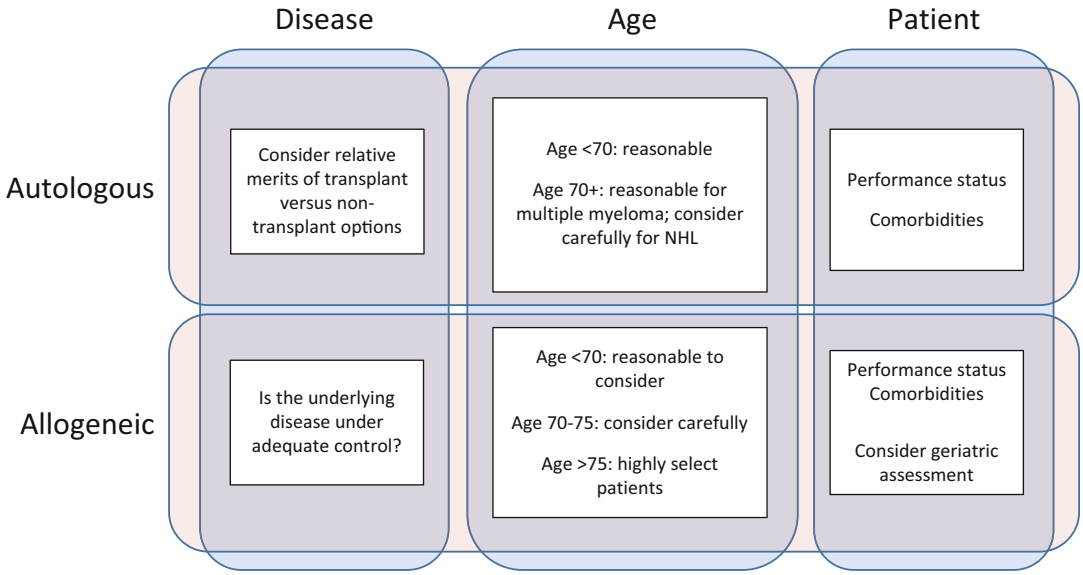

Fig. 1 Evaluation of autologous or allogeneic transplant candidacy in older patients including disease-specific and patient-specific factors (Adapted from Artz and Olin 2016)

transplant regimen, excellent disease control is paramount in reducing the risk of rapid post-transplant relapse before the graft versus malignancy effect can occur, particularly in highly proliferative malignancies. In the current era of minimal residual disease testing, more and more refined estimations of disease control is now possible. That said, it is not clear that additional therapy to achieve MRD negativity warrants the delay in time to transplant, with the associated risk of disease relapse. Overall, the best approach may be to refer for consideration of transplantation soon after diagnosis, and consider intermediate intensity preparative regimens for patients with positive MRD, if tolerated, by incorporating patient fitness as below.

Assessing Candidacy for alloHT: Patient-Specific Factors

Chronologic Age

For alloHCT, older age increases rates of TRM even adjustment for other parameters affecting treatment tolerance (Sorror et al. 2014; Muffly et al. 2014). While most patients in their 60s are now routinely offered allogeneic and autologous transplant, one should be much more cautious in patients 70 years and older and consider only the most robust adults 75 years of age or greater for alloHCT. A clinical trial is highly preferred.

Performance Status

Physician-rated performance status, most commonly measured using the Karnofsky index (KPS), performs well as a screening tool. The majority of older adults undergoing allogeneic transplant have a high KPS of $\geq$80%, making performance status a relatively coarse measure for prognostication. Performance status has been associated with TRM and overall survival after allogeneic transplant; specifically KPS $\leq$80 was associated with decreased overall survival in a large CIBMTR analysis of AML patients (Alousi et al. 2013). Older patients with KPS less than 80% should be scrutinized before offering allogeneic transplant. Patients with an inter current event or recent treatment may recover KPS but loss of performance status and delayed time to recover may still reflect impaired reserved.

Comorbidity

Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) has become the most

validated comorbidity measure for TRM and OS in alloHCT independent of age (Sorror 2009; Sorror et al. 2005, 2011, 2014, 2015; Raimondi et al. 2012; Keller et al. 2014). Sorror et al. proposed the composite Comorbidity-Age index, which can risk stratify patients based on the combination of these two variables (Sorror et al. 2014). We prefer, based on larger registry studies showing an independent effect of older age by categories, to consider age separately and inspect fitness more closely. Of note, outcomes for nontransplant therapy will also suffer in the presence of higher comorbidity (Giles et al. 2007; Sperr et al. 2010). Therefore, the decision of whether to avoid transplant based solely on high comorbidity is complex.

Considering comorbidity prior to transplant testing must account for incomplete testing and realize all data on the HCT-CI derives from the immediate pretransplant period among transplanted patients. The most common comorbidity of pulmonary will usually require pulmonary function testing for accurate assessment of respiratory function and may result in a falsely low score if PFTs are not performed. Alternatively, DLCO results may falsely elevate the HCT-CI score, depending on the specific calculation methodology (Dinkara vs. Cotes) used by each PFT lab (Coffey et al. 2013). Laboratories value may fluctuate in the pretransplant period (e.g., renal, liver) and alter the final HCT-CI score.

Higher comorbidity, such as HCT-CI of 3 and particularly 4 or more, is associated with high rates of TRM (Sorror et al. 2015). However, we caution against decisions based on the score alone and advise clinical interpretation for severity. For example, an HCT-CI score of 3 will be obtained from either an early stage breast cancer remotely resected without additional therapy or locally advanced bladder cancer after chemoradiation, though only the latter would markedly impair transplant tolerance. Finally, comorbid conditions not scored by the HCT-CI often have relevance, such as other concurrent hematologic malignancies, hip fracture, dementia, or thromboembolic disease.

Functional Status and Geriatric Assessment (GA)

Functional impairments and frailty may develop in older age without comorbidity per se. Functional status summarizes physiologic health through self-report and performance-based testing. Patient self-reported function holds consistently high predictive value in geriatrics as this offers insight into both function and environmental adaption to limitation and ultimately offers insight into life expectancy (Cruz et al. 2013). Limitations in functional status may be due to a single severe functional deficit or more commonly a combination of vulnerabilities that may not be readily apparent to the treating physician. Performance-based or objective functional status measures can isolate and quantify functional impairment, often through simple bedside tests and may promote objectively tracking changes over time.

GA represents a comprehensive health assessment designed to measure a wide variety of health domains including functional status, comorbidity, cognition, nutritional status/weight loss, social support, psychological health, and polypharmacy, among others. GA has found widespread application in the field of oncology (Wildiers et al. 2014). Brief cancer-specific geriatric assessments have been employed to predict chemotherapy related toxicity in older solid tumor patients, as well as survival in older AML patients (Hurria et al. 2011; Klepin et al. 2013). Recent evidence suggests that GA is feasible in the older stem cell transplant population, and can uncover significant vulnerabilities not captured by more traditional measures such as performance status.

The largest study of GA prior to allogeneic transplant, reported by Muffly et al., included 166 allogeneic transplant recipients aged 50–73 who were clinically deemed fit for transplant and underwent abbreviated GA; 51% were found to be prefrail and 25% were frail, using the widely accepted Fried Frailty Index (Muffly et al. 2013). Forty percent had limitations in their Instrumental Activities of Daily Living (IADL), a measure of functional status; among patients with an ECOG performance status of 0, 28% were still limited in IADL. Holmes et al. described a series of

50 clinically selected allogeneic transplant patients who underwent a more extensive GA and confirmed high prevalence of functional limitations, with 22% of patients characterized as frail (Holmes et al. 2014). Finally, Olin et al. reported a 42% incidence of IADL impairment in patients over the age of 50 undergoing allogeneic or autologous transplant, with high rates of impairment even in patients with good performance status and few comorbidities (Olin et al. 2014). By comparison, surveys of community-dwelling older adults show <10% prevalence of IADL impairment (Lin et al. 2012). Thus, even in patients who are deemed by their physician to be fit for allogeneic transplant, significant functional limitations still exist.

Evidence also suggests that such baseline functional limitations may predict transplant outcome. In one study, the presence of IADL limitation, slow walk speed, and poor mental health were each independently associated with reduced overall survival, even when adjusted for traditional prognostic factors such as age, comorbidity, and active disease (Muffly et al. 2014). Using a simple risk score with 1 point each for IADL impairment and HCT-CI score $\geq$ 3, 2-year overall survival was 63%, 29%, and 0% for 0, 1, and 2 points, respectively, among the cohort 60 years and older. The specific measure used to quantify functional limitation may be important, as another study found that the 6-min-walk test among all aged patients (an objective measure of functional status) did not add prognostic ability beyond Karnofsky performance status (Jones et al. 2015).

Other GA measures standardly include cognitive function, social support, emotional health, nutrition, and polypharmacy. Cognitive function in particular may be one of the most important and yet one of the most challenging to measure, given the time and personnel required to perform these assessments in combination with the relative insensitivity of most cognitive screening tests for subtle degrees of cognitive impairment. Estimates of the rate of cognitive impairment in the transplant eligible population range from 16% on screening tests (Holmes et al. 2014) to 67% by comprehensive neuropsychological testing (Artz, unpublished data).

Although GA in pretransplant patients reveals vulnerabilities which may predict posttransplant outcome, an unanswered question is whether pre or posttransplant intervention to improve functional status will ameliorate adverse outcomes. Although intuitively appealing, studies will be required to address such a strategy. This may involve a standardized intervention for all patients (e.g., an exercise program (Jacobsen et al. 2014)), a multidisciplinary geriatric oncology approach targeting each patient's unique vulnerabilities (Randall et al. 2016) or both. Table 3 summarizes GA domains, specific measures, and potential targeted interventions.

Donor Considerations

A matched sibling donor remains the established optimal donor for allogeneic transplant, regardless of disease type or transplant center. However, for older patients whose siblings are also older, concerns may arise about the health of the donor or the donor's hematopoietic cell regenerative capacity. Indeed, older donor age has been associated with mobilizing fewer CD34+ progenitor cells after G-CSF (Richa et al. 2009). In general, a medically cleared donor aged 50–70 will likely have an adequate collection, but there is little data on donors >70 years of age.

A CIBMTR analysis of 2172 recipients aged $\geq$50 years compared transplant outcomes using grafts from matched siblings >= 50 years versus unrelated donors <50 years suggested matched related donors are preferred (Alousi et al. 2013). Rates of both acute and chronic GVHD were higher after an unrelated allograft. For older recipients with preserved performance status (KPS of 90% or more), survival was better after matched sibling allografts. However, for recipients with KPS $\leq$80, there was no difference in outcomes between sibling and unrelated donor sources. Few related donors, however, were 70 years and older. In a registry study by Muffly et al. of alloHCT patients 70 years and older with AML, MDS, and NHL, outcomes for matched related and unrelated donors were similar (Muffly et al. 2016). Smaller series generally show at least equivalent outcomes using older sibling versus unrelated donors, with one exception (Sorror et al. 2011; De Latour et al. 2012; Kroger et al. 2013). Therefore, a matched

Table 3 Geriatric assessment domains, specific measures, and potential interventions

Domain	Measures	Interventions
Comorbidity	Hematopoietic cell transplantation comorbidity index (HCT-CI) Cumulative illness rating scale (CIRS)	Subspecialty consult for optimization of comorbid conditions
Functional status – Patient reported	Performance status Activities of daily living (ADL) Instrumental activities of daily living (IADL) Falls	Structured prehabilitation Physical and occupational therapy Home assessment
Functional status – Performance based	4-m walk Timed-up and go 6-min-walk test Grip strength Short physical performance battery (SPPB)	
Social support	Illness-specific subscales of social support (ISSS) Medical outcomes study social support (MOS)	Family meetings Request secondary caregivers Social work involvement
Cognition	Mini-mental status examination (MMSE) Montreal cognitive impairment Mini-Cog Blessed orientation memory concentration (BOMC)	Delirium precautions Medication avoidance Assessment of ability to adhere to treatment Technology support to provider reminders
Psychological	Geriatric depression scale (GDS) Hospital anxiety and depression scale (HADS) Mental health inventory (MHI)	Cognitive therapy and/or medical management
Nutritional status	Body mass index Unintentional weight loss	Nutritional planning Supplementation
Polypharmacy	>5 medications or >8 medications	Hold any unnecessary medications

Adapted from Artz (2016)

sibling donor aged <70 years is currently the preferred donor for an older transplant recipient; however, for siblings >70 years, careful consideration of underlying health conditions should be pursued. We recommend a parallel unrelated donor search especially for a young well-matched unrelated donor (Kollman et al. 2016). Advance collection and cryopreservation of the stem cell product may be a useful option to ensure that the CD34+ cell yield is adequate in older donors.

In the absence of a suitable sibling or well-matched unrelated donor, "alternative" graft sources, such as haploidentical or umbilical cord blood should be considered (Kasamon et al. 2015; Rafii et al. 2016). In particular, haploidentical transplant using the Johns Hopkins approach with posttransplant cyclophosphamide offers low rates of GVHD, albeit with the possible trade-off of a higher incidence of relapse. In a recent retrospective comparison of 8/8 matched unrelated donor versus haploidentical donor transplants for AML, in which 93% of the nonmyeloablative transplants were in patients aged 51–70, haploidentical transplant was associated with lower risk of acute and chronic GHVD with no difference in survival (Ciurea et al. 2015). Since evidence suggests that younger donor age may improve outcome in the haploidentical setting, consideration may even be giving to using an older patient's grandchild as a haploidentical donor in some circumstances (Showel et al. 2015).

Allogeneic Transplant: Case Studies

A 70-year-old woman was diagnosed with AML while on an extended hiking trip to Europe with her daughter. Her medical history was notable for localized hormone receptor positive breast cancer 1 year prior, treated with surgery, radiation, and

hormonal therapy. She was otherwise healthy. At diagnosis, cytogenetics were positive for inversion 16 and molecular testing was negative for kit mutation; this was consistent with therapy related myeloid neoplasia with inversion 16, which can be seen in association with prior radiation (Andersen et al. 2002). She was treated with 7 + 3 chemotherapy. HLA typing revealed that her brother was not a match, and unrelated donor search revealed only 9/10 B-mismatched donors.

Discussion: Inversion 16 is still associated with a better prognosis in older patients with AML, compared to intermediate or poor risk cytogenetic features. However, standard chemotherapy still yields worse overall survival for older patients with inversion 16 AML compared to younger patient harboring the same cytogenetic abnormality (~30% OS at 5 years) (Grimwade et al. 2001; Prebet et al. 2009). Moreover, therapy-related disease tend to have worse outcomes. After discussing allogeneic transplant or chemotherapy alone consolidation, the patient wanted to proceed with transplant but was wary of GVHD. She was motivated by recent encouraging haploidentical transplant data, and elected to receive a transplant from her daughter.

A 75-year-old woman was diagnosed with FLT3 ITD+ AML. Her medical history was notable for diabetes. She had limited social support. She received azacitidine plus sorafenib with palliative intent, and did not undergo HLA typing.

Discussion: This patient's age would require that she have excellent functional status and medical health in order to consider transplant. In her case, her concomitant diabetes was not optimally controlled, and her limited social support appropriately concerned the patient and her treating physician. She also had a reasonable alternative treatment which involved targeting the FLT3 ITD mutation, and was interested in clinical trials of novel FLT3 inhibitors should she did not respond to azacitidine/sorafenib. This also reflects the importance of overt decisions for or against transplant early in the disease course rather than delaying until time of disease progression.

Autologous Transplant

Multiple Myeloma

Effect of Increasing Age on Autologous Transplant Outcomes:

For autologous transplant to be feasible, adequate numbers of hematopoietic stem cells must be obtained. Older patients with multiple myeloma may have more difficulty mobilizing adequate CD34+ progenitor cells than younger patients. A large cohort study of multiple myeloma patients did demonstrate an inverse correlation of age with CD34+ cell collection; however, 92% of older patients were able to collect adequate stem cells for a single autologous transplant (Morris et al. 2003). The advent of Plerixafor has improved rates of successful mobilization even further (Micallef et al. 2013).

Historically, in the era of TBI-based autologous transplants and bone marrow stem cell grafts, the rate of TRM for older patients was 25–35%. In the modern era, using a melphalan-based preparative regimen, peripheral blood stem cells and better supportive care, tolerability, and TRM have been greatly improved. As a result, the definition of "older" for patients with multiple myeloma has shifted. Modern studies investigating the safety and efficacy of patents $\geq$65 or $\geq$70 years with multiple myeloma reflect excellent tolerance with TRM in the 0–5% range. Several retrospective studies have examined the effect of increasing age on transplant outcome, with variable results (Jantunen et al. 2006; Lenhoff et al. 2006; Kumar et al. 2008; El Cheikh et al. 2011) (Table 4).

Bashir et al. published a series of 84 patients $\geq$70 years with multiple myeloma receiving a melphalan-based autologous transplant (65% received 200 mg/m^2) (Bashir et al. 2012). There was no comparator group of younger patients; however, results were impressive with an 85% overall response rate, 3% TRM, a time to

Table 4 Studies evaluating effect of increasing age on autologous transplant outcomes for multiple myeloma

	Population	ORR	TRM	TTP	OS
Jantunen et al. (2006) (Finland)	N = 22 ≥ 65 N = 79 < 65	No effect (94% ORR)	No effect (0%)	No effect (median 23 month PFS)	No effect (median 57 month OS)
Lenhoff et al. (2006) (Nordic)	N = 120 60–64 N = 294 < 60	No effect (90% ORR)	No effect (1%)	Worse EFS in 60–64 (19% at 4 years)	Worse OS in 60–64 (50% at 4 years)
Kumar et al. (2008) (Mayo)	N = 33 > 70 N = 60 < 65 (matched controls)	No effect (97% ORR)	No effect (3%)	No effect Median 28.5 month TTP	No effect Median not reached
El Cheikh et al. (2011) (France)	N = 82 > 65 N = 104 60–65	–	No effect (3.7)	Worse PFS in >65	No effect 32% @ 10 years
Sharma et al. (2014) (CIBMTR)	N = 5818 18–59 N = 4666 60–69 N = 946 ≥ 70	–	No effect (0%)	No effect (3 year PFS 33% in ≥70)	Worse OS by age but similar myeloma specific mortality (72% at 3 years for age ≥ 70)

ORR overall response rate, *TRM* treatment related mortality, *TTP* time to progression, *PFS* progression free survival, *EFS* event free survival, *OS* overall survival
Adapted from Artz and Olin (2016)

progression of 27% at 5 years, and an overall survival of 67% at 5 years. In a large CIBMTR study including over 900 patients age ≥70, 1-year NRM was 0%, PFS 33% at 3 years, and overall survival of 72% at 3 years (Sharma et al. 2014). Overall survival was worse with increasing age, but myeloma-specific survival was no difference, suggesting that age primarily influences non-myeloma mortality. While NRM and PFS were similar between older and younger patients, outcomes after relapse were worse.

Autologous Transplant Versus Other Therapy

Even in the era of novel treatments, autologous stem cell transplant is still an important therapeutic modality for multiple myeloma. In younger patients, stem cell transplant as part of first-line therapy is associated with improved survival compared to no transplant, and improves PFS when compared to delayed transplant (Cavo et al. 2016; Attal et al. 2015).

Three studies have examined the effectiveness of autologous transplant relative to nontransplant therapies in older adults ≥65 with multiple myeloma. Wildes et al. reported a retrospective study of 146 patients aged 65–77 and compared those who received stem cell transplant versus nontransplant therapy. After adjusting for other prognostic factors, stem cell transplant was associated with improved overall survival (Wildes et al. 2015). On the other hand, Offidani et al. compared outcomes of adults ≥65 who received chemotherapy followed by transplant if eligible versus chemotherapy alone if ineligible for transplant; there was no difference in PFS or OS (Offidani et al. 2010). Finally, Facon et al. reported results of a trial randomizing older patients aged 65–75 to receive melphalan and prednisone (MP) chemotherapy, MP with addition of thalidomide, or MP followed by transplant (melphalan 100 mg/m^2) (Facon et al. 2007). The winning arm was the thalidomide-containing regimen, and there was no survival benefit of chemotherapy plus transplant versus chemotherapy alone. However, the study used a low melphalan dose of 100 mg/m^2; higher doses may be tolerated in fit older patients, likely with improved efficacy.

In conclusion, while the relative benefit and morbidity of transplant for older patients with

multiple myeloma remains unclear, autologous transplant in select older patients is well tolerated with low TRM. Based on the Facon data, if a given patient is felt to require melphalan dose reduction to 100 mg/m^2, the relative merits of stem cell transplant for that patient should be reconsidered.

Determining Treatment Tolerance and Transplant Eligibility

The development of novel therapies for multiple myeloma has resulted in significantly improved survival over the past decade. However, older patients with multiple myeloma have experienced only a modest improvement in survival over this time period (Brenner et al. 2008; Pulte et al. 2011; Turesson et al. 2010). This disparity between younger and older patients is likely due to impaired treatment tolerance, as a result of comorbidities and decreased physiologic "reserve."

Whether for transplant or nontransplant therapy, assessment of the "fitness" of an older patient is paramount. In a large CIBMTR study, performance status was associated with overall survival even after controlling for other risk factors in multivariate analysis (Sharma et al. 2014). The International Myeloma Working Group recommends assessment of fitness using not only age but also comorbidities and GA (of particular use are the functional assessments to detect frailty and disability) (Palumbo et al. 2014). In transplant ineligible patients, components of GA have been shown to predict survival and treatment tolerance (Palumbo et al. 2015). Although data in older transplant eligible patients are currently lacking, studies are ongoing to evaluate this question.

The lower risks of NRM after a myeloma autograft enable older and less fit patients undergo therapy. Although transplant eligibility will be less strict, a GA may still be informative to capture health information to anticipate toxicities.

Non-Hodgkin Lymphoma

Several studies, including some very large international database studies, have compared the toxicity and efficacy of transplant in older patients with relapsed NHL (indolent, aggressive, and mantle cell) (Jantunen et al. 2008, 2012; Lazarus et al. 2008; Wildes et al. 2008) (Table 5). Older age is variably defined as >55 to >65 years. Although the smaller studies have tended to show no difference in NRM, PFS, or OS, the larger studies have shown worse PFS and OS in older patients.

Evidence from small series of selected patients with lymphoma demonstrates feasibility of autologous transplant in patients over the age of 70. Elstrom et al. published a series of 21 patients aged 69–86 (Elstrom et al. 2012). Nonrelapse mortality at 100 days was 19%. Age $\geq$ 75 was associated with worse PFS and borderline worse OS in a small number of patients. High comorbidity score by HCT-CI predicted worse outcome.

Table 5 Studies evaluating effect of increasing age on autologous transplant outcomes for NHL

	Population	NRM	PFS	OS
Jantunen et al. (2008) DLBCL	N = 463 $\geq$ 60 N = 2149 < 60	Worse (8.7% at 1 year)	Worse (51% at 3 years)	Worse (60% at 3 years)
Lazarus et al. (2008) NHL indolent	N = 173 $\geq$ 55 N = 615 < 55	No effect (7% at 5 years)	Worse (29% at 5 years)	Worse (54% at 5 years)
Lazarus et al. (2008) NHL aggressive	N = 632 $\geq$ 55 N = 1334 < 55	Worse (15% at 5 years)	Worse (19% at 5 years)	Worse (30% at 5 years)
Wildes et al. (2008) NHL	N = 59 > =60 N = 93 < 60	No effect (8.5%)	No effect (median 22 months)	No effect (median 48 months)
Jantunen et al. (2012) MCL	N = 79 $\geq$ 65 N = 633 < 65	No effect (3.8%)	No effect (29% at 5 years)	No effect (61% at 5 years)

NRM nonrelapse mortality, *NRM* nonrelapse mortality, *PFS* progression-free survival, *OS* overall survival, *DLBCL* diffuse large B-cell lymphoma, *NHL* Non-Hodgkin lymphoma, *MCL* mantle-cell lymphoma
Adapted from Artz and Olin (2016)

Andorsky et al. published results on 17 patients ≥70; NRM was 18% at 100 days and 35% at 1 year (Andorsky et al. 2011). Compared to 39 patients aged 65–69, relapse mortality and overall survival were both worse in the older cohort. In this series, a history of falls (which may be a marker of frailty) was associated with worse outcomes. Compared to myeloma autografts, advancing age seems to be a stronger marker for worse outcomes, likely in part to more intensive regimens given for lymphoma relative to melphalan only for myeloma. The prior treatments for lymphoma may also exact a greater toll on patients relative to novel myeloma-based induction regimens.

In determining whether autologous transplant should be performed for a given older patient, consideration should be given to functional status and frailty, although there are not yet strong data to support this in the literature. Higher HCT-CI has a statistically significant but clinically small effect on rates of TRM and OS after autologous HCT (Pasquini et al. 2012). As well, given the number of novel treatments which have been developed for NHL in recent years, including immunotherapy, the relative merits of transplant versus nontransplant approaches should be weighed.

Cross-References

- Acute Myeloid Leukemia in Older Adults
- Diffuse Large B-Cell Lymphomas in Older Adults
- Low-Grade Lymphomas (Other than CLL/SLL) in Older Patients
- Multiple Myeloma in Older Adults

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Part VI

Solid Tumors

Etienne Brain

Early-Stage Breast Cancer in Older Adults

38

Kwok-Leung Cheung, Lorenzo Livi, and Etienne Brain

Contents

Abstract

Breast cancer is the most common cancer afflicting women worldwide. Its incidence peaks around 70, while mortality increases greatly after 75 years old. Given the competing risks on mortality with multimorbidities, geriatric assessment is a leitmotiv and is considered as the mandatory and non-opposable strategy to use for personalizing treatment. This is especially true for strategies used in early-stage breast cancer since benefits are expected to come with long follow-up.

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Therefore treatment choice needs careful assessment of the benefit/risk balance and guidance according to a general health status assessment, in order to avoid jeopardizing functional status and quality of life.

This chapter will highlight the unmet clinical needs, future opportunities and adjusted strategies for local treatments (surgery and radiotherapy), and systemic treatments (chemotherapy, endocrine therapy, and anti-HER2 treatment) in the older patients with early-stage breast cancer.

Keywords
Adjuvant · Neoadjuvant · Breast cancer · Chemotherapy · Endocrine therapy · Radiotherapy · Surgery · Anti-HER2 therapy

Introduction

Around 40% of breast cancers (BC) occur in women aged 65 and older and 20% in women over 75. Mortality increases greatly after 75 (Biganzoli et al. 2012). This contrasts sharply with the iconic and unfair portrayal of BC in the media and social attitudes. Of note, comorbidities increase in number and severity according to age. They compete with BC prognosis and make necessary to prioritize medical problems and to individualize treatment referring to a geriatric assessment.

A further problem is that older BC patients in trials are fitter than the wider population of older patients, creating important gaps between approvals and applications in routine practice. Indeed the lack of trial guidance for older BC patients has resulted in both overtreatment (given the higher risk of toxicities and competing causes of mortality) and undertreatment (because of age-based restrictions).

As for more advanced and/or metastatic cases, management of early-stage BC in the older person requires specific adjustments and considerations for the different modalities available: surgery, radiotherapy, and systemic treatments.

Surgery

An ancient dictum says, "Good surgeons know how to operate, better ones when to operate, and the best when not to operate." Can we not operate or operate "less" on BC in the older adults in relation to the primary tumor and the axilla? Differing tumor biology according to age, the use of systemic therapy, and mortality due to competing causes of death are the core issues to consider behind this question.

Surgery to the Breast

Over a century ago, George Beatson, a surgeon from Glasgow, first reported the use of endocrine manipulation (using a surgical approach at the time, i.e., oophorectomy) in inducing a complete clinical response on a young woman with inoperable recurrent BC (Beatson 1896). A Cochrane review of 7 small randomized controlled trials comparing surgery with primary endocrine therapy, primarily using tamoxifen for estrogen receptor (ER) unselected tumors, in a total of 1,571 older adults, does not show any significant difference in overall survival (OS) (Hind et al. 2006). A later systematic review of 6 of these trials and also 31 non-randomized studies demonstrates an advantage for surgery over primary endocrine therapy in terms of disease control and a likely survival benefit in older adults with a predicted life expectancy of 5 years or more (Morgan et al. 2014). Patients treated only with aromatase inhibitors (AI) were found to have superior rates of disease control when compared to tamoxifen. Our group was involved in two of these randomized controlled trials, and the long-term results show a significant correlation between the efficacy of primary endocrine therapy and ER status, e.g., the 10-year local failure rate decreased from 80% to 43% from the first trial (ER unselected) to the second one (ER H (histochemical)-score $\geq$ 100 (out of a maximum of 300) required) (Chakrabarti et al. 2011; Johnston et al. 2012). We have also analyzed a consecutive cohort of 1,065 older women with ER (H-score $\geq$ 50)-positive tumors treated by either surgery or primary endocrine

therapy over a 37-year period in a single institution and noted no difference in BC-specific survival rates between both groups when the H-score was ≥250 (Syed et al. 2011). With tamoxifen being used in 69.3% of the patients receiving primary endocrine therapy, the median time to progression was 49 months (4–132 months), which was significantly prolonged with the use of an AI (Syed et al. 2011). All this data suggests that primary endocrine therapy may produce comparable survival outcome to that of surgery in patients with strongly ER+ tumors. Our work along a similar line shows that not just that BC in older adults tend to be ER+, they are more ER rich. In a series of over 3,000 primary BC patients, the peak H-score in all age groups was found to be between 100 and 200 with the exception of those ≥70 years, when it was between 200 and 300 (Cheung et al. 2008). Partitional clustering of a panel of 24 biomarkers measured by immunohistochemistry (IHC) of tissue microarrays constructed from surgical specimens from our institution has also demonstrated differing biology according to age, with a unique subtype, "low ER luminal," showing low ER expression and overexpression of luminal cytokeratins), identified in the older population (Syed et al. 2013). In summary, if we were to consider not operating on an old adult with BC, someone with an ER-rich tumor (approaching an H-score of 300 or equivalent) may be the right person from the biological perspective, as long as systemic endocrine therapy, preferably an AI as opposed to tamoxifen, is being used.

Surgery to the Axilla

Recent pivotal studies have revolutionized the application of the time-honored axillary lymph node dissection (ALND) as surgical treatment to the clinical node-negative axilla. The Z011 trial randomized patients with positive sentinel lymph node biopsy (SLNB) following breast-conserving surgery and receiving postoperative whole breast irradiation and adjuvant endocrine therapy (for ER+ tumors) to proceed to ALND or no further axillary treatment (Giuliano et al. 2011). Omitting ALND did not show an inferior survival. In the AMAROS trial where patients with positive SLNB were randomized to receive either ALND or radiotherapy to the axilla, showing no difference in recurrence or survival, the omission of surgery was associated with a significantly lower incidence of lymphedema (Donker et al. 2014). The use of preoperative ultrasound assessment, a widely practiced standard of care in the UK, coupled with the use of SLNB, means that for those patients undergoing SLNB (implying a negative preoperative axilla on imaging with or without needle cytology or biopsy), the chance of finding a huge tumor burden in the remaining axilla is expected to be even lower than as shown in these trials. As a result, a number of national and international guidelines have changed advocating the omission of axillary treatments, including ALND and even SLNB in selected cases (Coates et al. 2015; Lyman et al. 2014; Association of Breast Surgery Consensus Statement 2015). In contrast to the trials mentioned above in relation to primary endocrine therapy versus surgery to the breast primary, these trials investigating axillary treatments were not specific to the older population. Given the argument in terms of differing biology with a higher chance of ER+ and ER-rich tumors in the older adults, it is not difficult to imagine that the proposed approach to *all* patients as per these changing guidelines should be even more applicable to the older population.

Other Factors to Consider and Future Directions

When compared to their younger counterparts, older adults have shorter life expectancy due to comorbidities or competing causes of death (Yancik et al. 2001). None of the above studies demonstrate any impact on survival with the use of "less" surgery, which however has been shown to be beneficial in terms of local control in the cases of treating the primary tumors (Hind et al. 2006; Morgan et al. 2014; Chakrabarti et al. 2011; Johnston et al. 2012). This effect however may be offset if the life expectancy of the person is

reduced. Our work shows that the median time to progression for primary endocrine therapy using anastrozole was around 5 years as compared to approximately 4 years for tamoxifen, regardless of ER H-score (as long as it was ≥50) (Syed et al. 2014). More potent and novel endocrine agents continue to be developed. Fulvestrant, a selective ER downregulator, has recently been shown in a phase III trial to be significantly more efficacious than anastrozole when used in advanced BC (Robertson et al. 2016). Based on all these factors, primary endocrine therapy with a more potent agent, if used in an older adult with shortened life expectancy due to comorbidities, and a very strongly ER+ tumor, may produce the optimal outcome in terms of local control, survival, and health-related quality of life (HRQoL). The same principles should apply to the selection for axillary surgery. Future research should also aim to personalize treatments (surgery or no or "less" surgery) taking full account of both biological (e.g., biomarkers other than ER, exploiting other techniques such as genomics) and geriatric (e.g., frailty, patient choice) (Hubbard) information into consideration.

Radiotherapy

Radiotherapy in older BC patients follows much less standard guidelines than in younger ones and is omitted in 40% after 75 (Schonberg et al. 2010; Biganzoli et al. 2012).

Radiotherapy Omission

Some authors have investigated the possibility to omit it after breast-conserving surgery in older patients, in ER+ cases with very good prognosis (Hughes et al. 2013). With long follow-up beyond 10 years, they have reported that although radiotherapy decreases local and regional relapse, it does not impact on OS in these patients aged 70 and above. This is in partial agreement with the Oxford overview which has shown an OS benefit of locoregional radiotherapy, observed as early as from 5 years of follow-up, but in the general adult population. Therefore, omitting adjuvant radiotherapy after breast-conserving surgery in older patients with small tumors and very good prognosis has been adopted by important guidelines as the NCCN. However, it remains debated and attitudes vary greatly across countries. The psychological burden of local recurrence should not be neglected, and compliance to endocrine therapy should be closely monitored. When considered, final decision to omit adjuvant radiotherapy should always take into account an estimate of life expectancy.

Innovations

The International Society of Geriatric Oncology (SIOG) recommends tailoring radiotherapy to patients using specific techniques and schedule modalities that will minimize toxicities without reducing effectiveness: position (lateral or prone), volume (partial), once-per-week fractionation, and accelerated partial breast irradiation (PBI) (Kunkler et al. 2014).

Hypofractionated schedules are validated and provide good alternatives to standard fractionation, sparing expensive and burdensome transportations, especially in case of long distance from home (Fast 2011; Kirova et al. 2009).

Potential advantages of accelerated PBI include shorter treatment time, improved cosmesis, and cost reduction compared with standard whole breast radiotherapy (e.g., IMPORT trial (Coles et al. 2017)). Intensity-modulated radiotherapy (IMRT) has the theoretical advantage of a further increase in dose conformity compared with three-dimensional techniques, with increased normal tissue sparing, with potential benefit in older patients (Meattini et al. 2015). This is particularly important since age > 70 years seems to be one of the most significant factor for the occurrence of ischemic heart disease induced by radiotherapy (Darby et al. 2013).

Moreover, according to the BASO-II trial (Blamey et al. 2013), patients treated with either exclusive adjuvant radiotherapy or endocrine therapy show the same low yearly locoregional relapse rate (0.8%). This questions the systematic

use of both strategies in very good prognosis cases, especially for older patients in whom mostly HRQoL drives treatment's choice, making patient's information crucial to avoid compliance issues observed with extended endocrine treatment or burdensome transportations with radiotherapy.

Systemic Treatment

Systemic treatment for early-stage BC must be interpreted in the context of the important effort led to identify subgroups of tumors with different prognosis according to in-depth biology. Since the shift in treatment decision from prognosis to prediction which happened during the first 2000 decade, treatments have evolved toward more personalization combining both aspects (Curigliano et al. 2017). One now considers treatments relying first on several biological features, expression of hormonal receptors [ER and progesterone receptors (PgR)], and HER2, distinguishing roughly three groups: luminal cases (ER+ and/or PgR+), triple-negative tumors (ER-, PgR-, and HER2-), and HER2+ disease (overexpression of HER2 by IHC or amplified by F(C)ISH). The proliferation rate (e.g., Ki67) is used to differentiate further luminal cases that are aggressive from others, knowing that its optimal threshold (around 20–25%) is still a matter of debate.

Based on this evolving strategy, priority systemic treatments match all these categories: endocrine therapy for luminal cases, chemotherapy for triple-negative tumors, and when proliferation is considered as high, anti-HER2 treatments for HER2+ tumors but combined with chemotherapy as a standard since the benefit seems to derive from a high synergism between both classes of compounds.

In the general population, all these "priority" treatment modalities can be combined, either out of principle (e.g., anti-HER2 treatment and chemotherapy) or because of the benefit that can be expected from the different actions (e.g., chemotherapy if more than three lymph nodes involved in addition to endocrine therapy in ER+ and/or PgR+ tumors).

However, in adjuvant setting, treatments are applied blindly postoperatively based on a risk estimate summarizing the delicate trade-off between benefit sought through treatment (correction of a risk of relapse and death) and potential side effects. By essence, the long-term projections of benefit for such strategy aiming at postponing as much and as late as possible – if not cancelling – the risk of relapse collides bluntly with the list of comorbidities and competing risk for mortalities, all increasing in incidence and in severity with aging (Kendal 2008; Piccirillo et al. 2008).

One can look at each systemic treatment modality.

Endocrine Therapy

Given the clear gradual increase of the proportion of luminal cases according to age (Jenkins et al. 2014), most of older patients are beforehand candidates for adjuvant endocrine therapy. The historical debate between AI versus antiestrogen (tamoxifen) is over. Although there is a small additional benefit on disease-free survival (DFS) favoring AI, the true impact on OS is limited to one or two trials, stressing the need to pay attention first and foremost to side effects to ensure good compliance and regular intake. Indeed older patients with bone and joint disease are more at risk of stopping treatment with increased arthralgias and fractures as reported with the use of AIs (Coates et al. 2007). Risk of side effects or poor compliance may be worsened after an ALND or even a SLND, in those with a carpal tunnel syndrome or with severe osteoporosis. On the other hand, decreased functionality with low mobility may expose to a higher risk of thromboembolic events, more frequent with antiestrogen as tamoxifen.

Chemotherapy

Key cytotoxic agents in BC management are more difficult to handle in older patients because of the higher risk of side effects: congestive heart failure with anthracyclines (Swain et al. 2003), peripheral neurotoxicity and taxanes (Biganzoli et al. 2016),

and myelosuppression with most cytotoxic agents requiring a wider use of G-CSF for primary prophylaxis of febrile neutropenia (Biganzoli et al. 2012). Adjuvant chemotherapy can provide similar benefits in older patients than in younger ones, but the risk of toxicity is higher, including fatal events (x10) and should be cautiously monitored (Muss 2005). This is also why selecting cases relevant for such strategy is crucial, especially since so few patients older than 65 have been included in most trials of adjuvant chemotherapy, preventing from drawing any solid conclusion, and breaking the usual implemented misconception of the extrapolation of data obtained in younger patients to older ones.

Chemotherapy is clearly beneficial in patients with ER- disease, with up to 25% mortality (BC-specific and global) reduction and an early effect, at 2–3 years when relapse peaks. Therefore it should be always considered for ER- disease, even in older patients, after careful general evaluation. This has been very well highlighted in retrospective works on large series where benefit vanishes as soon as the ER- population is mixed with the ER+ one (Elkin et al. 2006; Giordano et al. 2006), as well as in prospective trials as the CALGB 49907 where there was a high interaction between ER status and the efficacy of standard chemotherapy (Muss 2009).

Validated regimens are fuddy-duddy and include four cycles of doxorubicin/cyclophosphamide (AC) and the old cyclophosphamide/methotrexate/fluorouracil (CMF) (Muss 2009) or four cycles of docetaxel/cyclophosphamide (TC) (Jones et al. 2009). Sequential schedules (anthracyclines followed by taxanes) have never been rightly investigated after 65 years and usually double the length of chemotherapy period which is highly influential on the risk of serious side effects as identified in the last work led by the late Arti Hurria (Hurria et al. 2018), reflecting the decline of functional reserves with age.

For chemotherapy, the main question mark remains whether selected patients with ER+ disease may derive some additional benefit from chemotherapy without triggering high rates of side effects and jeopardizing the whole therapeutic plan. This explains why so much expectation has been put in multiparametric tests assessing the in-depth biology of the tumor with genome profiling. However, despite large trials with number of patients often exceeding 5,000 each, none has been led consistently with accrual closed to patients aged 65 and above, making the extrapolation of the use of such signatures in older patients from the data obtained in younger ones very theoretical and inadequate. A solution could be to factor part of the age-linked heterogeneity and competing risks in these algorithms. More recent research, as the ASTER 70s randomized phase III, addresses this issue and might help in the future fine-tuning indications of chemotherapy for ER+ BC in older patients (Coussy et al. 2016). Until this happens, adjuvant chemotherapy for ER+ BC patients above 65–70 should be considered only as optional and in a very limited number of cases, endocrine treatment bringing already an important benefit.

Anti-HER2 Treatments

Despite accounting for 40% of BC patients, few older women have been included in pivotal trials: only 16% of patients in the key studies of adjuvant trastuzumab were 60 and above. Trastuzumab, pertuzumab, and neratinib are all approved for (neo) adjuvant therapy.

The benefit of adding trastuzumab to adjuvant chemotherapy is independent of age as shown in most large adjuvant trials like HERA (Cameron et al. 2017). Attempts to use anthracycline-free regimen potentially decreasing the cardiac risk as in the BCIRG 006 with docetaxel and carboplatin (TCH regimen) cannot be considered valid in the older population which was excluded from the trial (Slamon et al. 2015).

Indeed, establishing the standard adjuvant trastuzumab regimen in older patients is difficult since the accompanying chemotherapy remains poorly defined. Data are lacking for sequential chemotherapy, leaving us with the old-fashioned four AC, six CMF, and four TC. The attractive results from a single-arm study led in patients with low-risk HER2+ node-negative BC with weekly paclitaxel x12, and trastuzumab have opened by extrapolation such use for older ones but with a

very low level of evidence and the risk of neuropathy (Tolaney et al. 2017).

Although most trials of short-duration trastuzumab (6 months or 9 weeks vs. 1 year) failed to show the non-inferiority of shorter duration, PERSEPHONE did find that 6 months trastuzumab was non-inferior to 12 months (Earl et al. 2018). Some subgroup analysis suggests also that patients with small node-negative tumors would not derive extra benefit from extending trastuzumab beyond 6 months (Kramar et al. 2014). In these studies showing lower rate of cardiac dysfunction with the shorter-duration arm, shorter duration might be relevant in older patients at increased cardiac risk.

Of note, data from the Surveillance, Epidemiology, and End Results (SEER) registry show that patients >65, especially octogenarians and those with comorbidities, often receive incomplete ($\leq$ 9 months) treatment (Vaz-Luiz et al. 2014), whether related to the chemotherapy partner or to the antibody. Delay or cessation was seen in 15–40% of cases. Thirty percent of patients developed an LVEF decrease $\geq$10% and 3–11% were hospitalized for cardiac events within 1–2 years of follow-up.

As oral formulation for chemotherapy, subcutaneous trastuzumab would help older patients avoid the need to travel to hospital if approved for administration at home.

Although approved for extended treatment after trastuzumab, neratinib, an irreversible TKI of HER1, HER2, and HER4, gives more than 40% of grade 3–4 diarrhea making it unlikely such a strategy will suit the general older population (Chan et al. 2016).

Dual blockade with pertuzumab (or lapatinib) and trastuzumab is another attractive innovative strategy (von Minckwitz et al. 2017). Disappointingly, studies exploring this concept had no greater success than previous ones in enrolling patients >65. Moreover, to the issues of selecting the right chemotherapy partner and controlling the increased risk of side effects, dual blockade adds the difficult selection of older patients according to frailty status for a modest absolute benefit.

Actually the crucial research question remains whether HER2+ BC can be adequately treated by adjuvant anti-HER2 therapy alone, as suggested by the randomized Japanese study (RESPECT) (Sawaki et al. 2018).

Table 1 summarizes some of the key points regarding adjuvant chemotherapy and anti-HER2 treatment in older early-stage BC patients, based on SIOG recommendations (Biganzoli et al. 2012; Brain et al. 2019).

Table 1 Summary of key points on chemotherapy and anti-HER2 treatment in older early-stage BC patients

Chemotherapy	
Indications	Focus on ER- and HER2+ tumors if pT > 5 mm
Regimens	
4 AC (or 6 CMF), 4 TC	Validated
Weekly paclitaxel x 12	Option?
Liposomal doxorubicin	Potential interest (lower cardiac toxicity) but no data
"Sequential" chemotherapy (anthracyclines and taxanes)	No data
Capecitabine or docetaxel weekly	No indication
Primary prophylaxis of febrile neutropenia with G-CSF	From a lower threshold of risk of febrile neutropenia than the standard one used in the adult population (20%)
Trastuzumab	
Indications	No restriction if chemotherapy indicated
Regimens	
4 TC + trastuzumab	Most validated
Weekly paclitaxel x 12 + trastuzumab (Tolaney et al. 2017)	Option
TCH x 6	Very unlikely in older patients since carboplatin AUC 6!
Trastuzumab without chemotherapy	Can be considered, especially for unfit patients (+ endocrine therapy in the case of ER+ tumors)
Duration	1 year Shorter duration (6 months) may be considered in small node-negative tumors or in patients at increased cardiac risk

Neoadjuvant Strategy

The neoadjuvant approach in older patients can be difficult since this strategy generally involves chemotherapy rather than endocrine treatment, possibly jeopardizing subsequent surgery by causing a deterioration of health status. However, as discussed previously in the surgery section, primary endocrine therapy may be a good alternative to upfront surgery. It allows also exploring new treatments and selection processes, enabling investigating strategies omitting aggressive treatments as chemotherapy through multiple blockade of the HER2 and associated pathways such as ER.

Cross-References

- Biomarkers of Aging (With a Clinical Potential in Oncology)
- Comorbidity in Aging and Cancer
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Principles of Radiation Therapy in Older Adults
- Research Methods: Clinical Trials in Geriatric Oncology
- Systemic Treatment of Metastatic Breast Cancer in Older Adults

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Systemic Treatment of Metastatic Breast Cancer in Older Adults

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Abstract

The management of older adults with breast cancer poses a challenging dilemma to most treating oncologists given the under-representation of older age groups in most pivotal clinical trials. Older patients are at risk of undertreatment, which may be due to physician bias and/or patient preference. There is mounting evidence suggesting that older patients with breast cancer may derive as much benefit from treatment as their younger counterparts. However, generalizing treatment for all older breast cancer patients without further health

assessment poses the risk of over-treatment. Although the efficacy outcomes may be similar across age groups, the tolerance to toxicity may differ, as determined mostly by comorbidities, organ function, and aging heterogeneity. In metastatic breast cancer, the main goal of care is to offer the least toxic treatment that can control symptoms, prolong survival, and preserve the quality of life. Therefore, defining the goals of treatment while carefully assessing the overall health status in addition to risk-benefit ratio is paramount to the treatment decision-making.

Keywords
Breast cancer · Older adults · Systemic therapy · Metastasis

Introduction

Breast cancer (BC) is the leading cause of cancer diagnosis and death in women worldwide, and the risk increases with aging. The BC specific incidence and mortality in women ≥70 years are 21% and 31%, respectively (Ferlay et al. 2013). The incidence of de novo metastatic BC (MBC) is approximately 6–10% (American Cancer Society, Inc. 2015) and unknown in those with metastatic recurrence, although estimated to be higher of around 20–30% (O'Shaughnessy 2005). Managing older women with MBC can be challenging, mainly due to limited evidence from lack of representation in clinical trials and aging heterogeneity. Experts' collaboration has recommended guidelines for managing older adults with MBC (Biganzoli et al. 2012; Cardoso et al. 2017). This chapter will focus on specific treatment considerations and options in managing this complex patient group.

Special Treatment Considerations in Older Adults with Metastatic Breast Cancer

As with any metastatic disease, the goal of care in patients with MBC is to optimize the length and quality of life. Treatment decision is based both on patient and tumor characteristics, as well as on previously received therapies (Fig. 1). As the treatment benefit is seen regardless of age group, age alone is not sufficient to determine the type and intensity of treatment (Cardoso et al. 2017). However, it should be kept in mind that age-related physiological changes are expected to affect various organs and functions, as discussed in section (Patho) physiology of Aging

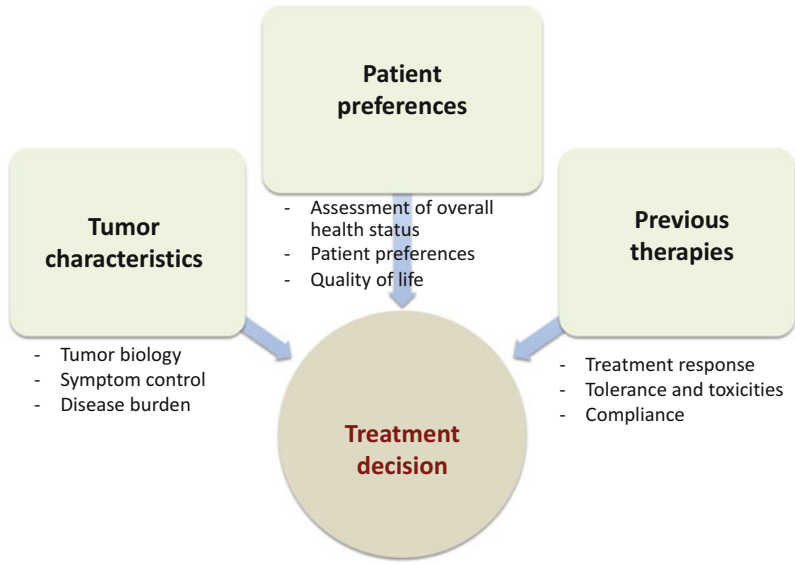

Fig. 1 Treatment considerations for treating older patients with metastatic breast cancer

and Cancer. This can subsequently affect certain pharmacokinetic and pharmacodynamics of numerous anticancer drugs and reduce tolerability of organs/systems to the negative effects of drugs. Understanding the age-related physiological changes and homeostatic reserve in addition to comorbidities is therefore essential.

Several age-related factors can influence the management plan in older adults with MBC. Comorbidities can affect the treatment choice and tolerability; concurrent medications can have important interactions; cognitive and psychological status can impact strategy understanding and consent; adherence to complex treatment regimens and toxicity management, nutrition, and physical function can define tolerance and prognosis; and socioeconomic factors can also influence adherence to treatment. The comprehensive geriatric assessment (CGA) is a multidimensional assessment of the overall health status based on validated geriatric tools that identifies potential health problems on functional, nutritional, emotional, comorbid, and cognitive domains, providing opportunity for interventions, particularly if these are potentially reversible. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) and the Cancer and Aging Research Group (CARG) have both developed an objective scoring system that predicts the risk of chemotherapy toxicity in older patients based on various clinical and laboratory factors (Extermann et al. 2012; Hurria et al. 2011, 2016), which may be useful in assisting with treatment decision-making. CGA has been discussed extensively in section Geriatric Assessment and Management in Oncology.

Systemic Treatment Options and Clinical Evidence

Treatment of Choice for Older Women with Hormone Receptor-Positive Metastatic Breast Cancer

Hormone therapy is the preferred standard option for hormone receptor-positive (HR+) MBC, even in the presence of visceral disease, unless there is a concern or proof of endocrine resistance or visceral crisis, needing a rapid response (Biganzoli et al. 2012; Cardoso et al. 2017). Current endocrine treatment options for older patients are similar with younger postmenopausal patients and must be continued until there is evidence of treatment refractory. Recent data have revealed a significant improvement in the progression-free survival (PFS) when inhibitors to mechanistic target of rapamycin (mTOR) or cyclin-dependent kinases 4 and 6 (CDK 4/6) were added to endocrine therapy, though evidence for overall survival (OS) benefit is still lacking.

The BOLERO-2 study is a phase III, randomized trial comparing exemestane (25 mg/d) plus everolimus (10 mg/d), an mTOR inhibitor, to placebo in 724 postmenopausal women with HR+ MBC recurring or progressing after treatment with nonsteroidal aromatase inhibitors. Depending on the age cutoff of 70, both age groups have shown an improvement in PFS (4.10 months in <70 years and 5.26 months in ≥ 70 years), favoring everolimus combination (hazard ratio, HR 0.44 and 0.45, respectively), and had similar incidences of adverse events (AE), i.e., stomatitis, infection, rash, pneumonitis, and hyperglycemia, although more on-treatment deaths were noted among older patients (7.7% vs. 1.3%) at 18 months of median follow-up (Pritchard et al. 2013). This was attributed to the overall health status that was mainly driven by the comorbidities noted in older patients at baseline. The expanded-access multicenter European trial (BALLET) studied similar patient population as the BOLERO-2 and has reported similar trends in the overall safety of everolimus + exemestane among 2133 women, although the elderly group (26.4%) had a slightly shorter median duration of drug exposure, more frequent dose reductions and interruptions, grade 3/4 adverse events (AE), and treatment-related AE leading to treatment discontinuations and death (Jerusalem et al. 2016). Although recent investigation on everolimus pharmacokinetics suggests no difference among patients aged <70 versus ≥ 70 years and is somewhat reassuring (Willemsen et al. 2016), one cannot make any conclusive statement regarding the utility of dose adjustment strategy,

even if potentially pharmaco-guided. Pharmacokinetics indeed does not investigate functional reserves of drug-targeted organs that are potentially affected by aging and thus cannot be singled out to explain pharmacodynamics as shown for docetaxel, for instance (ten Tije et al. 2005). The new modulators of endocrine resistance present different patterns of toxicity than chemotherapy and deserve similar cautious consideration.

Recently, palbociclib or ribociclib, an oral, small-molecule CDK 4/6 inhibitor, has shown a growth-inhibitory effect in HR+ BC cells by preventing cell-cycle progression from the G1 to S phase (Rocca et al. 2014) and works synergistically with endocrine agents. Subgroup analysis of patients <65 vs. ≥65 years in the PALOMA-1/TRIO-18 trial that assessed the efficacy and safety of palbociclib plus letrozole as first-line treatment for HR+, HER2-negative (HER2-) MBC has shown a significant improvement in PFS and clinical benefit rate (CBR) in both age groups with comparable safety profile at 29.6 months of median follow-up (Finn et al. 2015, 2016). Neutropenia, leukopenia, fatigue, and anemia had similar incidence (>10%) in both age groups receiving combination therapy; nausea was more common in ≥65 and alopecia in <65 age group. Irrespective of age, there was no significant differential incidence of permanent or temporary discontinuations and dose reductions due to AE (Finn et al. 2016). Similarly, palbociclib in combination with fulvestrant has shown a significant PFS improvement at 5.6 months follow-up in 521 women with HR+, HER2- MBC who progressed during prior endocrine therapy, where 24.8% were aged ≥65 years (Turner et al. 2015). Same trends were presented in the pooled analysis of the PFS benefit of palbociclib + endocrine therapy in 872 older patients (25% were ≥65–74, 10% were ≥75 years) without any new safety concerns identified (Rugo et al. 2016). Although patients aged ≥75 developed more myelosuppression, grade ≥3 incidence was similar across all age groups. A phase III trial on ribociclib combined with letrozole for first-line treatment of 668 postmenopausal women (44% aged ≥65 years) with HR+, HER2- recurrent or MBC has also shown increased PFS and a higher rate of myelosuppression (Hortobagyi et al. 2016). Dose interruptions and reductions due to AEs were more common in ribociclib arm. Although the subgroup age analysis on AE has not been reported, similar if not worse trends may be anticipated in older patients, and future investigations need to be explored particularly in the presence of comorbidities, polypharmacy and risk of interactions, and functional impairments. A summary of age comparison on efficacy and safety of novel endocrine treatment options for older adults treated for MBC is reported in Table 1.

Treatment of Choice for Older Women with Hormone Receptor-Negative, Triple-Negative, Hormone Refractory, or Rapidly Progressive Metastatic Breast Cancer

Chemotherapy is the best treatment option for MBC patients with hormone receptor-negative (HR-), hormone-refractory, triple-negative, or rapidly progressive disease (Biganzoli et al. 2012), regardless of age. A 7-year retrospective, single-center analysis of 117 patients aged ≥75 years has shown that chemotherapy administration can be tolerated in this population (Debled et al. 2011). Nevertheless, a significant age-related variation in chemotherapy use has been observed in older patients with MBC (Wan and Jubelirer 2015) highlighting that they are less likely to be offered treatment. Older patients have lesser tolerance to chemotherapy toxicities. A retrospective chart review of 318 patients aged 80+ years initiating chemotherapy (69% with ECOG 0–2; 12% for BC) found a high risk of hospitalization (32%) due to toxicity despite dose delays (31%), reductions (37%), and omission (15%) (Sud et al. 2015). Therefore, it is advocated that single-agent chemotherapy with better safety profile be chosen over combination regimens (Biganzoli et al. 2012). Several chemotherapy regimens have been studied in older women with MBC showing considerable efficacy and safety. The treatment choice will rely on tolerability to toxicities as determined by comorbidities, prior

Table 1 Age comparison of efficacy and safety based on subgroup and pooled analyses on recent pivotal clinical trials on the management of older adults with advanced breast cancer with endocrine therapy

Trial	Treatment	Median follow-up (months)	Efficacy	Safety
Endocrine therapy				
BOLERO-2 (Pritchard et al. 2013)	Everolimus + exemestane vs. exemestane + placebo	18	Median PFS, months (95% CI):	Treatment discontinuation due to AE (%):
***n* = 724**			<**70**: 8.11 vs. 4.01 (0.36–0.54) HR 0.44	<**70**: 6.3 vs. 4.1
<**70**: 77%			≥**70**: 6.77 vs. 1.51 (0.30–0.68) HR 0.45	≥**70**: 17.4 vs. 0
≥**70**: 23%			CBR (%):	On-treatment deaths with AE (%):
			<**70**: 56.6 vs. 27	<**70**: 1.3 vs. 1.3
			≥**70**: 35.5 vs. 23	≥**70**: 7.7 vs. 0
BALLET (Jerusalem et al. 2016)	Everolimus + exemestane vs. exemestane	4.6	Median duration of treatment exposure, months:	Dose reductions and interruptions (%):
***n* = 2133**			<**70**: 5.2 vs. 5	<**70**: 26.7, 54.2
<**70**: 74%			≥**70**: 4.1 vs. 3.8	≥**70**: 37.7, 69.5
≥**70**: 26%				AE-related discontinuations (%):
				<**70**: 13
				≥**70**: 23.8
PALOMA-1/ TRIO-18 (Finn et al. 2016)	Palbo + let vs. let + placebo	29.6	Median PFS, months (95% CI):	Grade 3–4 AE (%):
			<**65**: 18.8 (12.8–26.1) vs. 7.7 (2.8–10.9) HR = 0.315	<**65**: 80.4 vs. 10
***n* = 165**			≥**65**: 26.2 (12.6-NE) vs. 12.9 (5.7–22.2), HR = 0.505	≥**65**: 73 vs. 32.4
<**65**: 54%			CBR (%):	
≥**65**: 46%			<**65**: 80.9 vs. 54.8	
			≥**65**: 81.1 vs. 61.5	
Pooled analysis	PALOMA	–	PALOMA-1 and PALOMA-2	Any treatment-emergent grade ≥3 AE occurring ≥20% with vs. without Palbo treatment (%):
	1: Palbo + ET		Median PFS, months, HR (95% CI):	
PALOMA-1, PALOMA-2, PALOMA-3	2: Palbo + Let		≥**64–74**: 27.5 vs. 21.8, HR 0.66 (0.45–0.97), $p = 0.016$	
(Rugo et al. 2016)	3: Palbo + Ful			
***n* = 608**			≥**75**: NE vs. 10.9, HR 0.31 (0.16–0.61), $p = 0.0002$	≥**64–74**: 78 vs. 26
≥**64–74**: 73%				≥**75**: 83 vs. 19
≥**75**: 27%			PALOMA-3	Any grade ≥3 AE occurring ≥1% with vs. without Palbo treatment (%):
			Median PFS, months, HR (95% CI):	
			≥**64–74**: 16.1 vs. 3.7,	≥**64–74**: 20 vs. 14
			HR 0.25 (0.14–0.45) $p < 0.0001$	≥**75**: 24 vs. 9
			≥**75**: 13.6 vs. 7.4, HR 0.87 (0.27–2.79) $p = 0.40$	
MONALEESA-2 (Hortobagyi et al. 2016)	Ribociclib + let vs. placebo + let	15.3	PFS, HR (95% CI) in favor of ribociclib:	–
***n* = 668**			<**65**: 0.52 (0.38–0.72)	
<**65**: 56%			≥**65**: 0.61 (0.39–0.94)	
≥**65**: 44%				

AE adverse events, *CBR* clinical benefit rate, *CI* confidence interval, *ET* endocrine therapy, *Ful* fulvestrant, *HR* hazard ratio, *Let* letrozole, *NE* non-estimable, *Palbo* palbociclib, *PFS* progression-free survival

treatment, dosing schedule, and patient preference. A summary of age comparison on treatment efficacy and safety in older adults treated for MBC using chemotherapy is reported in Table 2.

Capecitabine is a relatively safe and effective oral chemotherapy to use in older women with MBC and has been favored as first-line treatment and as subsequent treatment for those previously treated with anthracyclines and taxanes. In a study of 73 patients aged ≥65 years (median age 73), the dose of 1000 mg/m^2 twice daily was better tolerated than the standard dose of 1250 mg/m^2, particularly in patients with pre-existing renal impairment, with fewer patients needing dose reductions and lower overall incidence of grade 3/4 toxicities reported (Bajetta et al. 2005). The use of a lower-dose capecitabine was supported in a retrospective study on 89 patients aged ≥70 years, even in the first-line setting, confirming that dose reduction, although frequently required in this population, did not affect outcomes (Kotsori et al. 2010).

Vinorelbine has also shown efficacy and safety in MBC without any age-related pharmacokinetic difference (Sorio et al. 1997). Single-agent intravenous vinorelbine had a 35% and 32% objective response rate for first- and second-line treatment, respectively, in a multicenter, nonrandomized, open-label phase II study on 107 women (45% aged ≥65 years) (Weber et al. 1995). The objective efficacy appears to be rather modest when using oral preparation, but this might be biased

Table 2 Age comparison of efficacy and safety based on subgroup and pooled analyses on recent pivotal clinical trials on the management of older adults with advanced breast cancer with chemotherapy

Trial	Treatment	Median follow-up (months)	Efficacy	Safety
Chemotherapy				
CALGB 9342 and 9840 (Lichtman et al. 2012)	Paclitaxel	–	Age had no effect on tumor response, OS, and PFS	Grade 3–4 neurotoxicity (%):
***n* = 300**				<**55**: 23
<**55**: 33.3%				**55–64**: 28
55–64: 33.3%				≥**65**: 48
≥**65**: 33.3%				
EMBRACE (Muss et al. 2014)	Eribulin	–	Median OS (months):	Grade 3–4 AE (%):
Study 201			<**50**: 11.8	Asthenia/fatigue
Study 211			**50–59**: 12.3	<**50**: 5.9
***n* = 827**			**60–69**: 11.7	**50–59**: 6.9
			≥**70**: 12.5	**60–69**: 10.2
<**70**: 90%				≥**70**: 13.9
<50: 30%			Median PFS (months):	Peripheral neuropathy
50–59: 35%			<**50**: 3.5	<**50**: 4
60–69: 25%			**50–59**: 2.9	**50–59**: 7.3
≥**70**: 10%			**60–69**: 3.8	**60–69**: 8.7
			≥**70**: 4	≥**70**: 10.1
			CBR (%):	
			<**70**: 61.4	
			<**50**: 20.2	
			50–59: 20.8	
			60–69: 20.4	
			≥**70**: 21.5	

AE adverse events, *CBR* clinical benefit rate, *PFS* progression-free survival, *OS* overall survival

by the limited number of patients investigated and the varying drug bioavailabilities. In a phase II trial specifically conducted on 25 women aged ≥65 years, CBR was only 12%, median time to progression was 4.7 months, and fatigue and neutropenia were the most commonly reported severe toxicities (Baweja et al. 2006). Fractionated, metronomic dose regimen (50 mg flat dose 3× a week) has provided a comparable efficacy with good tolerability, posing a valid option among less fit older patients who are unable to tolerate the standard regimen (Addeo et al. 2010).

Therefore both capecitabine and vinorelbine are valid alternative to the two main classes of cytotoxic agents used in BC management, anthracyclines and taxanes (Biganzoli et al. 2015).

Anthracyclines indeed increase risks for cardiac toxicities. The risk is higher with older age, independent of comorbidities and performance status; current or history of cardiac dysfunction, hypertension, diabetes and coronary artery disease; prior treatment with anthracyclines; higher cumulative doses (≥400 mg/m^2); and short duration infusion (Aapro et al. 2011a). The International Society of Geriatric Oncology (SIOG) recommends screening for risk factors, rigorous monitoring of cardiac function and early interventions, and use of specific strategies to alleviate cardiotoxicity in this population (Aapro et al. 2011a). Bi-weekly 20 mg/m^2 of pegylated liposomal doxorubicin has been studied in 32 women ≥70 years with locally advanced or MBC (Basso et al. 2013). Response rate was 33.3% in the 27 evaluable women, median time to progression was 10.3 months, and 9.4% had treatment interruption due to toxicities, regardless of the frailty status (vulnerable vs. fit) based on the multidimensional geriatric assessment (Basso et al. 2013).

Conventional, solvent-based paclitaxel and docetaxel have shown significant efficacy when used in MBC. However, peripheral neuropathy is common, especially when given for an extended period of time, and due to the risk of hypersensitivity reactions, steroid premedication is usually administered, causing potential problems with hyperglycemia or even delirium. Older women aged ≥65 years have derived similar efficacy benefit with paclitaxel as younger women for first- or second-line treatment for MBC (Lichtman et al. 2012). However, older patients were noted to have a higher risk for developing specific hematological and non-hematological AEs, particularly more so among patients receiving it as second-line therapy (Lichtman et al. 2012). Weekly paclitaxel at a dose of 80 mg/m^2 was highly active in 46 older women with MBC (median age 74), having an ORR of 53.7%, but was associated with a 15.2% unacceptable toxicity, including febrile neutropenia, severe allergic reaction, pulmonary embolism, and somewhat troublesome and unusual congestive cardiac failure (Del Mastro et al. 2005). Tolerance to docetaxel, either weekly or three-weekly regimen, may also be difficult especially with fatigue, in addition to neurotoxicity, both potentially impacting the level function. It is certainly not to be given above 75 mg/m^2 in routine practice (Biganzoli et al. 2016), unlike in younger adults where 100 mg/m^2 is approved, although rarely used. Nanometer-sized albumin-bound paclitaxel (nab-paclitaxel) allowed safe drug infusion of higher paclitaxel doses, at shorter infusion time, without needing any premedications (Gradishar et al. 2005) and may be a cost-effective alternative when the cost of managing the toxicity is considered (Biganzoli et al. 2016). Prospective data on the optimal dosing, safety and efficacy of nab-paclitaxel in older patients with MBC is lacking. Post hoc analysis of two studies on different nab-paclitaxel dosing schedules vs. solvent-based taxanes in 114 older patients (≥65 years) with MBC has revealed better tolerability and efficacy of weekly nab-paclitaxel over that of the three-weekly schedule and solvent-based taxanes (Aapro et al. 2011b). Recent multicenter, noninterventional, prospective studies that included older MBC patients who were given nab-paclitaxel in a real-life setting have confirmed its efficacy and safety (Potthoff et al. 2016; Steger et al. 2016). The final results of the recently completed EFFECT trial are awaited, where preliminary results have shown that both doses of 100 and 125 mg/m^2 can be safely administered in this population, though non-hematological toxicities were more prevalent in the higher dose (Mislang et al. 2015).

Age subgroup analysis from 827 heavily pretreated patients who received a non-taxane microtubule inhibitor, eribulin mesylate, given at 1.4 mg/m^2 on days 1 and 8 on a 21-day cycle, revealed no age difference on efficacy outcomes in terms of OS, PFS, overall response rate (ORR), or CBR (Muss et al. 2014). No overall age effect was seen on the incidence of AE including neuropathy, neutropenia, and leukopenia, although patient aged ≥70 had a higher observed grade 3/4 treatment-related asthenia/fatigue and peripheral neuropathy (Muss et al. 2014).

Treatment of Choice for Older Women with HER2-Positive Disease

Patients with HER2+ disease should receive HER2-targeted therapy preferably in combination with chemotherapy or with endocrine therapy or as monotherapy depending on the HR status, disease burden or organ crisis, level of fitness, and patient preference (Biganzoli et al. 2012). Trastuzumab, pertuzumab, trastuzumab emtansine, and lapatinib are four HER2-targeted agents that have been approved for treatment of advanced BC with HER2 amplified disease. Meta-analysis of eight pivotal trials on unselected age groups has confirmed the efficacy benefit of adding HER2-targeted agents to standard therapy, with 22% improvement in OS, 37% improvement in PFS, and 67% increase in ORR (Harris et al. 2011). A prospective, multicenter, observational cohort (registHER) study of 1023 patients (17% aged ≥65 years) described the treatment patterns and clinical outcomes of patients with HER2 + MBC (Kaufman et al. 2012). The study revealed that PFS was higher among patients given trastuzumab as first-line treatment regardless of age; however, a significant OS advantage was only noted for patients aged <65 years (Kaufman et al. 2012). In addition, cardiotoxic events during the 27 months of follow-up were higher in older patients, highlighting the need for careful monitoring in this age group who may already be predisposed to cardiovascular events due to pre-existing cardiovascular comorbidities.

Lapatinib in combination with capecitabine has shown superiority to capecitabine alone in women (median 54 years, range 26–80) with HER2+ advanced diseased who progressed after taxane and trastuzumab therapy (Geyer et al. 2006). Similar efficacy was noted regardless of age, although with higher incidence of grade 3 AE (33% vs. 19%) among patients aged ≥70 years and with longer duration of diarrhea (Crown et al. 2008).

Predefined subgroup PFS analysis of pertuzumab, trastuzumab, and docetaxel (CLEOPATRA) according to age has confirmed the efficacy of adding pertuzumab as first-line treatment in older patients with advanced HER2+ MBC, without increasing the risk of cardiac dysfunction, although diarrhea, fatigue/asthenia, anorexia, vomiting, and dysgeusia were more frequently noted in patients ≥65 years, and more peripheral neuropathy attributed to pertuzumab in older patients (Miles et al. 2013). This regimen, therefore, is the new treatment of choice regardless of age, though best given to selected, fit older patients with minimal to no contravening comorbidities (e.g., underlying neuropathy, cardiac dysfunction).

The EMILIA study is a phase III trial showing improved PFS, OS, ORR, and safety profile of trastuzumab emtansine (T-DM1), an antibody-drug conjugate incorporating the HER2 with a microtubule inhibitory agents (DM1), against lapatinib and capecitabine in patients with HER2+, unresectable, locally advanced, or MBC previously treated with trastuzumab and taxanes (Verma et al. 2012). The benefit among patients aged ≥75 years, however, is less definite, without a confidence interval strong enough to show conclusive benefit even if potentially due to limited numbers included in the study (2.5% of the population). When T-DM1 was compared to a physician's chemotherapy of choice after progression from two or more HER2 agents including trastuzumab and lapatinib (TH3RESA), a significant improvement in PFS was noted at 7.2 months median follow-up, favoring T-DM1 (Krop et al. 2014). The number of patients with serious AEs was lower with T-DM1 (18% vs. 21%) although with more common grade ≥3 thrombocytopenia

Table 3 Age comparison of efficacy and safety based on subgroup and pooled analyses on recent pivotal clinical trials on the management of older adults with advanced breast cancer with HER2-targeted therapy

Trial	Treatment	Median follow-up (months)	Efficacy	Safety
HER2-targeted therapy				
registHER (Kaufman et al. 2012)	Trastuzumab vs. non-trastuzumab-based regimens as first-line therapy	–	Median PFS, months (95% CI):	Incidence of any cardiac events (%):
***n* = 1001**			<**65**: 11 (10–11.7) vs. 3.4 (2.4–4); HR 0.40, $p = <0.01$	<**65**: 6.8
<**65**: 79%				**65–74**: 6.7
65–74: 14%			≥**65**: 11.7 (9–12.6) vs. 4.6 (3.3–7); HR 0.52, $p = <0.01$	≥**75**: 25.4
≥**75**: 7%			Median OS, months (95% CI):	
			<**65**: 40.4 (36.1–42.1) vs. 25.9 (19.8–31.4); HR 0.60, $p = <0.01$	
			≥**65**: 31.2 (26.3–34) vs. 28.5 (18.4-NE); HR 0.76, $p = 0.23$	
CLEOPATRA (Miles et al. 2013)	Trastuzumab and docetaxel + pertuzumab vs. placebo	19.3	PFS, months (HR, 95% CI):	Grade ≥ 3 AE, %:
***n* = 808**			<**65**: 17.2 vs. 12.5 (0.65, 0.53–0.80)	<**65**: 73.7 vs. 72.6
<**65**: 84%			≥**65**: 21.6 vs. 10.4 (0.52, 0.31–0.86)	≥**65**: 77 vs. 73.8
≥**65**: 16%			ORR, %:	
(≥75: 2%)			<**65**: 79.5 vs. 68	
			≥**65**: 84 vs. 75.9	
EMILIA (Verma et al. 2012)	T-DM1 vs. lapatinib + capecitabine	19.1	PFS, HR (95% CI) in favor of T-DM1:	–
***n* = 991**			<**65**: 0.62 (0.52–0.74)	
<**65**: 86%			**65–74**: 0.88 (0.53–1.45)	
65–74: 11%			≥**75**: 3.51 (1.22–10.13	
≥**75**: 3%				
TH3RESA (Krop et al. 2014)	Physician's choice vs. T-DM1	7.2	PFS, months (HR, 95% CI):	–
			<**65**: 3.4 vs. 5.8 (0.55, 0.44–0.70)	
***n* = 602**				
<**65**: 85%				
65–74: 12%			**65–74**: 3.2 vs. 6.9 (0.42, 0.22–0.80)	
≥**75**: 3%			≥**75**: 3 vs. NE (0.14, 0.02–0.79)	
KAMILLA (Barrios et al. 2015)	T-DM1	–	–	Any AE (%):
				<**65**: 91.4
***n* = 2001**				≥**65**: 93.6
<**65**: 81%				Grade ≥ 3 related to T-DM1 (%):
				<**65**: 16.1
≥**65**: 19%				≥**65**: 16.6

AE adverse events, *CI* confidence interval, *HR* hazard ratio, *NE* non-estimable, *ORR* objective response rate, *PFS* progression-free survival, *OS* overall survival, *T-DM1* trastuzumab emtansine

compared with more prevalent grade ≥3 neutropenia, febrile neutropenia, and diarrhea in the physician's choice arm (2% vs. 16%, 1% vs. 4%, and <1% vs. 4%, respectively) (Krop et al. 2014). In a pooled safety analysis of 884 patients from 6 studies who were given T-DM1 monotherapy, a numerically higher incidence of grade ≥3 AE was reported in patients aged ≥65 years (52% vs. 44%) (Dieras et al. 2014). The safety and tolerability of T-DM1 was presented in the preliminary results of the KAMILLA study, revealing no age difference in all-grade and grade ≥3 AE associated with T-DM1 (Barrios et al. 2015). A summary of age comparison on treatment efficacy and safety of these trials is reported in Table 3.

Conclusion

Chronological age, by itself, should not preclude access to newer systemic agents, particularly in fit older patients. Although many evidences suggest similar efficacy and safety in many cancer treatments specific to BC regardless of age, it is clearly evident that older patients are predisposed to tolerate their treatment less due to higher susceptibility to toxicities, compounded by the presence of competing comorbidities, compromised organ function, and underlying frailty, to name a few. Hence, older patients warrant explicit monitoring and proactive management of treatment toxicities, which could well match cautious dose escalation strategy especially for vulnerable or frail ones. Despite recent advances in the systemic treatment of MBC, management of older patients is still challenging, given the difficulty of generalizing available treatment regimens to this complex patient group, mostly from underrepresentation in many pivotal clinical trials, variable aging trajectory, and lack of data on managing less-fit or frail patients. Thus, treatment goals and regimens should be personalized taking into account the treatment safety and efficacy but, more crucially, symptom control and burden of disease, the tumor biology and mechanism of resistance, as well as the patient heterogeneity and preference.

Cross-References

- ▶ Biomarkers of Aging (With a Clinical Potential in Oncology)
- ▶ Comorbidity in Aging and Cancer
- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Geriatric Screening in Cancer Patients
- ▶ Normal and Abnormal Aging (General Perspective for the Oncologist)
- ▶ Pharmacology of Aging and Cancer

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Prostate Cancer: Management in Elderly Men Population in 2017

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Abstract

Prostate cancer is the most common cancer in elderly patients. Localized disease is treated following almost the standard of younger patients. However, the treatment depends on health status evaluation. Only patients in good health status with aggressive prostate cancer will benefit of curative treatment, based on the induced comorbidities. Surgery is often not the best option, based on the increased side effects with increased age, compared to external beam radiotherapy. In nonmetastatic situations, androgen deprivation monotherapy has only a minimal place, while it is the standard of care in metastatic situations. Most patients with castration-resistant disease can receive standard treatment. Early introduction of palliative care is mandatory in order to optimize the outcome. Disease aggressiveness and health status are the two main factors to consider, on top of patient's wishes for final decision-making.

Keywords

Prostate cancer · Elderly · Urologic oncology

Introduction

In the USA, there were 119.8 per 100,000 men new prostate cancer diagnosed per year with a mortality estimated of 20.1 per 100,000 men per year based on 2010–2014 data (Ries and Krapcho 2014). Approximately 11.6% of men will be diagnosed with prostate cancer (PCa) at some point during their lifetime (Noone et al. 2017). The GLOBOCAN statistics show 1.1 million new worldwide PCa diagnosed in 2012, representing 15% of the diagnosed cancer in men, ranking it as the fifth most dreadful cause of cancer (Noone et al. 2017).

Moreover, the mortality rate is higher among black population (42 per 100,000 in sub-Saharan Africa compared to 8.8 per 100.000 in Asia). According to the *US Surveillance, Epidemiology, and End Results* (SEER) registry (Ries and Krapcho 2014), the median age at diagnosis and at death was, respectively, 66 years and 80 years during the 2009–2013 period (Ries and Krapcho 2014), with 71% of PCa-related deaths occur in men aged >75 years (Ries and Krapcho 2014). The incidence of elderly patient with PCa will increase as the life expectancy increases (US Census Bureau DIS). Almost 70% of cases are diagnosed based on prostate-specific antigen (PSA). In fact, PSA measure combined with digital rectal examination (DRE) has incredibly changed the diagnosis as PCa is actually discovered earlier with lower extension and better prognosis (Catalona et al. 2017). The main problem is the management of senior adults with PCa. Comorbidities are still the major driver of patient's survival, leading to adapted diagnosis and treatment strategies. This highlights the importance of dedicated guidelines for senior adults. The *International Society of Geriatric Oncology (SIOG)* has updated new recommendations for the management of elderly patient with PCa (Griebling 2015), as well as the *National Cancer Center Network* (NCCN) (NCCN 2016).

Clinical Presentation

Elevation of PSA level associated with suspicious DRE usually constitutes the first step for PCa diagnosis. As for younger men, no systematic

screening is recommended in senior adults (Hayes and Barry 2014). Furthermore the PSA-based early diagnosis is highly questionable beyond 75 years of age based on life expectancy. This must be balanced by individual life expectancy. It is currently recommended to offer an early diagnosis only to those men with at least 10–15 years life expectancy. This might represent up to 20% of aged men (Walter and Covinsky 2001). Biopsies are performed based on an abnormal PSA, a suspicious DRE, or clinical symptoms of advanced cancer (Lavallée et al. 2016).

Nonspecific urological problems such as voiding problems with abnormal/suspect DRE, dysuria, and hematuria might suggest the need for further evaluation. A decreased renal function associated with bilateral ureterohydronephrosis might lead to suspicion, as well as symptomatic metastases such as painful bone lesions (usually inflammatory or related to pressure or movements, pathological fractures). On X-ray, suspicious lesions are usually dense ivory-like bone sign. Neurological symptoms especially those suggesting spinal cord compression might also represent unusual warning signal when the disease is unknown.

Diagnosis, Staging, and Prognostic Factors

Diagnosis

Several guidelines on this topic have been published and recently updated such as the European Association of Urology (EAU) (Mottet et al. 2016; Cornford et al. 2016) and the NCCN (2016).

PCa is usually suspected on the basis of DRE and/or abnormal PSA levels. Formal diagnosis is based on pathology following prostate biopsy cores. Sometimes the diagnosis is made after non-oncological procedures such as transurethral resection of the prostate (TURP) or prostatectomy for benign prostatic enlargement (BPE).

PSA level increases with age (Cochetti et al. 2016) and must be performed in a non-inflammatory, noninfectious, and nontraumatized urinary tract (such as catheterization) matter period.

There is no specific serum PSA level (except when above several hundred ng/ml) which can confirm a PCa. An elevated PSA of $\leq$100 ng/mL can be seen in patients with acute prostatitis. PSA is mainly a signal that might lead to biopsy. Even if biopsy might be questionable in rare unequivocal situations (very high PSA, unequivocal DRE, and images of bone metastases), the standard of care is to confirm the diagnostic with histology, if such a diagnostic is useful. The method to be used for prostate biopsy – transrectal or transperineal biopsies – is still a matter of debate. Anti-aggregants (except aspirin) and anticoagulants must be stopped before biopsying. They are usually performed as outpatient procedures under ultrasound guidance, after an antibiotic prophylaxis. When a nodule is palpable, directed biopsies are done. When a curative approach is considered, 10–12 core biopsies must be obtained (Mottet et al. 2016). When palliation is the goal, less extensive sampling is enough. The role of a pre-biopsy multiparametric MRI (mpMRI) is still a matter of debate for the first biopsy round but is mandatory when a second round is considered based of persistent abnormality after a first negative round (Mottet et al. 2016).

Histological data should clarify the following points: the number of cores, presence or absence of cancer, length of cancer on each core, and, most importantly, modified Gleason score (Epstein et al. 2016), as well as the ISUP 2014 Gleason grade (Epstein et al. 2016). The Gleason score consists of the Gleason grade of the dominant component plus the highest grade, irrespective of its extent.

Staging Procedures

Accurate tumor staging is essential for treatment decision. It is based on the TNM staging (AJCC 2017). The clinical local staging is based on DRE and sometimes mpMRI. For extra-prostatic extension, only mpMRI is helpful, even if clearly suboptimal. Locoregional evaluation (i.e., lymph node involvement) is based on CT or MRI. Images are not specific, and suspicion is

only based on nodal size (1 cm in the shorter axis). The standard for nodal evaluation is histology following an extended lymph node dissection. Distant metastases are assessed by bone scan and CT scan or MRI. Bone scan is not disease-specific but only reflects the bone activity. If curative treatment is considered, a complete workup is needed. MRI is far superior to CT scan for local staging, and whole-body MRI is better compared to bone scan to rule out metastases. PET-FDG has no place in PCa management; PET-choline has no place in initial statement (Mottet et al. 2016).

Prognostic Factors

The optimal management of patients with PCa requires accurate assessment of the risk of unfavorable outcome. The most widely used prognostic factors are clinical T stage, pretreatment serum PSA level, and Gleason score on prostate biopsy. These factors are the basis of a stratification tool developed by D'Amico et al. (Pashtan et al. 2014; D'Amico et al. 2003). The low-risk group is defined as T1c–T2a, PSA level <10 ng/mL, and Gleason score ≤ 6. The high-risk group is based on either a T stage $\geq$T2c or a PSA >20 ng/mL or a Gleason score ≥ 8, whereas other patients are classified in the intermediate-risk group. This classification has been widely published and validated (Mottet et al. 2016).

Post-surgery results (pathology status: pT, pN, Gleason score of the specimen, margins) and the treatment result (PSA nadir) are the most predictive factors of survival (Mottet et al. 2016). Post-treatment scores and nomograms are still a matter of debate in terms of real practical clinical interest. They have to be externally validated. In case of prostate cancer recurrence, there is evidence that after radical prostatectomy or radiation therapy, PSA doubling time (PSA-DT) can identify patients at highest risk of distant metastases or death from the disease (D'Amico et al. 2004). The usual threshold is 12 months and the lower the PSA-DT, the worse the outcome.

In metastatic situations, median survival is 42 months in newly diagnosed patients (James et al. 2015), but the population is heterogeneous: survival is influenced by performance status, age, Gleason score, and metastases localization (visceral vs. bone only and bone localization). Survival is also based on the PSA-level 7 months after ADT. A study showed that PSA <4 ng/mL is a good prognostic factor in metastatic situations with a median overall survival around 13 months if PSA >4 ng/ml compared to 75 months if <0.2 ng/ml (Hussain et al. 2006).

In senior adults, on top of specific survival, overall survival is mainly driven by comorbidity. Age itself has almost no impact for non-cancer-specific death in localized PCa treated with RP (Tewari et al. 2004). At 10 years, most men with a Charlson Comorbidity Index (CCI) score >2 had died from competing causes, irrespective of age or tumor aggressiveness. Currently, the Cumulative Illness Score Rating-Geriatrics is the best tool for assessing mortality risk unrelated to PCa (Groome et al. 2011). Evaluation of these factors must be considered before doing anything, starting from requesting a PSA and a DRE in completely asymptomatic men.

Health Status Evaluation in Senior Adults

The working expert group of the SIOG guidelines (Droz et al. 2017) has highlighted the importance of health status evaluation in senior adults with PCa. The gold standard is the comprehensive geriatric assessment (CGA) (Decoster et al. 2015), including evaluation of the possibility for a patient to make decisions about his own treatment (Extermann et al. 2005). The following paragraph is a summary of these proposals.

Evaluation of Health Status

The G8 screening tool (Kenis et al. 2014) is the recommended screening tool, done in less than 5 min, even by a dedicated nurse. A score <14 means the need for a further geriatric evaluation starting with the simplified geriatric evaluation. A decision-making tree (Fig. 1) can help to evaluate health status (Tables 1 and 2).

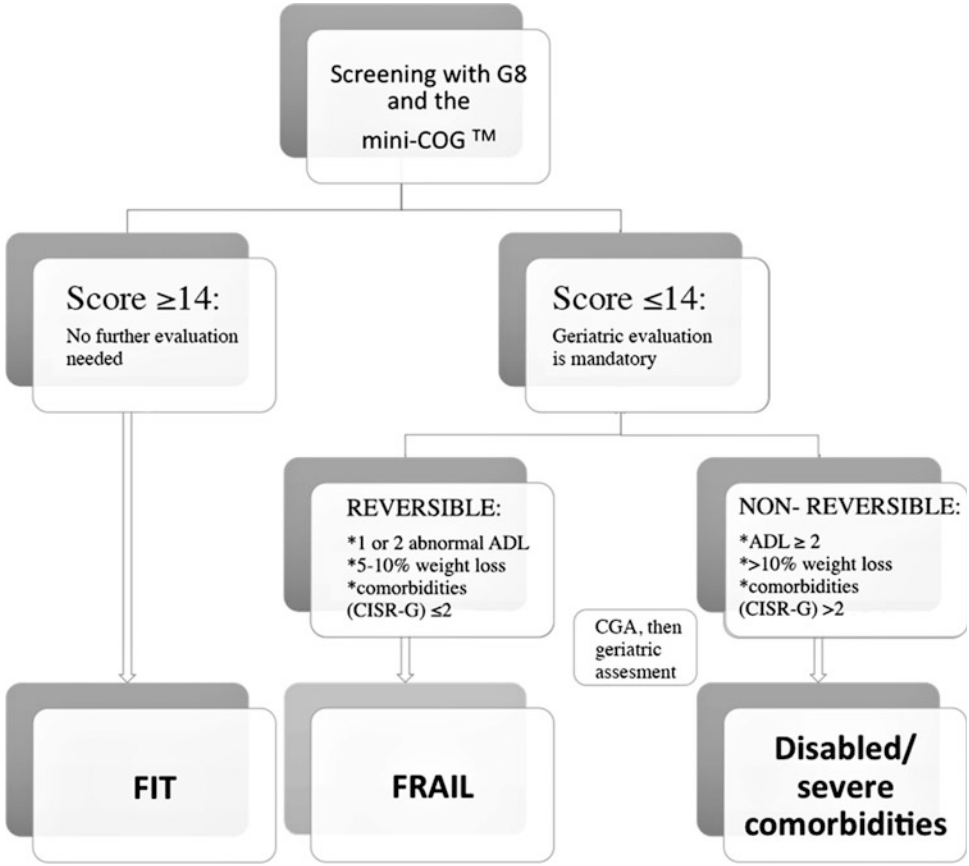

Fig. 1 Decision tree to determine patient health status. *mini-COG™* mini-COG™ cognitive test, *ADL* activities of daily living, *CIRS-G* cumulative illness rating score-geriatrics, *CGA* comprehensive geriatric assessment. (Adapted from Droz 2017)

Cognitive Screening

Patient's capacity to integrate and analyze information is essential to evaluate. The Mini Mental State Examination (MMSE) is a valid questionnaire to screen for cognitive impairment (Isenberg-Grzeda et al. 2016). A score of more than 24 points out of 30 means a normal cognition. A quicker alternative is the Mini-COG test, also possibly done by a dedicated nurse (Borson et al. 2003). Here a full geriatric assessment is needed if the score is $\leq$3 out of 5.

Simplified Geriatric Evaluation

It includes the measure of dependence through the activity of daily living (ADL) (Table 3) as well as the instrumental activity of daily living (IADL) (Table 4) (Lawton and Brody 1969), the analysis of the global comorbidities by the Cumulative Illness Score Rating-Geriatrics tool (CIRS-G) (Table 5) (Parmelee et al. 1995), and the approach of the nutritional status through weight loss during the past 3 months.

Patient Staging and Treatment Strategy After Geriatric Evaluation

The individual life expectancy estimation is based on both age and comorbidity (Heidenreich and Pfister 2016). It is well established that in localized prostate cancer situation, life expectancy should be $\geq$10 years. In metastatic castration-resistant

Table 1 G8 screening tool

Items	Possible responses	Score
(A) Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	Severe decrease in food intake	0
	Moderate decrease in food intake	1
	No decrease in food intake	2
(B) Weight loss during the last 3 months?	Weight loss >3 kg	0
	Does not know	1
	Weight loss between 1 and 3 kg	2
	No weight loss	3
(C) Mobility?	Bed or chair bound	0
	Able to get out of bed/chair but does not go out	1
	Goes out	2
(D) Neuropsychological problems?	Severe dementia or depression	0
	Mild dementia	1
	No psychological problems	2
(E) Body mass index (BMI)? (weight in kilograms)/(height in square meters)	BMI <19	0
	BMI 19 to <21	1
	BMI 21 to <23	2
	BMI ≥23	3
(F) Takes more than three prescription drugs per day?	Yes	0
	No	1
(G) In comparison with other people of the same age, how does the patient consider his/her health status?	Not as good	0
	Does not know	0,5
	As good	1
	Better	2
(H) Age	>85	0
	80–85	1
	<80	2
Total score 0–17	**Cutoff ≤14**	

situations, shorter life expectancy is expected and can be predicted with available electronic tools (University California San Francisco 2016). The Charlson Comorbidity Index (CCI) has been developed and seems to be the most reliable tool to predict non-prostate-cancer-related mortality. It contains 19 categories of comorbidity and predicts the 10-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned with a score of 1, 2, 3, or 6 depending on the risk of dying associated with this condition. Then, a life expectancy >10 years is the threshold that leads to an active PCa therapy, whereas a life expectancy <10 years favors the use of watchful waiting.

Patients can be directed to one of the four categories according to previous health status based on G8 score >14 (*fit* patient) versus G8 score <14 (included in *vulnerable* or *frail* patient). This will lead the treatment strategy combined with the patient's wishes:

- Fit patient should access standard treatment as the youngest one. They are expected to tolerate the standard treatment, but modalities and the choice of particular must be discussed with the patient.
- Vulnerable patients have reversible comorbidities (CIRS-G grade 2 comorbidities or a single grade 3; one to two reversible deficiencies in ADL and malnutrition). Once reversed with geriatric intervention, they should receive standard treatments.
- Frail patients have irreversible comorbidities that will negatively impact on their life

Table 2 MMSE

Maximum score	Patient's score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly and then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until the patient learns all of them, if possible. Number of trials
5		"I would like you to count backward from 100 by sevens." (93, 86, 79,72, 65, . . .) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them
1		"Repeat the phrase: 'No ifs, ands, or buts'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All ten angles must be present and two must intersect.)
30		Total

Instructions for Administration and Scoring of the MMSE

Orientation (10 points):

• Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer

• Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer

Registration (3 points):

• Say the names of three unrelated objects clearly and slowly, allowing approximately 1 s for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0–3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested

• After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while"

Attention and Calculation (5 points):

• Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers

• If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backward. The score is the number of letters in correct order (e.g., dlrow = 5, dlorw = 3)

Recall (3 points):

• Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0–3)

Language and Praxis (9 points):

• **Naming**: Show the patient a wristwatch and ask the patient what it is. Repeat with a pencil. Score 1 point for each correct naming (0–2)

• **Repetition**: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1

• **Three-Stage Command**: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score 1 point for each part of the command correctly executed

• **Reading**: On a blank piece of paper, print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score 1 point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence

(*continued*)

Table 2 (continued)

Maximum score	Patient's score	Questions
• **Writing**: Give the patient a blank piece of paper, and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary		
• **Copying**: Show the patient the picture of two intersecting pentagons, and ask the patient to copy the figure exactly as it is. All ten angles must be present, and two must intersect to score 1 point. Ignore tremor and rotation		
Interpretation of the MMSE		
Method	**Score**	**Interpretation**
Single cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for eighth grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24–30	No cognitive impairment
	18–23	Mild cognitive impairment
	0–17	Severe cognitive impairment

Table 3 Activity of daily living (ADL)

Activities point (1 or 0)	Independence (1 item = 1 point)	Dependence (1 item = 0 point)
Bathing	Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area, or disabled extremity	Needs help with bathing more than one part of the body, getting in or out of bathtub or shower. Requires total bathing
Dressing	Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners/may have help tying shoes	Needs help with dressing self or needs to be completely dressed
Toileting	Goes to toilet, gets on and off, arranges clothes, and cleans genital area without help	Needs help transferring to the toilet, cleaning self, or using bedpan or commode
Transferring	Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable	Needs help in moving from bed to chair or requires a complete transfer
Continence	Exercises complete self-control over urination and defecation	Is partially or totally incontinent of bowel or bladder
Feeding	Gets food from the plate into the mouth without help. Preparation of food may be done by another person	Needs partial or total help with feeding or requires parenteral feeding
Score = 6 (independent)	**Score = 0 (dependent)**	

expectancy. These included patients with more than two deficiencies in ADL, multiple grade 3 comorbidities on CISR-G or any grade 4 comorbidity, or a weight loss >10%. The treatment must be adapted to the symptoms and the disease aggressiveness. Here the quality of life (QoL) is the main priority, and patients will often only be able to receive a suboptimal specific treatment.

- The last category represents terminal illness patient that should only receive palliative treatment. They should only be representing symptomatic patients, as none should have undergone any diagnostic workout if asymptomatic.

If mini-COG ™ score is abnormal, a complete neuropsychological assessment is wishable. Prospective studies are necessary to validate these tools in this specific elderly

prostate cancer population, like G8. Furthermore this classification in four groups must be validated by specific prospective studies.

Treatment of Localized Disease

Introduction

Many men with screening-detected localized PCa will not benefit from definitive treatment, and 45% of them are candidates for deferred management (Mottet et al. 2016). Overall mortality is a balance between specific and non-specific mortality, the latter being linked to comorbidities. In high-risk groups and in some intermediate ones, the disease aggressiveness outweighed comorbidity, even at 10 years. The ProtecT trial (Hamdy et al. 2016) has shown that specific survival at 10 years is equivalent in treated and actively monitored low-/intermediate-risk patients, close to 99%, highlighting the major role of individual life expectancy, especially in senior adults.

Decisions in senior adults must take into account the disease aggressiveness, the risk of dying from another cause, the risks of treatment, and the patient's preferences.

Senior adults have often a concomitant benign prostatic hyperplasia (BPH) associated with their PCa. If bothersome, BPH requires a specific treatment, even sometimes surgery that must be distinguished from the cancer treatment. However BPH might have a major impact in the treatment choice, regarding the various available modalities.

Deferred Treatment (Watchful Waiting, Active Surveillance)

Watchful waiting is a possible option in asymptomatic patients with localized PCa and limited life expectancy since PCa often progresses slowly (Adolfsson 2008). Active surveillance is an option only if the expected life expectancy is long in a subgroup of low-risk situations. It is based on repeated biopsy with the aim to postpone any active treatment as long as not definitively needed. The results of the active monitoring regimen described in the ProtecT trial (Hamdy et al. 2016) for low- and intermediate-risk patients, based on clinical and PSA follow-up with less rebiopsy, really question the exact place of active surveillance in senior adults, or at least in patients with less than 15 years life expectancy. No specific survival difference was observed at 10 years, and the chance that a difference is observed before 15 years is really minimal. Active treatments mostly benefit patients with intermediate- or high-risk disease and the longest expected survival or those with symptoms related to the disease itself.

Radical Prostatectomy

This treatment is the only one that has been associated with survival benefit compared to watchful waiting in a randomized controlled trial (Bill-Axelson et al. 2014). It allows a precise pathological staging. It is however associated with side effects such as incontinence and impotence, leading to a decreased physical health-related quality of life (HRQoL) (Mottet et al. 2016), even if this was recently discussed from the ProtecT trial. These side effects are directly linked to age (Adejoro et al. 2016), especially for incontinence and impotence. The observed results might therefore not be applicable to senior adult patients, as none were included. This increased risk of incontinence must be clearly presented to patients during the initial discussion for treatment choice.

The surgical approach (open, laparoscopic, or robotic) does not seem to have a major impact in the functional outcome (Yaxley et al. 2016), even if suggestions have been made favoring of the robot (Ficarra et al. 2012). Robotic prostatectomies do not reveal any difference in complications and continence between patients above or below 70. Only potency recovery appeared to be better in younger patients (Basto et al. 2014). Surgery will treat at the same time the disease and the voiding troubles, if present and severe.

In high-risk lesions, surgery in a multimodal strategy (i.e., combined with adjuvant and/or salvage modalities) leads to up to

Table 4 Instrumental activity of daily living (IADL)

Item	Instrumental activity	Score
A. Telephone	1. Operates telephone on own initiative, looks up and dials numbers, etc.	1
	2. Dials a few well-known numbers	1
	3. Answers telephone but does not dial	1
	4. Does not use telephone at all	0
B. Shopping	1. Takes care of all shopping needs independently	1
	2. Shops independently for small purchases	0
	3. Needs to be accompanied on any shopping trip	0
	4. Completely unable to shop	0
C. Food preparation	1. Plans, prepares, and serves adequate meals independently	1
	2. Prepares adequate meals if supplied with ingredients	0
	3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet	0
	4. Needs to have meals prepared and served	0
D. Housekeeping	1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1
	2. Performs light daily tasks such as dishwashing, bed making	1
	3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
	4. Needs help with all home maintenance tasks	1
	5. Does not participate in any housekeeping tasks	0
E. Laundry	1. Does personal laundry completely	1
	2. Launders small items, rinses stockings, etc.	1
	3. All laundry must be done by others	0
F. Mode of transportation	1. Travels independently on public transportation or drives own car	1
	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
	3. Travels on public transportation when assisted or accompanied by another	1
	4. Travel limited to taxi or automobile with assistance of another	0
	5. Does not travel at all	0
G. Responsibility for own medications	1. Is responsible for taking medication in correct dosages at correct time	1
	2. Takes responsibility if medication is prepared in advance in separate dosages	0
	3. Is not capable of dispensing own medication	0
H. Ability to handle finances	1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	1
	2. Manages day-to-day purchases but needs help with banking, major purchases, etc.	1
	3. Incapable of handling money	0

Scoring: The patient receives a score of 1 for each item A–H if his or her competence is rated at some minimal level or higher. Add the total points circled for A–H. The total score may range from 0 to 8. A lower score indicates a higher level of dependence

91% cancer-specific survival. Survival can reach 95% with one risk factor (Gleason >7 or T > T2 or PSA >20 ng/ml) and 79% with three risk factors (Joniau et al. 2015). Thirty-day mortality after radical prostatectomy increases with age; it is only 0.66% in men aged 70–79, with risk of death or major complications depending on comorbidities (Alibhai et al. 2005).

External Beam Radiotherapy

External beam radiotherapy (EBRT) combined with androgen deprivation therapy (ADT) is another standard of care for intermediate- or high-risk (localized or locally advanced) PCa. EBRT is associated with the same cancer-specific survival compared to surgery in low/intermediate risk (Hamdy et al. 2016), but a formal comparison

Table 5 Cumulative Illness Rating Scale (CIRS-G)

Rating strategy	
0	None
1	Mild (or past significant problem)
2	Moderate (moderate disability or morbidity, requires first-line therapy)
3	Severe (constant significant disability/uncontrollable chronic problems)
4	Extremely severe (immediate treatment required/end-organ failure/severe impairment in function)
Items	Score (0–4) per item
Heart	
Vascular	
Respiratory	
Eyes, ears, nose, throat, and larynx	
Upper GI	
Lower GI	
Hepatic	
Renal	
Genitourinary	
Musculoskeletal/integument	
Neurological	
Endocrine/metabolic	
Psychiatric illness	

Patients are classified as:
- **Fit** if they have no Grade 3 score
- **Vulnerable**: one or two Grade 3 scores
- **Frail**: >2 Grade 3 or any Grade 4 scores
- **Too sick**: multiple Grade 4 scores

for the high-risk group is still lacking. The treatment-related comorbidities with EBRT are independent of age for dose >72Gy using intensity-modulated or image-guided radiotherapy (Mottet et al. 2016). They are mainly represented by gastrointestinal morbidity and with those associated with ADT. Usually EBRT is combined with ADT in intermediate- and mainly high-risk situations. Duration of ADT is related to the risk category: 6 months for intermediate risk while 18 months to 3 years needed for high risk (Mottet et al. 2016). The initial cardiac status might decrease this duration, especially in intermediate- and high-risk localized disease. ADT has been shown to be associated with increased cardiovascular mortality in patients with a previous history of cardiovascular morbidity in a small cohort (D'Amico et al. 2008), and the practical impact of this finding must be balanced with the added benefit of ADT with high-risk lesions. Shortening the ADT duration to 18 months compared to 36 months might be an option. Moderate hypo-fractionation (20 fractions in 4 weeks) might represent the new standard for EBRT (Mottet et al. 2016), at a cost of a slightly increased bowel toxicity (Motwani and Tendulkar 2016). Brachytherapy is another form of radiotherapy, restricted mainly to low- and also for some low-intermediate-risk patients, with a prostate size <50 g and no or minimal voiding symptoms. It has no specific side effects in senior adults compared to younger ones (Mottet et al. 2016).

Androgen Deprivation Therapy (ADT)

ADT alone is inferior to ADT plus radiotherapy in terms of specific survival and must be considered as a real undertreatment (Mottet et al. 2016). In patient with localized or locally advanced PCa not

suitable or unwilling for a local treatment, immediate ADT should be only used in patients requiring symptom palliation or for those with a PSA level >50 ng/mL or with a PSA doubling time <12 months (Mottet et al. 2016).

Minimally Invasive Therapies

The real place of minimally invasive therapies such as HIFU, cryotherapy, photodynamic therapy, and laser therapy is still highly debatable (Valerio et al. 2017) and should only be considered as experimental (Mottet et al. 2016). In older patients, an increased rate of postoperative genitourinary complications such as incontinence and stricture when compared with the same procedure in younger men has been reported (Adejoro et al. 2016).

Treatment of Advanced Disease

Metastatic Hormone-Naïve Prostate Cancer

ADT is the first-line treatment in hormone-sensitive metastatic PCa. Since 2016 docetaxel associated with ADT is recommended for newly diagnosed metastatic patients fit enough for chemotherapy (James et al. 2015; Sweeney et al. 2015; Vale et al. 2016), leading to a 9% absolute survival benefit (Vale et al. 2016). Risk benefit must be discussed in senior adults (median age in trials <67 years) – as well as for those patients with a low volume disease, as suggested in one trial (Sweeney et al. 2015).

ADT is associated with several side effects that might have a real impact on QoL. ADT increases bone fracture risk, cognitive impairment, diabetes, thromboembolic events, and all-cause mortality in cardiovascular past medical history (Cornford et al. 2016).

These must all be considered and prevented as much as possible. A detailed review is far beyond the scope of this chapter but may be found in various guidelines (Mottet et al. 2016). Increased physical activity seems to be always of major benefit, whatever the considered side effect. Bone problems represent a major issue in senior adults. The SIOG recommends the evaluation of baseline bone mineral density and prevention of osteoporosis by calcium and vitamin D supplement (Droz et al. 2017). Neither monthly zoledronic acid nor denosumab has any place here as none has any impact on survival- or skeletal-related events (Mottet et al. 2016; Droz et al. 2017). They might be used for osteoporosis treatment, with specific dosages and regimen.

Castration-Resistant Prostate Cancer (CRPC)

When PCa becomes castration resistant (requiring a testosterone level checking), ADT must be continued lifelong. Major progresses have been made in metastatic castration-resistant PCa (mCRPC), while M0 situations, induced by the early use of ADT. The median life expectancy in mCRPC is around 30 months, highlighting the importance of QoL preservation. Guidelines regarding the best choice have been published but are clearly limited by the lack of dedicated trials (Cornford et al. 2016).

Endocrine Therapy

Abiraterone is a CYP17 inhibitor. It must be used with 10 mg prednisone daily to suppress the induced mineralocorticoid effect based on the increased ACTH level. It has been associated with an improved survival either before (Ryan et al. 2015) or after (Fizazi et al. 2015) docetaxel in mCRPC. It has an overall good tolerance, even in senior adults. The liver and cardiovascular function must be regularly checked, especially during the 1st months of treatment (Mottet et al. 2016). Enzalutamide is a new androgen receptor antagonist. It increases survival in mCRPC patients before (Beer and Tombal 2014) and after (Scher et al. 2012) docetaxel. Its tolerance is good, with different side effects compared to abiraterone. With both drugs, a 19–37% survival benefit has been observed, depending on the drug, the control arm, and the timing of treatment

regarding chemotherapy. Outside specific side effects and contraindication, no specific guidelines exist on the drug choice.

Chemotherapy

Docetaxel-based chemotherapy is the other standard drug in fit and vulnerable older men. Docetaxel 75 mg/m^2 every 3 weeks plus daily prednisone is the standard regimen for mCRPC (Droz et al. 2017). Overall survival benefit in men older than 75 years old is similar to that in younger patient (Droz et al. 2017) at a cost of more G3/G4 toxicities requiring either dose reduction or the early use of GCSF factors. A 50 mg/m^2 every 2 weeks regimen has been shown to be effective and better tolerated compared to the 75 mg regimen (Kellokumpu-Lehtinen et al. 2013). Following docetaxel treatment, cabazitaxel, another taxane, has been shown to improve survival. This regimen is feasible and as safe in senior adults as in younger ones, provided GCSF and diarrhea prevention are systematically considered (Heidenreich and Pfister 2016; Droz et al. 2016).

The chemotherapy toxicity in senior adults can be evaluated and predicted using two published models based on the geriatric health status, type of chemotherapy, and biological characteristics (Droz et al. 2017). Senior adults must be monitored closely considering the increased toxicity risk and possible regimen adaptation in senior adults (Droz et al. 2017). They should never be denied chemotherapy just based on age.

Radiotherapy, Radiopharmaceuticals, and Bone-Targeted Therapy

Elderly men with mCRPC and localized painful metastasis can benefit from palliative radiotherapy. In patients with painful bone metastases, without visceral metastases, radium-223 has been shown to extend overall survival, delay bone-related events, and improve life quality (Droz et al. 2017).

In mCRPC with bone metastases, zoledronic acid (4 mg IV) or denosumab (120 mg s/c) every 4 weeks is recommended to decrease skeletal-related complications (bone pathological fractures). Vitamin D and calcium supplementation are needed. Before using both drugs, an initial dental check is highly recommended (Mottet et al. 2016), and the duration of treatment should probably be limited to 2 years, considering the risk of devastating jaw necrosis.

Vaccine (Sipuleucel-T)

Not available outside the USA, with very limited data on senior adults.

Choosing the Right Treatment and Sequencing

No available data exist regarding these two points. No upfront comparison between drugs is available, and it is therefore impossible to select a best option in senior adults (Cornford et al. 2016). The selection will mainly be based on specific side effects and previous comorbidities. General rules suggest that it is better to alternate a hormonal treatment and a chemotherapy regimen, except in very selected populations, far beyond the scope of this chapter.

Palliative Care

The patient might benefit from very early introduction of palliative care (Cornford et al. 2016; Droz et al. 2017). This approach reduces treatment side effects, improve patient quality of life, and maximize the efficacy of therapies through the avoidance of dose reductions and treatment discontinuations (Scotté 2012). Major benefits are expected on anxiety and time spent in hospital reduction. Improving the quality of life is essential especially in the elderly.

Conclusion

Half of the patients with newly diagnosed prostate cancer are older than 70 years. Specific recommendations are available with the recently updated

SIOG guidelines (Droz et al. 2017). The key message is that elderly patients should be managed according to their health status and not according to age. They are best treated if a multidisciplinary team is involved, including geriatricians and dedicated nurses, on top of treatment specialists.

Evaluation of health status is essential with validated screening tools (the G8 questionnaire for health status, CISR-G scale for the assessment of comorbid conditions, the ADL for the degree of dependence, the weight loss estimation for nutritional status, the MMSE score for cognitive screening). Approach in the fit elderly should be the same as in younger patients and based on existing international recommendations, while it must be adapted in those with severe uncorrected comorbidities. This attitude is the only one able to reduce the undertreatment of senior adults and improve both the quality and the quantity of life.

Cross-References

- Comorbidity in Aging and Cancer
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Decision Making and Safety Issues in Older Cancer Patients
- Drug Interactions in Aging and Cancer
- Frailty in Cancer Patients
- Geriatric Interventions in Oncology
- Geriatric Screening in Cancer Patients
- Integrating Geriatric Oncology into Clinical Pathways and Guidelines
- Normal and Abnormal Aging (General Perspective for the Oncologist)
- Organizing the Clinical Integration of Geriatrics and Oncology
- Pharmacology of Aging and Cancer
- Population Trends in Aging and Cancer
- Principles of Cancer Surgery in Older Adults
- Principles of Cancer Targeted Therapy in Older Adults
- Principles of Chemotherapy in Older Adults
- Principles of Radiation Therapy in Older Adults

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Bladder Cancer in Older Adults

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Abstract

Bladder cancer (BC) is a disease of the elderly. Considering the increasing aging of the population, BC will become a more important public health challenge to manage in a very close future. However, the current treatment of BC in the elderly remains controversial. The purpose of this article is to review the previous literature to summarize and gather the current

knowledge in order to describe the management and treatment of BC in the elderly, in all its aspects. Original articles in English as well as reviews and editorials were selected based on their clinical relevance. The definition of elderly can differ as it is based on varying chronological ages. However, it is commonly found in most BC literature reviews that the elderly may be affected more severely than the younger people. Even if the management of non-muscle-invasive BC (NMIBC) does not strongly differ from younger patients, the impact of adjuvant intravesical immunotherapy might be inferior. Patients with muscle-invasive BC (MIBC) may benefit from a multidisciplinary geriatric evaluation. Radical cystectomy (RC) remains the curative treatment to BC, and elderly patients should not be withheld a potentially lifesaving intervention only based on chronological age. Bladder-sparing techniques may be a potential replacing treatment approach for unsuitable patients to a major surgical approach. Geriatric assessment could help identify the frail elderly and customize their perioperative care. In conclusion the treatment of BC in the elderly has to be patient-centered and focused on biological age and functional reserves. Age per se should not be the key driver.

Keywords
Bladder cancer · Elderly · Geriatrics assessment · Treatment

Introduction

Bladder cancer (BC) is the 11th most common cancer worldwide, with higher incidence in more developed regions such as in Europe and North America, where it is the 5th most common cancer (Fitzmaurice et al. 2016). The age-adjusted incidence has been stable to slightly decreasing in the USA and Europe over the past few decades; however, these statistics belie important changes in the total burden of BC especially in elderly patients (Burger et al. 2013; Yazbek-Hanna et al. 2016).

The individual risk of BC, reflected in age stratum-specific incidence rates, increases dramatically over the age of 65, with the highest rates in patients aged 75–84 (Howlader et al. 2013). More men than women are affected by BC, at a ratio of 3:1, extending to 3.6:1 after 80 years of age (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-One). Reductions in mortality from cardiovascular disease coupled with aging of the "baby boom" generation have radically changed the demographic structure of the population at risk for BC. For instance, there were 49,000 new cases in the USA in 1990, with a median age at diagnosis of 70 (http://onlinelibrary.wiley.com/doi/10.3322/canjclin.40.1.9/pdf). In 2005, 63,210 individuals were diagnosed at a median age of 72 (http://onlinelibrary.wiley.com/doi/10.3322/canjclin.55.1.10/full), and in 2016, an estimated 76,960 adults will be diagnosed, at a median age of 73 (http://seer.cancer.gov/statfacts/html/urinb.html) – the highest median age at diagnosis of all cancer sites (http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-048074.pdf) (Fig. 1).

Based on US Census and SEER data, it is estimated that the number of cancer survivors in the USA will increase from 15.5 million in 2016 to 26.1 million by 2040, with the proportion of survivors >65 years old rising from 62% to 73% (Bluethmann et al. 2016). 765,950 BC survivors have been estimated in the USA as of January 1, 2016, to which 76,960 cases will be added this year as newly diagnosed BC patient. A tragic growth of the BC in older adults is highly likely to occur in the coming years, considering the constantly increasing number of cases over the past two decades and the continuous aging of the population forecasted over the next decades.

In the elderly patients, there is an impact of complex comorbidity from multiple chronic conditions, and more than half of them have moderate to severe comorbidity burden (by Charlson index – Fig. 2), substantially exceeding that of age-matched patients without cancer (Bluethmann et al. 2016). These estimates of the prevalent comorbidities in the population of older adults with BC are likely conservative, given common conditions not included in the Charlson (e.g., hypertension, arthritis, atrial fibrillation,

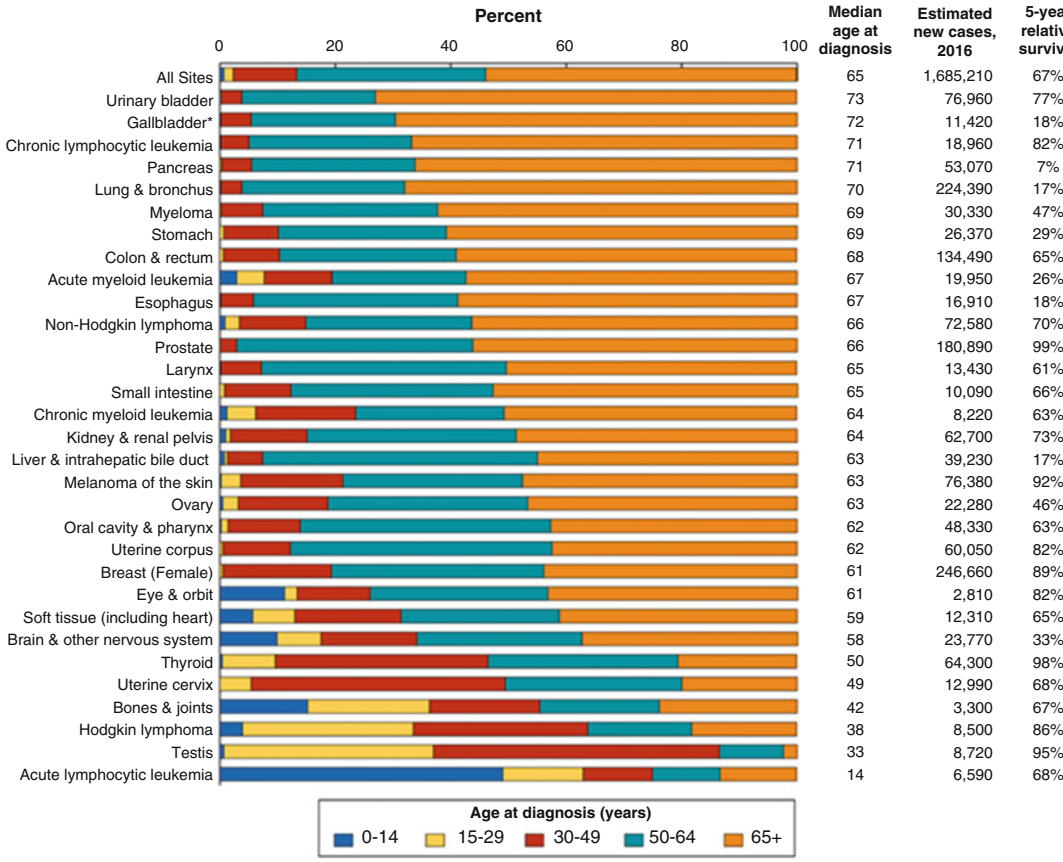

Fig. 1 Age distribution (%), median age at diagnosis, 5-year relative survival, and estimated number of cases by cancer type (http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-048074.pdf)

chronic ischemic coronary artery disease, thromboembolic disease. . .). Moreover, elderly patients have other geriatric syndromes, including frailty, functional dependence, and cognitive impairment, underreported in large observational datasets. These factors present both competing risks for mortality and specific vulnerabilities for toxicity or complications of guideline-recommended treatment protocols.

Even though older patients are highly affected by cancer, the amount of studies toward this population stay minor (Levit et al. 2013) as highlighted in the US cooperative group clinical trials finding, with patients over 65 years of age representing only 56% of patients enrolled in BC trials, at a time when approximately 75% of patients in the population were in this age group (Hutchins et al. 1999).

Clinical Presentation

Macroscopic, asymptomatic hematuria is the most frequent although nonspecific sign of BC. Irritative voiding symptoms such as urgency, frequency, and nocturia can be caused by BC.

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic Solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Fig. 2 Charlson comorbidity index scoring system (Bluethmann et al. 2016)

Gross hematuria from tumor growth results in frequent emergency department visits, catheterizations, surgical intervention to prevent bleeding and relieve clot burden, as well as hospitalizations for continuous bladder irrigation. A significant anemia may also be caused by a large bleeding tumor, possibly requesting blood transfusions. Local pelvic symptoms as well as lower extremity pain from nodal and nerve involvement (Bellmunt et al. 2014) or upper tract obstruction may suggest a muscle-invasive situation, as well as symptomatic metastases.

Etiology and Risk Factors, Pathology, Natural History, and Tumor Biology

Etiology and Risk Factors

BC has been induced by tobacco smoking for 65% of all cases of BC in the male and 30% in the female population. Non-smokers have two to four times lower relative risk (RR) of developing BC compared to smokers. Aromatic amines including amphetamines, and specifically benzidines and derivatives, are likely to be involved in tobacco smoking as well as in the occupational environment (i.e., industrial manufacturing of chemicals, hair dyes, rubber, and metal). In Middle East, schistosomiasis has been a major risk factor, leading to a slightly different histological lesion.

Pathology

BC is also known as urothelial carcinoma, 90% of cases being transitional cell carcinoma (TCC). Among all the TCCs, 90% are observed in the urinary bladder, 8% in the renal pelvis or calyx, and the remaining 2% within the ureter. More rarely, the urothelial lining of the urethra can also be a site of disease. This TCC can be associated with metaplasia (adenocarcinoma or squamous cell) but are still considered as TCC. The remaining 10% of BC cases correspond to the pure adenocarcinoma, squamous cell carcinoma (mainly schistosomiasis induced), and small cell carcinoma, with a different prognosis and often a different treatment strategy.

A disease limited to the mucosa or submucosal layer through the lamina propria represents about 75% of cases and is referred to as non-muscle-

invasive BC (NMIBC) (Siegel et al. 2016; Aldousari and Kassouf 2010). Infiltration into the muscular wall or beyond is referred to as muscle-invasive BC (MIBC) situation. NMIBC shows an intrinsic tendency toward recurrence in about 50–80% of cases. Progression to MIBC can be observed in up to 50% of cases, chiefly depending on grade and stage of initial lesions.

While MIBC is always high grade, NMIBC is likely to represent two distinct diseases: low-risk or low-grade papillary malignancy that rarely invades or metastases but may recur. High-risk diseases are less common, with high-grade lesions invading the submucosa (about 15–25% of cases), with a high tendency to recurrence and invasion, possibly leading to metastases and ultimately death.

In general, cancer-specific survival ranges from 70% to 85% at 10 years in high-grade NMIBC and is even higher for low-grade disease (Palou et al. 2012).

Peculiar features are shown by carcinoma in situ (CIS) or Tis and consist of a high-grade flat, intraepithelial lesion. Macroscopically, its recognition is inconstant, but when visible, it is discernible by reddish velvety spots. CIS can be found in association with established high-grade NMIBC or MIBC. Although the natural origin of the presence of CIS is not entirely known, it may have a substantially negative influence on prognosis.

Patients and clinicians are provided numbers of clinical decision support tools to help them estimate the risks of NMIBC recurrence and progression, according to the patients' clinical and pathologic characteristics. The European Organization for Research and Treatment of Cancer (EORTC) has provided a risk calculator, which is a scoring system that combines data from seven clinical trials of NMIBC to predict recurrence and progression (Sylvester et al. 2006).

Diagnosis, Staging, and Prognostic

Diagnosis: Imaging, Cystoscopy, and Urinary Cytopathology

The diagnosis of BC is based on histology. But endoscopy is the main imaging process allowing to characterize the lesions: number, location, size, aspects of the lesions, and the base. This endoscopy can be optimized with fluorescence (especially for CIS detection) that will decrease the rate of missed lesions. This endoscopy is always the first step of a transurethral bladder resection but can represent an independent procedure when the diagnosis of bladder lesion is questionable.

A bladder sonography is only helpful if positive, but false positivity exists as well (clots, stones). It allows checking the potential impact of the tumor on the upper urinary tract with an upper tract dilatation. The general staging is obtained through an abdomen and pelvic computed tomography (CT) scans with contrast medium. Real bladder wall infiltration on CT scan is neither very sensitive nor specific, with underestimation and overestimation of up to 50%. MRI might be an alternative with at least the same definition (Witjes et al. 2016).

Urine cytopathology (UC) is mandatory and particularly helpful in the diagnosis of lesions which are not detectable at cystoscopy (CIS), as tumors of the urothelium exfoliate cells in the urine. Only positive findings are relevant.

Staging

The 2002 TNM classification approved by the Union Internationale Contre le Cancer (UICC) was updated in 2009 (7th version) and then in December 2016 when the TNM 8th edition was published (Figs. 3 and 4) (Brierley et al. 2016).

Stage and grade are significant prognostic factors for recurrence, progression, and survival and, therefore, are critical for the appropriate treatment and management of MIBC (Epstein et al. 1998).

Additional descriptors include lymphatic vessel invasion (L) and venous invasion (V).

Accurate pathological diagnosis, grading, and staging of BC represent the cornerstone for treatment strategy.

Prognosis of BC

Tumor recurrence and progression are the clinically relevant events associated with the diagnosis of NMIBC. Generally, high-grade NMIBC

T - Primary tumour			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Ta	Non-invasive papillary carcinoma		
Tis	Carcinoma *in situ*: 'flat tumor'		
T1	Tumor invades subepithelial connective tissue		
	Tumor invades muscle		
T2		T2a	Tumor invades superficial muscle (inner half)
		T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue		
		T3a	Microscopically
		T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall		
		T4a	Tumor invades prostate, uterus or vagina
		T4b	Tumor invades pelvic wall or abdominal wall
N - Lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)		
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)		
N3	Metastasis in common iliac lymph node(s)		
M - Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
		M1a	positive nodes in the retroperitoneal
		M1b	visceral metastases

Fig. 3 TNM classification of urinary BC

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading system [papillary lesions]
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

Fig. 4 Histopathologic grading (G) of urinary BC/WHO grading in 1973 and in 2004

including CIS tends to behave aggressively, whereas low-grade pTa and pT1 tumors have a good prognosis with a very low lethal potential. About 66% of patients have tumor recurrences and new occurrences during follow-up depending on several factors such as stage, grade, number, and size of initial lesions. A reliable and strong prognostic factor for outcome is the presence of recurrence at the first 3-month cystoscopy. Progression, defined by developing muscle invasion from initial NMIBC, differs depending on stage, grade, number, and size of initial lesion(s) from approximately 4% for low-grade Ta tumors to 50% for high-grade T1 tumors. The risk of progression is highly increased when there is an associated CIS.

The 5-year survival after radical cystectomy (RC) for MIBC is generally unsatisfactory. It varies from 40% to 60% for stage pT2 N0 M0 to around 15% for stage pT4. With surgery alone, the median survival for pN+ patients may vary from 6 to 24 months.

Patients who do not consider a treatment for a diagnosed BC have to concede the potential threats on their QoL and survival. However the natural history of untreated BC is poorly documented.

Geriatric Assessments (GA)

GA is used to detect earlier unrecognized conditions that can influence treatment tolerance, efficacy, and surgical outcomes. Recognizing areas of vulnerability may assist for specific correction and in decision-making.

Comorbid conditions and impairments of activities of daily living are experienced by many older patients with BC and may lead to a higher competing risk of non-cancer mortality (Fung et al. 2014; Messing et al. 2009; Noon et al. 2013). The negative effect of age on overall and BC-specific survival may be explained by an increase disease aggressiveness with age or by an undertreatment of senior adults compared to their younger counterparts (Messing et al. 2009; Noon et al. 2013; Nielsen et al. 2007). To increase BC outcomes, decision-making process must be improved including HRQoL into the treatment choice but also specific interventions, such as exercise or GA (Karvinen et al. 2007; Wildes et al. 2013).

The elderly patients with MIBC are defied for taking a decision about various treatment interventions. Clinical trials that establish the safety and efficacy of cancer treatment (surgery and chemotherapy) include patients who are on average 10 years younger than those with the disease in the general community and include patients without significant health status issues (i.e., minimal comorbidity and good performance status). Thus, there is not many data regarding the safety and efficacy of standard treatment regimens in older patients, especially those who are aged $\geq$75 years and have other health status issues (Hutchins et al. 1999). Many of those patients, especially those with a smoking history, are much more likely to have underlying health issues that can increase complications and reduce the efficacy of cancer interventions. "Fit" older patients should have treatment as needed for their MIBC, regardless of their age, whereas those with significant health issues leading to a shortened life expectancy may not benefit from aggressive modalities and may be more vulnerable to harms from treatment. Medical concomitant disease impacts the feasibility and tolerability of cystectomy and perioperative chemotherapy (Goossens-Laan et al. 2014) and may increase the risk of mortality from surgery or chemotherapy toxicity. Comorbidities, functional impairments or mobility disability, and geriatric syndromes (including cognitive impairment) provide clinically useful, reasonably accurate estimates of individual life expectancy (Walter and Covinsky 2001). The independent effects of health status considerations such as functional impairments, mobility disability, and geriatric syndromes have not been well studied in patients with BC, while all those elements have been independently associated with a higher risk of surgical complications, morbidity, and mortality from

chemotherapy in other cancers (Mohile et al. 2012; Koroukian et al. 2010). Thus, sarcopenia, as measured by decreased lumbar skeletal muscle thickness, was independently associated with all-cause mortality (hazard ratio 1.93; $P = 0.004$) on multivariable analysis in over 200 patients who were to undergo cystectomy (Psutka et al. 2014).

Both patient-reported outcomes and objective tests of functional are included in GA tools. Their importance has been highlighted in several guidelines, such as the EAU (Witjes et al. 2016). It encompasses measurements of functional status, cognitive status, comorbidities, self-assessed health status, mobility, nutritional status, psychological status, and social circumstances (Mohile et al. 2012; Pal et al. 2010). GA has been applied in oncological clinical practice and trials (Hurria et al. 2005, 2010). Higher geriatric depression score, cognitive impairment, and decreased functional status independently predicted worse 30-day and 90-day major complication rates after surgery (OR, 4.02, 95% CI 1.24–13.09) and increased likelihood of discharge to a facility (OR 3.16, 95% CI 1.99–13.02) (Balducci and Extermann 2000a; Gill et al. 2003; Hewitt et al. 2015). Frailty was also associated with longer postoperative hospitalization and greater mortality at 30 and 90 days (OR 4.0, 95% CI 1.1–15.2 and OR 3.0, 95% CI 1.3–7.4, respectively) (Hewitt et al. 2015).

GA can detect patients with highest risk for serious toxicities from chemotherapy (Hurria et al. 2011). A predictive risk stratification tool was developed for the incidence of chemotherapy toxicity. It was shown to be superior to the Karnofsky Performance Status, the existing standard use by oncologists for assessment of fitness. GA can help identify patients with cognitive impairment, which has implications for consent to any form of treatment and increases risk from therapies such as surgery and chemotherapy (Ketelaars et al. 2013).

With the intention to classify elderly patients with BC for any treatments, information from the GA can categorize patients into three groups that correlate with life expectancy (Mohile et al. 2009). Patients who are "fit" have no significant functional impairments and/or comorbidities. Those ones should be treated as the younger ones. Patients classified as "frail" demonstrate dependence in basic functional tasks, significantly impaired mobility and significant comorbidities (Balducci and Extermann 2000a). They are at highest risk for toxicities from cancer treatment, and adapted treatment strategy must be considered: less toxic, with an acceptable benefit/risk balance, but maybe suboptimal in terms of cancer control. In the third group, patients have concomitant mild functional or cognitive issues, well-controlled and non-life-threatening comorbid conditions, and/or depression. They are considered as vulnerable leading to a more complex decision. Targeted interventions must be proposed with the aim of getting better outcomes from cancer-directed therapy. For example, "prehabilitation" to improve physical functioning may improve the likelihood of tolerating treatment for patients with mobility disorders (Gill et al. 2003).

Treatments

Treatment of BC

Most senior adults will benefit from a multidisciplinary evaluation, including the geriatrician. Supportive care should be considered early, especially in senior adults considering the aggressiveness of the disease and related treatments, especially in MIBC. Standard definitive treatment raises a multitude of concerns including treatment toxicity or competing risk from morbidity in elderly patients with BC and is therefore less likely to be applied to them (Nielsen et al. 2007; Karvinen et al. 2007; Wildes et al. 2013). If left untreated, disease progression leading to severe bothersome symptoms impacting the QoL may arise. This is a special situation in MIBC where the active treatments are often difficult to conduct in senior adults with comorbidities where preserving the QoL might be considered as a more important objective compared to specific survival. Therefore decision-making among this population must reach a balance between treatment risks and

potential side effects according to the natural history of untreated BC within the context of individual patient's goals and preferences.

Calculating the risks of recurrence and progression might prove to be valuable when advising senior adults with NMIBC. Although these NMIBC are rarely lethal in the mid-term, their recurrence and progression might significantly impact the QoL and must be balanced with the surgical and anesthetic risks that goes along with repeated transurethral resection of bladder tumor (TURBT) for recurrences or toxicities and complications associated with adjuvant intravesical instillations sometimes needed. Shared decision-making for surveillance schedules and treatments between patients and providers is therefore mandatory.

The decrease specific survival in senior adults compared to younger ones might be partly based of lower rates of standard-of-care treatment (Goossens-Laan et al. 2014; Hollenbeck et al. 2004; Prout et al. 2005). In addition, poorer oncologic outcomes such as upstaged disease and worse cancer-specific mortality may be more prevalent among older adults (Nielsen et al. 2007).

Treatment of NMIBC

Non-muscle-invasive BC (NMIBC) represents 70% of all diagnosed cases of BC (Burger et al. 2013; Ferlay et al. 2015; Babjuk et al. 2017). The high recurrence rates of NMIBC with up to 80% can be managed via transurethral resection (TURBT) and intravesical treatments (e.g., BCG or chemotherapeutic agents) should the situation require it. Even though surgical procedures and the anesthesia may pose a significant risk for some highly morbid elderly, they are neither especially intrusive nor disruptive and generally well tolerated. The high risk associated with some morbid cases with multiple comorbidities might be handled through follow-up or fulguration under local anesthesia, especially in low volume and low-risk disease (Shariat et al. 2009; Hofbauer et al. 2014).

With NMIBC being a heterogeneous disease, it can be classified according to EORTC nomograms in the risk of recurrence and progression (Cambier et al. 2016). It was shown that tumor size (Cho et al. 2009), stage (Cho et al. 2009), grade (Cho et al. 2009; Shi et al. 2008), and multiplicity (Cho et al. 2009) are increasing with age, while surgical retreatments (Noon et al. 2013), frequency of installation therapies, and response to intravesical treatments (Joudi et al. 2006; Kohjimoto et al. 2010) are decreasing. As a result these factors lead to increased recurrence (Cho et al. 2009; Shi et al. 2008), decreased progression-free survival (Cho et al. 2009; Thomas et al. 2012), and increased specific mortality (Noon et al. 2013; Thomas et al. 2012) in the elderly (Hofbauer et al. 2014).

Transurethral Resection of Bladder Tumor (TURBT)

Transurethral resection of bladder tumor (TURBT) plays a key role as it is the only modality for accurate diagnosis, grading, and staging. The superficial part/s of the lesion/s as well as the underlying muscular wall are sampled and sent separately to the pathologist as "endoluminal" portion and a full-thickness sample of the detrusor muscle underlying the tumor.

TURBT also constitutes the standard treatment for NMIBC if all visible lesions are completely eradicated. This can be optimized using fluorescence (Babjuk et al. 2017). Although local control of the disease is achieved in less than one-third of the patients, morbidity and mortality after TURBT are low, and 5-year survival is high.

Laser treatment and fulguration are considered palliative treatments.

Intravesical Therapies

Intravesical treatments are recommended for intermediate- and high-risk lesions (Babjuk et al. 2017). For intermediate- and high-risk tumors, BCG is advised as standard of care, while in the case of intermediate-risk tumors, introduction of a chemotherapeutic drug is an option.

There is not much systemic absorption of the intravesical agents; hence they do not produce significant systemic effects to which elderly might be more vulnerable (Shariat et al. 2010).

Age above 69 years has been considered as an independent risk factor for BCG side effects (Heiner and Terris 2008). This was later challenged with a further analysis from the EORTC GU trial 30911. Although it suggests that elderly may have stopped treatment earlier, there was no association of age and toxicity leading to discontinuation of treatment in patients with NMIBC (Oddens et al. 2016).

The long-term prognosis in intermediate- and high-risk NMIBC patients treated with BCG that are >70 years old is rather poor, although BCG is more effective than epirubicin independent of patient age (Oddens et al. 2014). This condition might be explained by changes in the immune response among the elderly (Solana et al. 2006), while adjuvant BCG improves overall and cancer-specific survival in patients with NMIBC (Spencer et al. 2013). Storage and voiding problems might impair the feasibility of intravesical therapies. These problems have to be considered and evaluated. Additionally symptomatic side effects of an intravesical therapy might lead to a discontinuation or delay of treatment.

Alternative treatment strategies have been investigated recently or are currently under investigation, especially for patients with intermediate- and high-risk tumors or for those with BCG failure (Kamat et al. 2015; Lightfoot et al. 2011).

Treatment of MIBC

Surgical Treatment

Radical Cystectomy (RC)

The standard treatment for MIBC as well as for the recurrent NMIBC stages CIS, pTis, or pTis G3 is radical cystectomy (RC). RC includes the ablation of the bladder with the prostate and seminal vesicles in the male patient and the bladder, uterus, ovaries, and a portion of the anterior vaginal wall in the female patient. A bilateral pelvic lymphadenectomy is mandatory.

Generally speaking the 5-year recurrence-free survival rate in patients undergoing radical cystectomy for BC ranges between 58% and 68%, and 5-year cancer-specific survival ranges between 62% and 66% (Shariat et al. 2006; Nuhn et al. 2012; Stein et al. 2001).

It is standard of care to use a neoadjuvant cisplatin-based chemotherapy (Witjes et al. 2016). However most senior adult patients are not fit enough to receive it. Therefore upfront RC is often considered. Eligibility criteria for chemotherapy are discussed in the next paragraph (metastatic situations).

The increased average age of the population has led to an increased diagnosis of muscle-infiltrative BC especially among the elderly. The analysis of the SEER database found that RC is only performed in 21% of patients with MIBC and at an age over 65 years (Gore et al. 2010). Similar results were found in the US National Cancer Database, with cystectomy rates of 55%, 45%, and 21% in patients <70 years, 70–79 years, or >79 years, respectively. About half of the patients >80 years did not receive any treatment (Fedeli et al. 2011). Because of refinements in patient selection in the elderly and in perioperative management, RC is considered also in senior adults.

Urinary diversion encompasses several possibilities ranging from the simple ureterocutaneostomy and ureteroileostomy (also referred to as an ileal conduit) to more sophisticated forms of urinary diversion consisting in continent reservoirs obtained from intestinal segments. These reservoirs are referred to as orthotopic neobladders implanted at the anatomical site of the native bladder. An alternative can be the implementation of a continent catheterizable reservoir at a different site, most frequently the lower right abdomen, and those reservoirs are referred to as heterotopic reservoirs. Indications for a specific urinary diversion should be based on the features of both the tumor and the host. However, most cohorts suggest that an ileal conduit might most often be the most acceptable urinary diversion in senior adults, based on poor functional outcome with ileal neobladder.

The Eighth Annual BC Think Tank sponsored by the BC Advocacy Network reported and pointed out that interventions to enhance quality of life (QoL) for BC patients is an urgent, unmet need and should be a research priority (Apolo et al. 2015).

Many HRQoL questionnaire instruments are used to assess broad cancer treatment side effects, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 QLQ-C30 (EORTC QLQ-C30) and Functional Assessment of Cancer Therapy-General (Botteman et al. 2003; Parkinson and Konety 2004).

The majority of the HRQoL research in BC is concentrated on the effect of RC and urinary diversions on HRQoL of patients with MIBC, whereas HRQoL of patients with non-MIBC have hardly been studied (Singer et al. 2013; Mohamed et al. 2012). Eventually, limited study size and poor response rates (30.38–51%) have weakened the numbers of studies of HRQoL (Karvinen et al. 2007; Gilbert et al. 2007).

One study compared prospective modifications in HRQoL among 1,432 patients aged more than 65 years diagnosed with cancer through 9 cancer sites during 2 years with changes in HRQoL in a similar time frame among a set of matched control subjects without cancers (Reeve et al. 2009). The mean physical component score (PCS) of BC patients ($n = 89$) decreased significantly by 4.3 points (95% confidence interval [CI] −2.5, −6.1) over 2 years, whereas the decrease in the mean mental component score (MCS) was not statistically significant. A cross-sectional study of 1,476 BC patients (aged ≥65 years) compared HRQoL among those before and after BC diagnosis. Significant differences in mean PCS and MCS scores between the pre-BC and post-BC diagnosis groups were observed (Fung et al. 2014). In patients with NMIBC, the differences in the PCS (−1.9; $P < 0.01$) and MCS (−1.4, $P = 0.01$) scores were statistically significant but not clinically meaningful (less than 5 points (Norman et al. 2003)). In contrast, there was a statistically and clinically significant difference in the PCS score (−5.3; $P < 0.01$) for patients with MIBC, whereas the difference in the MCS score was not statistically significant (−2.7, $P = 0.07$).

Among patients with MIBC, decreases in HRQoL develop after RC with urinary tract reconstruction (i.e., ileal conduit, continent cutaneous diversion, or orthotropic neobladder), especially in the sexual and urinary area (Botteman et al. 2003; Roaldsen et al. 2014). Besides many studies comparing several forms of urinary diversion after RC, none has proven to achieve a formal superiority in regard to HRQoL (Mohamed et al. 2012; Roaldsen et al. 2014). There are advantages and drawbacks of each procedure; thus, it is important to give patients adequate information about each surgical approach to allow for an individual choice (Roaldsen et al. 2014). Decreased body image and self-consciousness and decreases in travel and activity levels are frequently experienced by patients with ileal conduits, whereas those with continent diversions report urinary symptoms related to use of a catheter (Botteman et al. 2003; Roaldsen et al. 2014). Among patients who underwent construction of orthotropic neobladders, nighttime leakage can negatively impact HRQoL (Botteman et al. 2003). In addition, acute and long-term adverse effects related to systemic chemotherapy and radiotherapy for treatment of MIBC may also affect HRQoL (Efstathiou et al. 2009; von der Maase et al. 2000).

Complications of RC and urinary diversion are reported in the range of 15–35%, mainly influenced by general patients' status and the complexity of the diversion.

RC is a major procedure. Perioperative morbidity and mortality are increased, and continence rates after orthotopic urinary diversion are impaired in elderly patients undergoing radical cystectomy. Complications are frequent in this population, particularly when an extended postoperative period (90 days instead of 30 days) is considered (Froehner et al. 2009). Although age alone does not preclude radical cystectomy for muscle-invasive or recurrent bladder cancer or for certain types of urinary diversion, careful surveillance is required, even after the first 30 days after surgery. Excellent perioperative management may contribute to the prevention of morbidity and mortality of radical cystectomy. Data on perioperative morbidity of cystectomy in elderly is controversial. While some studies show significant differences others do not, this discrepancy exists most likely due to a non-standardized record of perioperative complications or patient

selection. Mortalities are reported between 0% and 11% (Froehner et al. 2009).

Surgical Alternatives to Radical Cystectomy

Bladder-preserving techniques might represent an alternative for elderly patients diagnosed with MIBC who are unfit for RC or who decline major surgery.

Often unimodal treatments will result in a worse outcome with reduced cause-specific survival (CSS) and reduced rates of local tumor control and should not be used in a curative approach. None of those treatments have proven to be equally effective as cystectomy in prospective trials.

For some well-selected elderly patients, a bladder-sparing approach might be beneficial. This might result in a good functional outcome as well as a higher QoL and a very acceptable survival.

Radical TURBT Only

Large cystectomy series show pT0 rates in up to 18.9% of patients (Stein et al. 2001; Hautmann et al. 2012). These patients might be suitable for a TURBT and bladder-preserving approaches even if a 20% nodal involvement in organ-confined pT2 tumors is observed (Stein et al. 2001). Furthermore up to 22% of patients may have missed lesions with TURBT alone in MIBC (Herr 1999). Two prospective cohorts of very selected patients have shown 10 years specific survival of 79.5% and 76%. The first one was based on deep negative tumor bed biopsy (Solsona et al. 2010), while the second requested a formal deep negative reTURBT (Herr 2001). None accepted CIS. Therefore a radical aggressive TURBT alone is an option for very selected cases. Nevertheless, about 33% of the patients will show local recurrence with muscle-invasive disease.

Partial Cystectomy +/− Lymphadenectomy

For patient suitable for an open-surgical approach, a partial cystectomy combined with a pelvic lymphadenectomy might be a reasonable option for very selected cases, leading to 5-year relapse-free survival rates from 39% to 67% (Kassouf et al. 2006), 10-year metastasis-free survival of 66%, and cancer-specific survival rates of 63%. These results are in line with those observed with RC with 61% and 58%, respectively (Knoedler et al. 2012). They have been conformed in a SEER database including NMIBC and MIBC (Capitanio et al. 2009). However they must be restricted to selected patients with a single lesion up to 3 cm, located in the mobile part of the bladder, without concomitant CIS or hydronephrosis.

Nonsurgical Treatments/Organ-Sparing Treatments

Radio-Chemotherapy

Nonsurgical organ-sparing treatments have been investigated with the reason to keep up the native bladder in muscle-intrusive BC.

Chemotherapy (CT) is utilized at decreased amounts as radio sensitizer, after TURBT, in relationship with external irradiation. Five-year survival in the same range as observed after RC has been obtained, with a bladder remaining in place in around 40% of patients.

Radio-chemotherapy is considered as a treatment choice for patients with contraindications for surgery and as a viable option in some surgical candidates. 65 Gy are standard for the radiotherapy.

Mak et al. performed a pooled analysis of long-term outcomes in patients with MIBC enrolled across studies which evaluated bladder-preserving combined-modality therapy (CMT) for MIBC, reserving cystectomy for salvage treatment. Six multicenter, prospective RTOG bladder-preserving CMT protocols were analyzed. For similarly staged MIBC, a long-term disease-specific survival (DSS) comparable to immediate cystectomy studies was observed. A total of 468 patients (median age, 66 years) with clinical stage between T2 and T4a N0 were included. All protocols included chemotherapy with cisplatin (several dosages and several schedules), requesting a good renal function. Thirty-six percent of the patients were older than 70 years. Given the low incidence of late recurrences with long-term follow-up, CMT can be considered as an alternative to radical cystectomy, especially in

elderly patients not well suited for surgery (Mak et al. 2014). The best results are observed in patients with single T2 lesion and complete TURBT, no hydronephrosis, no CIS, no tumor invasion into stroma of the prostate, and with well-functioning bladder. A large cohort of CMT without cisplatin has been published and might represent a real alternative for those unfit for RC and having an impaired renal function (James et al. 2012). A formal systematic review has just been published highlighting the urgent need for specific trials dealing with senior adults and MIBC (Fonteyne et al. 2018).

Metastatic Bladder Cancer/Palliative Treatments

Cystectomy with urinary diversion has almost no place and should only be performed in locally advanced disease if there is no other option for relieve of symptoms (Witjes et al. 2016). In a palliative setting, TURBT or radiotherapy alone should be used to control symptomatic bleeding, pain, and urinary check.

In metastatic situation, chemotherapy is the gold standard, provided it is feasible. The standard first-line for fit patients is based on a cisplatin combination: either with methotrexate, vinblastine, and adriamycin (MVAC regimen) or gemcitabine (GC regimen). They prolong survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older combinations. According to Bajorin, three poor prognostic factors exist when a cisplatin-based regimen is used: Karnofsky PS of $\leq$80% and presence of visceral metastases and anemia (Bajorin et al. 1999). When no poor risk factor exists, the median survival is close to 36 months, 20 months with 1 factor, and only 12 months with 2 or more.

Senior adults have some important specific characteristics to be considered. They have a decreased bone marrow reserve, leading to a frequent use of primary GCSF prophylaxis and/or reduced primary dose or adapted schedule. These patients are underrepresented in clinical trials (Hutchins et al. 1999; Crome et al. 2011). Senior adults may have neuropathies with dose cumulative (platinum, taxanes) associated risk. They might worsen in 30% even after treatment discontinuation. Most importantly up to 50% of patients are ineligible for cisplatin (Dash et al. 2006; Balducci and Extermann 2000b). Galsky made in 2011 an update of the EORTC definition of "fit" and "unfit" for cisplatin: "fit" is GFR $\geq$ 60 ml/min and PS 0-1, while "unfit" represents a GFR <60 ml/min and/or PS $\geq$2 (Galsky et al. 2011; De Santis et al. 2011).

The first randomized phase II/III trial in this setting compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GCa) in patients unfit for cisplatin (De Santis et al. 2011). OS was not statistically significantly different between GCa (9.3 months) and M-CAVI (8.1 months) HR 0.94 (0.72–1.22). However less adverse effects were observed with GC (9.3%) compared to M-CAVI (21.2%). Finally it was shown that if PS 2 and GFR <60 (Bajorin poor prognosis group), the median OS was only 5.5 months (20% had only 1 cycle), suggesting that the best supportive care might be the best option in this group.

Vinflunine based chemotherapy might represent an alternative, based on a phase II trial (De Santis et al. 2014).

The second-line treatment chemotherapy is a challenge. Multiple small phase II trials use mainly single agents with high variability of response and heterogeneity of population. Gemcitabine seems active but is already used in first-line. Cisplatin can be rechallenged but only if the relapse is after 6–12 months, provided the patient is fit enough to receive it (Witjes et al. 2016).

The main drug for second-line treatment is vinflunine. In the critical stage III trial, it was compared with best supportive care (Bellmunt et al. 2013). Vinflunine was associated with a 2-month survival benefit (6.9 vs. 4.6 months) however not statistically significant ($p = 0.287$), and this drug is not considered worldwide as a standard regimen. Furthermore, based on decreased vinflunine clearance in patients above 80 years of age, the regimen should be adapted to age. Many different medications have been tried yet the outcomes are very frustrating with low reaction rates and short survival (Sonpavde et al. 2010).

New Drugs

The scene of treatment for urothelial carcinomas is evolving. New immunotherapy medicines with immune checkpoint inhibitors are assessed and appeared to be fascinating in cutting-edge urothelial carcinomas. As second-line treatment following platinum salt, two large phase II trials observed much better responses compared to standard second-line regimen. This was confirmed in a phase III trial comparing pembrolizumab to chemotherapy, with a HR for survival of 0.7 (0.59–0.91) (Bellmunt et al. 2017). This new class of compounds must be specifically tested in senior adults, even if there is apparently no difference in relapse-free survival based on age, from a meta-analysis of various CTLA-4 or PD-1 inhibitors (Nishijima et al. 2016). Elderly patients need to be formally analyzed and included in clinical trials.

Follow-Up

NMIBC

Patients with pTa, pT1, and low-grade tumors ought to get urinary cytology and cystoscopy three to four times each year for the initial 2 years and at 6-month intervals for the accompanying 3 years. Patients with high-grade lesions or CIS should be followed at 3-month intervals for the initial 3 years and at 6-month intervals from that point, based on the EAU guidelines which are of low grade (grade C) (Babjuk et al. 2017). No specific recommendation is available for senior adults.

MIBC

After Optimal Treatment

As the EAU guidelines advocate, an appropriate schedule for disease monitoring should be based on natural timing of recurrence, probability and site of recurrence, functional monitoring after urinary diversion, and possible treatment of recurrence. The follow-up after RC should monitor the urethra, pelvis, and additionally upper urinary urothelium, liver, lungs, and skeletal apparatus, as well as retroperitoneal nodes. It is not standardized and mainly based on expert opinion. It needs to be adjusted to patients' status. Patients after curative treatment, with a significant life expectancy, have to follow up in view of suggestion by the distinctive rules, e.g., EAU rules on MIBC (Witjes et al. 2016). Outside the clinic, biology and repeated CT scan represent the basis of this follow-up. Patients with bladder-preserving approaches with curative intent must be followed using the same parameters but also including cystoscopy and urinary cytology to monitor intravesical recurrence.

The functional complications after RC should be followed. They are related to the used bowel segment. They specifically include vitamin B12 deficiency, renal function, urinary infections, as well as chronic metabolic acidosis potentially associated with an increased long-term bone loss (Gupta et al. 2014). Specific complications such as ureterointestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction must also be considered. Particular attention should be paid to assess the quality of life.

Palliative Treatment

In non-curative or metastatic BC, HRQoL is reduced. There is limited literature describing HRQoL in BC patients receiving palliative care, but there are reports of bladder-related symptoms relieved by palliative surgery, RT, and/or chemotherapy. Palliative care must be considered as a priority and are optimized within a multidisciplinary team including a geriatrician team. Supportive measures have to be implemented as early as possible.

Cross-References

- ▶ Aging and Cancer Biology
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Frailty in Cancer Patients
- ▶ Geriatric Interventions in Oncology
- ▶ Normal and Abnormal Aging (General Perspective for the Oncologist)

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Kidney Cancer in Older Adults

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Ravindran Kanesvaran and Hui Shan Tan

Contents

Abstract

RCC is a relatively common cancer that predominantly afflicts the elderly. About one-third of all RCC patients are metastatic at diagnosis, while recurrence rates of those treated for

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localized disease are as high as 50%. There are a number of issues unique to the older adult with RCC which needs to be taken into account before assigning the appropriate treatment to them. Although new drugs approved for mRCC were assessed without age limitation and included patients over 65 years, no prospective trials dedicated to older RCC patients are available. All the phase III mRCC trials conducted thus far showed no differences in efficacy and toxicity in younger patients compared to older patients (>65 years old). A similar scenario is also observed in the setting of the treatment of localized RCC in the elderly. This textbook chapter aims to highlight the unique issues afflicting the elderly with both localized and metastatic RCC and comprehensively review the key treatment modalities that are currently used in their management.

Keywords
Geriatric · Older generation · Kidney cancer · Renal cell carcinoma · Guidelines

Introduction

Renal cell carcinoma (RCC) is the 16th most common cancer and 17th most lethal cancer in the world (Global Burden of Disease Cancer Collaboration et al. 2015). It afflicts over 290,000 people all over the world. RCC is a disease in which malignant cells are found in the lining of tubules in the kidney. RCC accounts for approximately 3% of adult malignancies and can exist in both sporadic and hereditary forms. Sporadic form of RCC is usually seen in older patients, whereas the hereditary cases are usually seen in the young. The hereditary form is mostly caused by a mutation in the Von Hippel Lindau (VHL) gene. The clinical presentation of RCC is usually described with the classic symptoms such as hematuria, flank pain, and fever. However with the advances in imaging modalities, more kidney tumors are now being detected incidentally. RCC is usually unilateral. Bilateral RCC comprises of only 2–4% of the cases. It is a clinically and pathologically heterogeneous disease, with clear cell renal cell carcinoma (CCRCC) being the dominant subtype accounting for over 75% of all RCCs. Other subtypes include papillary RCC (type I and type II), chromophobe RCC, hereditary cancer syndromes, multilocular cystic RCC, collecting duct carcinoma, medullary carcinoma, mucinous tubular and spindle cell carcinoma, neuroblastoma-associated RCC, Xp11.2 translocation-*TFE3* carcinoma, hereditary leiomyomatosis and RCC syndrome-associated RCC, succinate dehydrogenase-deficient RCC, tubulocystic RCC, acquired cystic disease-associated RCC, clear cell papillary RCC, and unclassified lesion (Moch et al. 2016). In general the treatment of RCC is divided into groups, namely, clear cell RCC and non-clear cell RCC.

Renal Cell Carcinoma in the Older Adults

RCC is predominantly a disease afflicting the elderly with a median age of diagnosis of 64 years. About one third of all RCC patients are metastatic at diagnosis, while recurrence rates of those treated for localized disease are as high as 50% (Bellmunt et al. 2009). Older adults are usually underrepresented in clinical trials, and the majority of data for both the localized and metastatic RCC setting arises from subgroup analyses. Although new drugs approved for mRCC were assessed without age limitation and included patients over 65 years, no prospective trials dedicated to older mRCC patients are available. All the phase III mRCC trials conducted thus far showed no differences in efficacy and toxicity in younger patients compared to older patients (>65 years old). A systematic review published by International Society of Geriatric Oncology (SIOG) Task Force in 2009 has also suggested that the survival benefits seen in patients aged 65 years and above were similar to those in younger patients and that the frequency and severity of major toxicities was not more in the older patients (Bellmunt et al. 2009). Another point to note

is that older patients included in pivotal studies typically have more robust general health than unselected older patients and fewer of the comorbidities that complicate management. It is hence important to use the information from the various sources of clinical research to incorporate into best practice approaches in the treatment of the older RCC patient taking into account issues unique to this group of patients.

Unique Issues Affecting Older Adults with RCC

Physiology of Aging and Treatment Implications

There is a decline in physiologic function as a person grows old. These physiologic changes can affect the pharmacokinetics and pharmacodynamics of various therapies used in the treatment of RCC. A decrease in liver mass and blood flow lead to a decline in liver function. Cytochrome P450 microsomal enzyme system has been reported to decline with the increase in age and may substantially impact on drug metabolism, given that the most of the targeted agents for mRCC are metabolized via that system (Wauthier et al. 2007). In the aging kidney, blood flow decreases and glomeruli are lost and replaced by fat and fibrotic tissue. The aging kidney coupled with the presence of renal cell carcinoma both lead to lower glomerular filtration rate which affects the pharmacokinetics of targeted therapies in mRCC. However some studies have shown that mRCC targeted therapy like sunitinib is efficacious with an acceptable toxicity profile in patients with impaired kidney function as well (Kim et al. 2014), hence still making it a viable option for older mRCC patients.

With the recent emergence of immune checkpoint inhibitors in mRCC, it can be assumed that age-related changes of the immune system (immunosenescence) might also affect the efficacy and toxicity of immunotherapy in elderly patients. It is known that the expression of immune checkpoints on T cells increases with age, hence making this potentially an important target with immune-oncology drugs (Hurez et al. 2017).

Decision-Making and Treatment Goals

Older patients differ from their younger counterparts when it comes to cancer treatment decision-making processes. They are different as they are less likely to trade off current quality of life for a prolonged overall survival compared to their younger counterparts (Yellen et al. 1994). Maintaining quality of life is often the primary goal of therapy in treating older cancer patients. As such tolerability of treatment-related side effects in older RCC patients as mentioned above plays a key role in the decision-making process. A recent systematic review found that one of the key reasons for declining cancer treatment in the older adults is the fear of side effects (Puts et al. 2015). It is then very important to address the specific concerns and treatment goals an older RCC patient may have in order to enable them to make the best informed decision possible.

Treatment Compliance

Compliance to treatment is also another issue to consider in treating older RCC patients. Treatment for mRCC predominantly involves oral therapies (in the first line, e.g., only bevacizumab and interferon are exceptions to this). This presents several advantages such as no complications related to intravenous access. However oral administration also comes with its own problems in the elderly, specifically with the issue of drug compliance. Older patients may be less compliant to oral medication compared to younger ones due to reasons like polypharmacy, cognitive decline (memory related), and general physical decline (eyesight, physical strength) (Biganzoli et al. 2015) . Poor compliance can lead to decreased drug efficacy and increased toxicities if the patient persists in taking medication during rest periods (with sunitinib, e.g., which has a 2-week rest

period after 4 weeks of treatment). As these drugs are taken at home with follow-ups only at certain intervals, there could also be issues with drug continuation and compliance. In order to increase compliance and ensure that the older mRCC patient is aware and is able to seek help for treatment-related toxicities, it would be very important to also ascertain the social support the patient has. If the social support is poor, and there is no community-based home visit help, prescription of these oral targeted therapies may not be appropriate in certain groups of older patients. In this instance and in circumstances where there are issues pertaining to compliance to oral therapies, an intravenous option like bevacizumab and interferon should be considered as an alternative option.

The Role of Geriatric Assessment (GA) in Older RCC Patients

In view of the multiple physical, psychological, and social issues that affect older RCC patients described above, it is important to ensure the appropriate tool is used in their assessment. This is where the role of a cancer-based GA comes in as the most appropriate tool to predict functional age of these older RCC patients (Kanesvaran et al. 2011). For example, should an mRCC patient have polypharmacy due to their multiple comorbidities, drug interactions become a major concern. For patients on vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI), proton pump inhibitors used concurrently can inhibit the absorption of the TKI leading to lower serum concentration levels and lower efficacy. In terms of nutritional status, a malnourished patient with mRCC planned to be treated with targeted therapy is at higher risk of dying compared to a well-nourished patient (Gu et al. 2015). Hence it is important for the treating oncologist to work in a multidisciplinary setting to ensure that older RCC patients who are found to have GA deficits are optimized. This will ensure they are fit for surgery in a case of localized RCC and fit for systemic therapies in a case of mRCC.

Localized Renal Cell Carcinoma in Older Adults

Surgical Resection

In a fit older patient with localized RCC, there are a number of treatment options available. These options vary depending on the size and site of the tumor. For solitary RCC that is 4 cm or larger, the treatment of choice would be a radical nephrectomy (RN), with removal of the entire kidney and tumor en bloc. This can be done safely laparoscopically with a recent study showing reduced morbidity in terms of genitourinary complication rate and blood loss in older RCC patients (Becker et al. 2014). With the rising use of imaging in the investigation of various symptoms in elderly patients, there has been an increase in the detection of small renal masses (<4 cm), of which a substantial number are RCCs (Sun et al. 2011). In these patients, nephron-sparing surgeries, or partial nephrectomy, are the treatment of choice for localized small RCC based on their location. In certain locations, partial nephrectomy (PN) may not be possible leading to RN instead. As mentioned in the paragraph above, there are numerous physiologic factors inherent in the older adults that may complicate the surgical procedure. Hence a key element in the management of an older RCC patient planned for surgery would be optimal preoperative assessment (Chow et al. 2012).

Adjuvant Systemic Therapies

After surgical resection of the RCC, there is currently some data to support the role of adjuvant therapy. Two recently published phase 3 randomized controlled trials (RCTs) – the ASSURE trial (Haas et al. 2016) and the S-TRAC trial (Ravaud et al. 2016) – have tested sunitinib and sorafenib (in ASSURE only) as an adjuvant treatment for high-risk, resected RCC with contrasting results. In the S-TRAC trial, sunitinib increased median disease-free survival in patients with clear cell RCC who were at very high risk of recurrence, but at the time of data cutoff, data were not mature

enough to evaluate overall survival (Ravaud et al. 2016). In contrast, in the ASSURE trial, adjuvant sunitinib and sorafenib have been reported to provide no additional survival benefit compared to placebo and caused an increase in treatment-related toxicities (Haas et al. 2016). A meta-analysis done in 2016 on the combined benefit-risk profile of adjuvant sunitinib for RCC failed to demonstrate survival benefit and confirmed increased toxicities with the use of sunitinib in the adjuvant setting (Gyawali and Ando 2017). The median age of the patients in the ASSURE trial was reported as 56 years for the sunitinib arm (range, 49–64) and 55 years for the sorafenib arm (range, 48–63 years); whereas for the S-TRAC trial, the median age of the patients for the sunitinib arm is 57 years (range, 25–83 years). This makes the data to some extent valid for older RCC patients as well in view of the fact that subsets of patients were over 65 years of age. However an area of concern here with regard to the use of adjuvant sunitinib in older mRCC patients would be its use for a prolonged period of 1 year, in which the toxicities of the treatment may be overwhelming. Another factor to take into consideration in the older adult would be competing comorbidities that may impact their life expectancy and hence nullify the benefit of adjuvant therapy. Hence these patients (who may have a shortened projected life expectancy) should be on an active surveillance protocol although there is currently no consensus on the exact frequency of imaging in the various guidelines (Williamson et al. 2016). Presently, there are no standardized guidelines for surveillance regimens and thresholds for implementation of delayed treatment.

Ablation Therapies

Ablative therapies have been developed for the treatment of small renal tumors as an alternative to nephron-sparing surgery, with the goal of reducing operative morbidity. The common methods of ablative therapy are radiofrequency ablation (RFA) and cryoablation. A systematic review comparing cryoablation versus partial nephrectomy reported higher rates of tumor progression with cryoablation, but both had similar low rates of distant metastases of less than 2% (Klatte et al. 2011), hence making it a suitable option for the frail elderly patient. Frail older patients with a shortened life expectancy with a solitary renal mass may not have many treatment options available to them. For large tumors (>=4 cm), these patients may not be fit for any form of surgery and will be treated expectantly for symptom control with palliative care.

Active Surveillance

Another feasible option for the frail older RCC patient would be active surveillance of their small RCC (Borghesi et al. 2015) due to the slow growth of small renal masses. Active surveillance has emerged as an alternative to surgical or medical intervention for small renal masses, especially for select patients with poor renal function and high operative risk or the elderly with comorbid disease.

Metastatic Renal Cell Carcinoma in the Older Adult

Clear Cell mRCC

Role of Cytoreductive Nephrectomy

There were two randomized control trials conducted more than a decade ago, in the cytokine era, which found a survival benefit for mRCC patients who had undergone cytoreductive nephrectomies (CN). In the study done by the SWOG group, the median age of patients undergoing CN was 58.8 years, although the oldest patient in the study was 87 years of age (Flanigan et al. 2001). In the European study done at about the same time, the median age of the patients was 61 years and the oldest patient enrolled was 76 years of age (Mickisch et al. 2001). More than age of the patients, it was the disease burden, site of disease (lung better prognosis), and performance status of the patients that stood out as key determinants of the success of CN. This further highlights the benefit of doing GA in this group of patients before selection for CN.

The role of cytoreductive nephrectomy had also been studied specifically in older mRCC patients, and there was no significant difference between the older and younger group of patients in terms of median overall survival (Kader et al. 2007). However that study also showed that the perioperative mortality of patients older than 75 years of age was significantly higher than that seen in younger patients. This was not surprising as similar surgical outcomes were seen with elderly cancer patients having other tumor types as well. Much of this increased risk can be attributed to the lower physiologic reserve of older RCC patients.

However in the targeted therapy era, we currently only have retrospective data that suggest that certain groups of mRCC patients may continue to benefit from CN. In the largest of these retrospective studies, the international metastatic RCC database consortium (IMDC) had relatively younger patients with a median age of 59.3 years (range 52.7–67.4 years) (Heng et al. 2014). Hence while waiting for prospective data on the benefit of CN in mRCC patients, current data seem to suggest that older mRCC patients when selected appropriately with adequate presurgical assessment and/or GA may be suitable for CN.

Systemic Therapies

Since 2005, a number of targeted therapies have been developed that has revolutionized the way we treat older mRCC patients. Apart from high-dose interleukin-2 which has shown efficacy in a small group of younger patients, there is no data to support cytokine use in the elderly (Fyfe et al. 1996). These mRCC patients should first be stratified into the appropriate prognostic risk group as defined by either the Memorial Sloan Kettering Cancer Center (MSKCC) or the International Metastatic Renal Cell Carcinoma Database (IMDC) criteria (Heng et al. 2009). Table 1 shows the various phase 3 clinical trials that have led to the approval of the targeted therapies for use in the different settings in the

Table 1 Summary of phase III trials for approved agents which had older mRCC patients enrolled in them

Line of treatment	Phase 3 trial	Patient population	Median age (years)	Age of oldest patient (years)	Median PFS (months)	Median OS (months)
1st	Sunitinib (Motzer et al. 2007)	Clear cell mRCC; no previous systemic therapy	62	87	11	26.4
1st	Bevacizumab + IFN-α (Rini et al. 2010)	Clear cell mRCC; no previous systemic therapy	61	82	8.5	18.3
1st	Pazopanib (Sternberg et al. 2010)	Advanced RCC/mRCC; with or without prior cytokine-based systemic therapy	59	85	9.2	22.9
1st (poor risk)	Temsirolimus (Hudes et al. 2007)	Poor prognosis mRCC; no prior systemic therapy	58	81	3.8	10.9
2nd	Nivolumab (Motzer et al. 2015)	Clear cell advanced RCC/mRCC; received one or two previous regimens of antiangiogenic therapy	62	88	4.6	25.0
2nd	Cabozantinib (Choueiri et al. 2015)	Clear cell advanced RCC/mRCC; received at least one VEGFR-targeting tyrosine kinase inhibitor	63	86	7.4	–
2nd	Everolimus (Motzer et al. 2008)	Clear cell mRCC; prior VEGFR TKI therapy	61	85	4	14.8
2nd	Axitinib (Rini et al. 2011)	Advanced RCC/mRCC; prior VEGFR TKI, cytokine-based systemic therapy	61	82	8.3	20.1

treatment of mRCC. Data for the older adults can be extrapolated from these phase III studies as about one third of the patients enrolled in them were over 65 years of age (Bellmunt et al. 2009). A key piece of data from these studies is that there is no upper limit to the age of the patients enrolled, with the oldest patients in these randomized trial well over 80 years in age (Table 1). The randomized trials of sunitinib and sorafenib reported no difference in survival benefit between subset of patients aged 65 years and younger and the older patients. The bevacizumab and interferon study showed that there was no statistically significant difference among older patients that received study treatment versus that receiving standard arm treatment, implying little benefit for the elderly. For MSKCC poor-risk patients, temsirolimus, which is the drug of choice, has not been shown to increase survival in patients over 65 years of age who were given temsirolimus compared to interferon which was unlike the finding seen in the younger age group which benefited from temsirolimus treatment (Hudes et al. 2007).

A recent study comparing patient preference between sunitinib and pazopanib reported that a majority of mRCC patients prefer pazopanib due to its better toxicity profile and quality of life (QOL) (Escudier et al. 2014). In a study which found pazopanib to be non-inferior to sunitinib in the first-line treatment of mRCC patients, there was a nonsignificant trend favoring the use of sunitinib in patients older than 65 years of age (Motzer et al. 2013). Although this was not an older adult specific study, the lower toxicities and better QOL assessment make it a suitable choice for them.

In the second-line setting, there are a number of drugs approved for use in the treatment of mRCC patients (Table 1). Recently reported studies in the second line indicate that treatment with nivolumab, a programmed death 1 (PD-1) checkpoint inhibitor, or cabozantinib, a multikinase inhibitor, may be suitable options for older mRCC patients after it was found to have superior efficacy and better tolerability when compared with everolimus (Motzer et al. 2015; Choueiri et al. 2015). The median age reported in the nivolumab trial was 62 years for both the nivolumab and everolimus groups (range, 23–88 years and 18–86 years, respectively) (Motzer et al. 2015). For the cabozantinib trial, the median age was 63 years for the cabozantinib group (range, 32–86 years) and 62 for the everolimus group (range, 31–84 years) (Choueiri et al. 2015). Axitinib, a second-generation inhibitor of VEGF receptors, is also approved as the second-line treatment of mRCC patients after the pivotal trial comparing its efficacy against sorafenib (Rini et al. 2011). Seven hundred twenty-three patients were included in the trial, and the median age was 61 years for both arms (range, 20–82 for axitinib group and 22–80 for sorafenib group) (Rini et al. 2011). Based on those age ranges, it is fair to say that both these drugs can be used in selected older mRCC patients in the second line.

Although these drugs have shown that it is reasonably well tolerated in the younger population in which it was tested on, it is important to note that older patients have a multitude of other issues (as described above) that need to be taken into account before they are treated. The potential toxicity with cytotoxic systemic therapy can pose special concerns in older patients; thus, it is important to put in extra care with prophylactic treatment, patient education, and monitoring of response, toxicity, and quality of life. Table 2 describes some of the common toxicities to look out for in older mRCC patients on systemic therapies.

There is still a lack of high-quality evidence to guide therapy choices in third-line setting of mRCC. A retrospective analysis conducted by a large collaborative consortium, the IMDC, has analyzed 1012 patients receiving third-line targeted therapy and reported that third-line therapy use in favorable- and intermediate-risk patients was associated with the greatest overall survival. The age distribution of the patient population was however not reported in the paper (Wells et al. 2017).

Active Surveillance

For older mRCC patients who are frail or choose not to have treatment initially, active surveillance

Table 2 Therapies and special consideration in older patients with mRCC

Line of treatment	Drug	Safety data	Data source	Specific considerations in older adults
1st	Sunitinib (Motzer et al. 2007)	Available	Elderly specific data	Monitor for GI toxicity, HFS, HTN, fatigue; first-line dose modification may be appropriate
1st	Bevacizumab + IFN-α (Rini et al. 2010)	Available	Elderly specific data	Monitor for HTN; screen for vascular risk factors
1st	Pazopanib (Sternberg et al. 2010)	Available; favorable toxicity profile in elderly patients (PISCES)	Pivotal trial	Monitor for GI toxicity, HTN, anorexia
1st (poor risk)	Temsirolimus (Hudes et al. 2007)	Available	Pivotal trial	Monitor for rash, fluid retention, hyperlipidemia, hyperglycemia
2nd	Nivolumab (Motzer et al. 2015)	Limited	Pivotal trial	Monitor for fatigue, nausea, pruritus, diarrhea
2nd	Cabozantinib (Choueiri et al. 2015)	Limited	Pivotal trial	Monitor for HTN, diarrhea, fatigue
2nd	Everolimus (Motzer et al. 2008)	Available	Elderly specific data	Monitor for stomatitis, rash, fatigue
2nd	Axitinib (Rini et al. 2011)	Available	Pivotal trial	Monitor for HTN, diarrhea, fatigue
2nd	Sorafenib (Escudier et al. 2007)	Available	Elderly specific data	Monitor for skin toxicity, diarrhea, fatigue, and rare serious AEs (HTN, cardiac ischemia)

in this group of patients may be a feasible option as well based on a recent multicenter phase 2 study (Rini et al. 2016).

Non-clear Cell RCC

Much of the data for non-clear cell RCC patients have been derived from subset analyses from large clinical trials that had both ccRCC and non-ccRCC patients. The earliest data from a phase III trial came from the temsirolimus study in poor-risk mRCC patients. There were a number of patients in that study who were older than 65 years; however, in the subset analyses, the hazard ratio for PFS did not show a clear benefit for this group of patients. Recently however there was a phase 2 study which looked at the various types of metastatic non-ccRCC, and their responses to the targeted therapies (ASPEN). In this study, the median age was 59 years for the sunitinib arm (range, 24–100 years) and 44 years for the everolimus arm (range, 29–90 years) (Armstrong et al. 2016). The study outcome showed that sunitinib significantly increased progression-free survival compared with everolimus in metastatic non-clear cell RCC. Overall survival, however, was not different between the two treatment groups, although there were differences in treatment effect between the various histologic subtypes and prognostic risk groups. Based on a subset of older patients enrolled into this study, the results may be extrapolated for use in this group of patients as well.

Guidelines

Currently, the only available treatment guideline for the treatment of metastatic RCC in older patients is based on the systematic review developed in 2009 by a SIOG task force (Bellmunt et al. 2009).

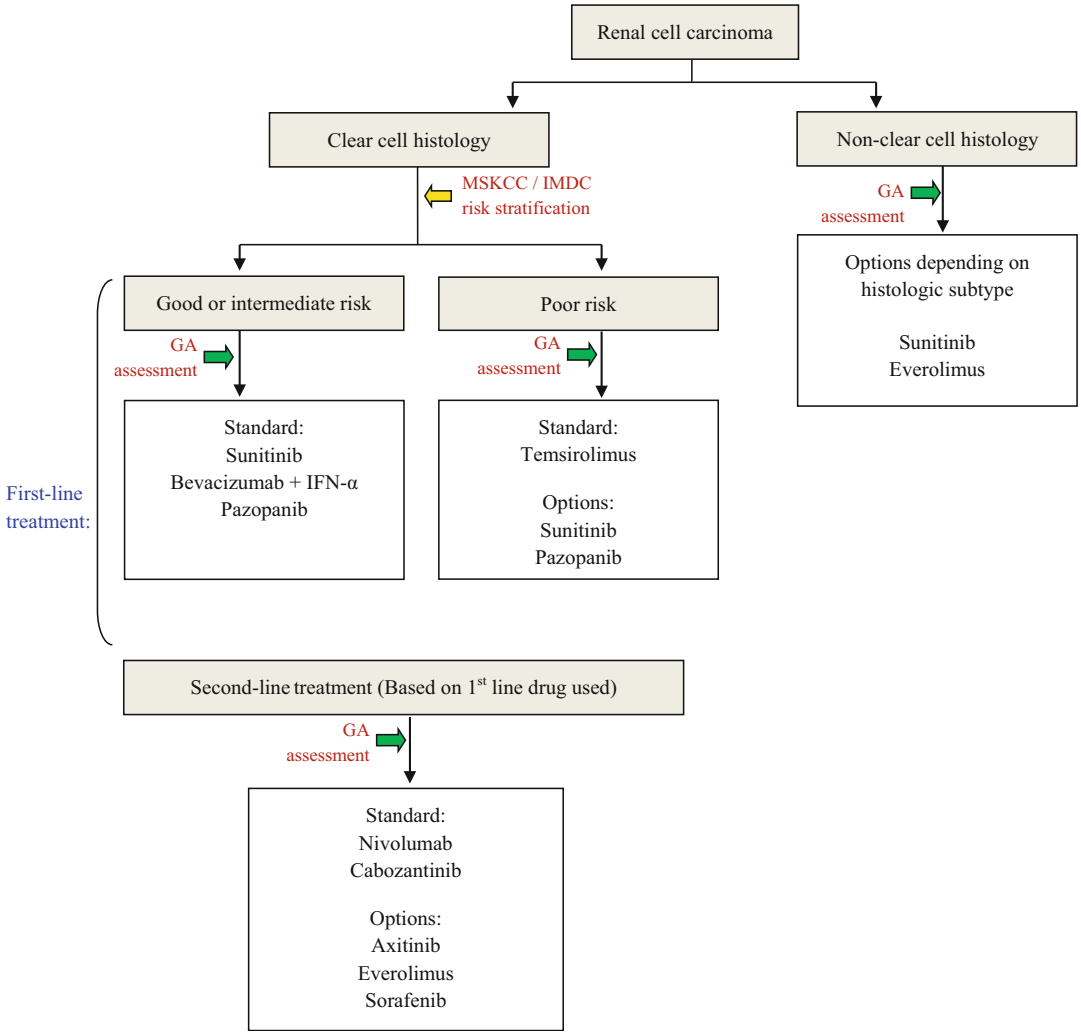

Fig. 1 Algorithm for systemic treatment in mRCC in older adults

SIOG has formed another mRCC task force to work on an update to the 2009 guidelines, which should be ready by the end of 2017. Figure 1 shows a suggested treatment algorithm for elderly mRCC patients incorporating the use of GA prior to treatment selection and the drugs with some data on older mRCC patients.

Summary

Although there is a dearth of data from older adult specific prospective clinical trials in the treatment of RCC, there are ample retrospective and subset analyses of trial data to assist us in choosing the most appropriate treatment for this vulnerable group of patients. Fit older patients with RCC should be offered surgery (RN or PN depending on the size and location of the lesion). Frail older patients with localized RCC may be offered local ablative therapy or active surveillance. In mRCC depending on their risk stratification, they should receive targeted therapies just like the younger counterparts. If they are frail, they can still be offered targeted therapies depending on their degree of frailty, concurrent medication use, and predicted life expectancy. Active surveillance is another option to consider in these mRCC patients

as well. The key factor in determining treatment choice would be a thorough assessment with a GA. All older RCC patients should have a GA done (including a discussion on treatment goals) and have their case discussed in a multidisciplinary tumor board before deciding on the most appropriate treatment for them.

Cross-References

- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Integrating Geriatric Oncology into Clinical Pathways and Guidelines
- Pharmacology of Aging and Cancer
- Principles of Cancer Targeted Therapy in Older Adults

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Colorectal Cancer in Older Adults: Systemic Treatments

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Contents

Abstract

Colorectal cancers are common in elderly patients. However, cancer screening is poorly used after 75. Elderly patients form a heterogeneous population with specific characteristics. Standards of care cannot therefore be transposed from young to elderly patients. Tumor resection is frequently performed, but adjuvant chemotherapy is rarely prescribed as there are no clearly established standards of care. In a metastatic setting, recent phase III studies have demonstrated that doublet frontline chemotherapy provided no survival benefit. Moreover, several studies have established the benefit of bevacizumab in association with chemotherapy. There is a lack of evidence for the efficacy of anti-epidermal growth factor antibodies in elderly patients. Geriatric assessments could help to select the adequate treatment strategy for individual patients. Geriatric oncology is now the challenge we have to face, and more specific trials are needed.

Keywords

Radiotherapy · Chemotherapy · Targeted therapy · Colorectal cancer · Elderly

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Introduction

Colorectal cancer (CRC) is one of the most frequent cancers. Currently, in Europe and the USA, the median age of CRC diagnosis is 70 years (Ferlay et al. 2013; Siegel et al. 2016). The specific questions about age arise mainly after 75 years. Given the ageing of the population, the proportion of patients with CRC aged over 75 years will increase even further in the coming years. Unfortunately the majority of organized mass screening programs for CRC are restricted to the population aged 50–74 years. The efficacy of CRC screening with fecal occult blood test (FOBT) has never been prospectively evaluated in elderly subjects (Quarini and Gosney 2009). Elderly patients form a specific population due to comorbidities, disability, and organ-specific physiological changes that have impaired their enrolment in clinical trials and thus the transposition of current guidelines established in younger patients (Frerot et al. 2015; Sorbye et al. 2009; Yee et al. 2003). The therapeutic strategy for CRC after 75 is often difficult to establish because of the lack of specific data for elderly patients. Recently, the International Society of Geriatric Oncology published recommendations for the treatment of CRC in elderly patients (Papamichael et al. 2015). Nevertheless, many issues remain unsolved (Aparicio et al. 2016c).

Geriatric Evaluation in Colorectal Cancer

Very few studies have assessed geriatric evaluation specifically in CRC. A comprehensive geriatric assessment (CGA) is recommended before CRC treatment decisions by the SIOG (Papamichael et al. 2015). However, the CGA is time consuming. Several screening tools are therefore used to identify frail elderly patients with cancer who are most likely to benefit from the CGA (Hamaker et al. 2012). Among these tools, the Geriatric 8 screening tool (G-8) may be the most sensitive to select patients for CGA (Bellera et al. 2012). In a recent study, significant differences were noted in the ability of G-8 to accurately detect frailty according to tumor site. In colorectal cancer, the G-8 screening tool identified frail elderly patients with high sensitivity (90%) but low specificity (23%) (Liuu et al. 2014). Relevant screening tools to assess frailty and predict morbidity must be adapted to the cancer stage, the primary site, and the treatment toxicities.

Predicting the toxicity of chemotherapy in elderly patient is an important challenge. A predictive score based on a cohort of elderly patients with several cancer types has been proposed. Age, gastrointestinal or genitourinary cancer, standard chemotherapy dosing, polychemotherapy, anemia, low creatinine clearance, hearing disability, falls, autonomy impairment, walking disability, and decreased social activities have been identified as predictors for toxicities (Hurria et al. 2011). Another score identified diastolic blood pressure, independent activity of daily living (IADL), ECOG performance status, mini mental health status (MMS), mini nutritional assessment (MNA), lactate dehydrogenase (LDH) level, and chemotherapy regimen as predictive factors for toxicity (Extermann et al. 2012). Nevertheless, these factors and others remain to be validated in the specific situation of adjuvant or metastatic settings in CRC.

In elderly patients, special attention must be paid to malnutrition that is still not sufficiently screened for and not sufficiently managed, although it is a major prognostic factor for all cancers especially for elderly patients (Soubeyran et al. 2012). Some geriatric syndromes, such as cognitive impairment and depressed mood, are independently associated with malnutrition in digestive cancers (Paillaud et al. 2014).

Adjuvant Chemotherapy After R0 Resected Colon Cancer

Stage III

Postoperative adjuvant chemotherapy combining fluoropyrimidine and oxaliplatin is the standard therapy after R0 resection of a colon cancer (Andre et al. 2004; Haller et al. 2011). Single-

center or registry studies indicate that adjuvant chemotherapy after resection of stage III colon cancer is less prescribed after 75 years than in younger counterpart (Aparicio et al. 2009; Faivre-Finn et al. 2002). Although this rate has increased more recently, a large proportion of elderly patients do not receive adjuvant chemotherapy (van den Broek et al. 2013) especially after 80 years (Bouvier et al. 2005; Lievre et al. 2014). The reasons of the absence of prescription of chemotherapy were usually poorly documented (Mahoney et al. 2000). Nevertheless, the increase rate of adjuvant chemotherapy in elderly in the last decade suggests that gastroenterologist, oncologist, and surgeon have taken in consideration the specificity of elderly patients.

Post hoc analysis of seven prospective phase III trials that enrolled patients after resection of a stage II or III colon tumor suggested a prognostic improvement with 5FU chemotherapy in patients over 70 years similar to that in younger patients (Table 1). However, only 15% of the patients enrolled were over 70 years and 0.7% over 80. This suggests that elderly patients were highly selected, and thus no conclusions can be drawn for patients over 80 years. With the exception of leukopenia, side effects were no more frequent in older patients (Sargent et al. 2001). The question about the benefit of fluoropyrimidine-based adjuvant chemotherapy in very elderly, unselected patients is still an issue.

The recommended adjuvant treatment for stage III cancer is a combination of fluoropyrimidine and oxaliplatin (Andre et al. 2004). However, this association has not demonstrated its effectiveness in elderly patients. An analysis of randomized trials comparing fluoropyrimidine adjuvant chemotherapy with or without oxaliplatin revealed no significant improvement in disease-free survival after age 70 (HR = 0.91 (95% CI, 0.75–1.11) after resection of stage III cancer (McCleary et al. 2013) and no overall survival (OS) advantage (Table 1). This lack of benefit with oxaliplatin in elderly patients was again observed in a subgroup analysis of the MOSAIC trial (Tournigand et al. 2012). Moreover, a registry study revealed that the combination of capecitabine and oxaliplatin did not confer a survival advantage compared to capecitabine alone (van Erning et al. 2017). A decrease in dose intensity is frequently observed in elderly patients treated by oxaliplatin and may explain the decrease of efficacy of this treatment (Laurent et al. 2018). Nevertheless, oxaliplatin could be beneficial in some selected elderly patients. Altogether, there are still two concerns: First, does fluoropyrimidine-based adjuvant chemotherapy procure any benefit in unfit elderly patients? Second, does oxaliplatin-based adjuvant chemotherapy procure any benefit for fit elderly patients? A prospective trial (PRODIGE 34 – ADAGE) is ongoing to evaluate the benefit of adjuvant chemotherapy in elderly patients (Aparicio et al. 2016a).

Stage II

The benefit of adjuvant chemotherapy is controversial for stage II tumors. The QUASAR study highlighted a 2.8% improvement in 5-year OS in patients receiving 5FU adjuvant chemotherapy

Table 1 Results of post hoc analysis of pooled clinical trials of adjuvant chemotherapy after colon cancer resection in subgroup of patient >70 years. (Adapted from Aparicio et al. (2016c))

	Patient number (%[a])	Adjuvant treatment arm	Disease-free survival HR (95% CI)	Overall survival [HR (95% CI)]
Sargent et al. (2001)	506 (15%)	Surgery alone	0.68 (0.60–0.76), $p < 0.001$	0.76 (0.68–0.85), $p < 0.001$
Stage II and III		5FU		
McCleary et al. (2013)	1119 (21%)	5FU	0.94 (0.78–1.13), NS	1.04 (0.85–1.27), NS
Stage II and III	–	5FU + oxaliplatin	0.91 (0.74–1.11), NS	–
Only stage III				

[a]Percentage of patients over 70 in the whole study population

after resection of stage II colon cancer. However, there was no advantage but even a trend for a deleterious effect for OS in the subgroup of patients over 70 years treated with adjuvant chemotherapy (Quasar Collaborative Group et al. 2007). The decision to give chemotherapy after stage II resection was based on the presence of pejorative factors such as T4 stage, tumor vascular invasion, high tumor grade, and occlusion at diagnosis, even though the benefit of adjuvant chemotherapy in high-risk stage II colon cancer patients is not clearly demonstrated (O'Connor et al. 2011).

Recently, some biological tumor characteristics have been recognized as prognostic factors. The deficient DNA mismatch repair phenotype (dMMR) has been demonstrated as a good prognostic factor (Ribic et al. 2003). In a post hoc analysis of five prospective trials comparing 5FU-based adjuvant chemotherapy to surgery alone, the patients with dMMR tumors did not benefit from adjuvant chemotherapy. Moreover, a reduced OS was associated with adjuvant chemotherapy in patients with dMMR stage II tumors (Sargent et al. 2010).

In elderly patients, MMR dysfunction is most often due to senescence-related hypermethylation of the *hMLH1* gene promoter. In the elderly, *hMLH1* epigenetic silencing is mostly associated with the *BRAF* gene V600E somatic mutation (Aparicio et al. 2014). Moreover, the frequency of the dMMR tumor phenotype increased with age, reaching 22% in patients over 75 years and 36% in patients over 85 years, and is associated with an excellent prognosis for stage II colon cancer (Aparicio et al. 2013b). In both studies, the frequency of the dMMR phenotype was higher in women than in men. The high rate of dMMR tumors in elderly patients was confirmed in another study, which reported 35% of dMMR tumors in patients over 80 years (Lievre et al. 2014). As the dMMR phenotype was associated with a lack of efficacy of 5FU adjuvant chemotherapy (Sargent et al. 2010), this tumor characteristic should be considered for adjuvant chemotherapy decisions, especially in elderly women.

In conclusion, adjuvant chemotherapy decisions remain unclear and should be decided in multidisciplinary meeting taking into account the geriatric assessment, tumor stage, and tumor phenotype. The best chemotherapy regimen remains an issue. Given the excellent prognosis of stage II tumors with dMMR and the lack of efficacy of 5FU adjuvant chemotherapy in this case, adjuvant chemotherapy is not recommended in these patients.

Specificities for Rectal Cancer

A meta-analysis of rectal cancer studies suggested that advanced chronological age should not, by itself, exclude patients from curative rectal surgery or from other surgical options that are available for younger patients. Although overall survival is lower in elderly patients than in younger patients, cancer-specific survival does not decrease with age (Manceau et al. 2012).

The functional results, after surgery, are impacted by neo-adjuvant treatment. Radiotherapy is less frequently used in elderly patients than in younger counterpart (Aparicio et al. 2009; Olsson et al. 2011). Some concerns have been raised about the benefit of neo-adjuvant radiotherapy in elderly patients (Jung et al. 2009). Nevertheless, preoperative radiotherapy improved local control in elderly patients compared with no preoperative radiotherapy (Martijn and Vulto 2007). Several preoperative radiotherapy schedules are used: short-course radiotherapy of 5 × 5 Gy in 1 week and long-course radiotherapy of 45–50 Gy in 5 weeks with or without oral or infusional fluoropyrimidine. Short-course radiotherapy is an attractive schedule for elderly patients, but when surgery is performed 1 week after the end of radiotherapy, tumor down-staging or downsizing could not be achieved. Moreover, compliance and toxicity for long-course radiochemotherapy is a concern in elderly patients. Other strategies should also be explored in the elderly, such as intensity-modulated radiotherapy to reduce toxicity, high-dose rate intraluminal brachytherapy, or *contact* X-ray therapy for T1 or T2 tumors. Moreover, a watch and wait strategy with the aim to avoid surgery among patients with complete tumor response after neo-adjuvant

radiochemotherapy is attractive in elderly patients (Maas et al. 2011).

Palliative Chemotherapy in Metastatic Patients

The current management of metastatic CRC (mCRC) involves various active chemotherapy agents, either in combination or as single agents: fluorouracil plus leucovorin (5-FU/LV), capecitabine, irinotecan, oxaliplatin, and recently trifluridine-tipiracil. In addition to these chemotherapy drugs, six biologic agents have been developed (bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, and regorafenib) which also improve survival outcomes for mCRC patients.

Evaluation of Chemotherapy for Treatment of mCRC in Elderly Patients

A meta-analysis of 22 trials evaluating 5FU monotherapy for mCRC, which enrolled 3825 patients, among whom 629 (16%) were over 70 years, revealed comparable tumor response rates, progression-free survival (PFS), and OS in patients under 70 years and over 70 years (Folprecht et al. 2004). A meta-analysis of four randomized trials comparing 5FU monotherapy with doublet chemotherapy of 5FU + irinotecan suggested that the benefit of irinotecan for PFS and OS was preserved in patients over 70 years. Nevertheless, regarding the subgroup of patients over 75, they represented only 6.9% of the randomized patients, and in this subgroup, irinotecan provided no significant improvement in PFS or OS. Neutropenia 33% vs 40% ($p < 0.05$) and stomatitis 5% vs 10% ($p < 0.05$) were more frequent after 70 years (Folprecht et al. 2008). A post hoc analysis of randomized trials comparing doublet with oxaliplatin versus 5FU alone in first-line and second-line treatment suggested that the benefit of oxaliplatin was also preserved in patients over 70 (Goldberg et al. 2006). In a retrospective series of selected fit elderly patients over 75, irinotecan or oxaliplatin combined with fluorouracil chemotherapy was manageable, but a dose reduction was done in 35% of the cure (Aparicio et al. 2003). A prospective phase II study evaluated the FOLFIRI regimen in patients over 70 year and concluded that the treatment was well tolerated and effective in selected elderly patients (Francois et al. 2008).

However, the results of two randomized trials specifically for elderly patients did not confirm these preliminary data (Table 2). The FOCUS 2, phase III study comparing frontline 5FU monotherapy, capecitabine monotherapy, 5FU + oxaliplatin, and capecitabine + oxaliplatin in elderly or frail patients with mCRC did not demonstrate a significant gain of PFS or OS with doublet compared with fluoropyrimidine alone. Moreover, there was more toxicity with capecitabine than with infusion 5FU (Seymour et al. 2011). The FFCD 2001–2002 phase III study assessed the efficacy of and tolerance to doublet 5FU + irinotecan vs 5FU alone in the first-line treatment of mCRC in patients over 75 years. Once again, neither PFS nor OS were improved by doublet treatment, but toxicity was increased (Aparicio et al. 2016b) (Table 2). Surprisingly, in the latter study, chemotherapy with 2 days of a 5FU bolus regimen was more efficient than those with only 1 day of a 5FU bolus regimen. Nevertheless, in both studies, response rates were significantly improved with doublet chemotherapy. Moreover, a compilation of published data of all of the above studies specific to elderly patients or to the elderly subgroup of trial patients with no age limit suggested that doublet chemotherapy prolonged PFS (HR = 0.82; [95% CI, 0.72–0.93]) but had no effect for OS (Landre et al. 2015).

All these observations underline the need to conduct specific studies in elderly patients to avoid inappropriate conclusions for the general population due to patient selection. The choice of the appropriate chemotherapy regimen for the patient is the main challenge in a metastatic setting. A CGA could help in this choice. An ancillary study of the FFCD 2001–2002 study revealed that cognitive and functional impairments were predictive of severe toxicity or unexpected

Table 2 Results of randomized clinical trials dedicate for elderly patients comparing different first-line therapy in metastatic colorectal cancer. (Adapted from Aparicio et al. (2016c))

	Patient's number	Treatment arm	Progression-free survival HR (95% CI)	Overall survival HR (95% CI)
Seymour et al. (2011)	459	Fluoropyrimidine monotherapy vs	4.5 vs 5.8 months	10.1 vs 10.7 months
		Oxaliplatin doublet	0.84 (0.69–1.02), $p = 0.073$	0.99 (0.82–1.19), $p = 0.916$
Aparicio et al. (2016b)	282	5FU monotherapy vs	5.2 vs 7.3 months	14.2 vs 13.3 months
		Irinotecan doublet	0.84 (0.66–1.07), $p = 0.157$	0.96 (0.75–1.24), $p = 0.750$
Cunningham et al. (2013)	280	Capecitabine vs	5.1 vs 9.1 months	16.8 vs 20.7 months
		Capecitabine + bevacizumab	0.53 (0.41–0.69), $p < 0.0001$	0.79 (0.57–1.09), $p = 0.18$
Price et al. (2012)	69	Capecitabine vs	–	–
		Capecitabine + bevacizumab	0.53 (0.32–0.86), $p < 0.001$	0.80 (0.47–1.36), $p = 0.48$
Aparicio et al. (2018)	102	LV5FU2 or FOLFOX or FOLFIRI vs	7.8 vs 9.7 months	19.8 vs 21.7 months
		Idem + bevacizumab	0.78 (0.53–1.17)	0.73 (0.48–1.11)

hospitalization (Aparicio et al. 2013a). Moreover, in the FFCD 2001–2002 trial, normal IADL was independently associated with better OS. In this study, an exploratory analysis suggests a PFS improvement in patients treated with doublet chemotherapy compared to 5FU monotherapy in the following subgroups of patients: <80 years, unresected primary tumor, leukocytes >11,000/mm^3, and carcinoembryonic antigen >2 N (Aparicio et al. 2017). More studies evaluating geriatric parameters are needed to develop an accurate predictive tool. Nevertheless, though fluoropyrimidine monotherapy appears to be the best option in the first line, a doublet should be discussed by the multidisciplinary team in cases of symptomatic tumor or the potential use of metastases resection.

Evaluation of Targeted Therapy for the Treatment of mCRC in Elderly Patients

Several targeted therapies have demonstrated activity in the treatment of mCRC. Regarding antiangiogenic pathway inhibition, most of the data for elderly patients were obtained with bevacizumab (anti-VEGF monoclonal antibody). Concerns have raise about cardiovascular tolerance of antiangiogenic therapy in elderly patients. US data from SEER-Medicare and French data from national insurance revealed that patients over 75 and patients with preexisting cerebrovascular disease were less likely to receive bevacizumab in first line (Doat et al. 2014; Shankaran et al. 2013). In the SEER-Medicare study, bevacizumab receipt was not associated with an increased risk of first adverse event compared with chemotherapy alone (Shankaran et al. 2013). An observational cohort in 2953 patients, which enrolled 363 (12%) patients older than 75 years treated with bevacizumab in combination with chemotherapy for mCRC, revealed that OS decreased according to age: 28 months <65 years vs 19.5 months >75 years. Severe thromboembolic events are more frequent in elderly patients (1.5% vs 4%) (Kozloff et al. 2009). A pooled analysis of four randomized trials that assessed bevacizumab in combination with chemotherapy in the first-line or second-line treatment for mCRC showed that, in the subgroup of patients ≥70 years, median PFS (6.4 months vs 9.2 months, $p < 0.0001$) and OS (14.1 vs 17.4 months; $p = 0.005$) were improved in

patients receiving bevacizumab (Cassidy et al. 2010). In this pooled analysis, only 24% of the patients were over 70 years; this suggests that elderly patients were highly selected. A subgroup analysis of a randomized phase III study comparing capecitabine with capecitabine + bevacizumab showed a significant PFS improvement in patients over 75, no significant additional toxicity, and similar quality of life (Price et al. 2012).

A prospective randomized phase III trial specifically for patients over 70 years compared first-line treatment of mCRC with capecitabine alone or in association with bevacizumab. The tumor response rate was significantly improved by the addition of bevacizumab (10% vs 19%, $p = 0.04$), and the median PFS was significantly increased from 5.1 to 9.1 months in favor of the bevacizumab arm (HR = 0.53, 95% CI, 0.41–0.69, $p < 0.0001$). OS was not significantly improved by bevacizumab (16.8 vs 20.7 months; HR = 0.79, 95% CI 0.57–1.09, $p = 0.18$), but the study was not designed to assess OS as the main endpoint. Grade 3 venous thromboembolic and arterial thromboembolic events occurred more frequently in patients treated with bevacizumab 4.4% vs 8.2% and 0.7% vs 3.7%, respectively (Cunningham et al. 2013). Another randomized phase II study enrolled patients over 75 years and compared 5FU monotherapy or doublet with or without bevacizumab. The primary endpoint, assessed 4 months after randomization, was a composite endpoint based on efficacy (tumor control, stable disease, or objective tumor response and the absence of a decrease in the Spitzer QoL index) and safety (absence of severe cardiovascular toxicities and unexpected hospitalization). This was the first study in the mCRC setting to assess such a combined endpoint, which evaluated the tumor, quality of life, and safety. The efficacy criteria were met in 58% of the patients in the chemotherapy-alone arm and in 50% of the bevacizumab + chemotherapy arm. The safety criteria were met in 71% of the patients in the chemotherapy-alone arm and 61% in the bevacizumab + chemotherapy arm. A normal IADL score and previous cardiovascular disease were predictive factors for the composite criteria. There is a trend in favor of bevacizumab arm for PFS (7.8 vs 9.7 months, HR 0.78, 95% CI 0.53–1.17) and OS (19.8 vs 21.7 months, HR 0.73, 95% CI, 0.48–1.11) (Aparicio et al. 2018a). Even though both studies revealed a trend in favor of improving OS with bevacizumab treatment, the difference was not statistically significant. Multivariate analysis revealed that a high baseline Köhne score (Köhne et al. 2002) was associated with a short PFS and that a low baseline Spitzer QoL index (Spitzer et al. 1981), albumin $\leq$35 g/L, CA 19.9 > 2LN, and high Köhne score were significantly associated with a short OS (Aparicio et al. 2018b). Interestingly, exploratory subgroup analyses suggested that bevacizumab significantly prolonged PFS in patients with impaired nutritional status and impaired ADL. Thus bevacizumab treatment should not be denied for patients with this kind of frailty characteristics. Further studies should be performed to assess patient subgroups who show a clear OS benefit with bevacizumab.

Concerning EGF receptor inhibitors, there are very few available data for elderly patients (Rosati et al. 2016). Cetuximab is a recombinant chimeric monoclonal antibody, and panitumumab is a recombinant, fully humanized that competitively inhibits the binding of EGF and other ligands on EGF receptor. The efficacy of anti-EGF receptor monoclonal antibody is restricted to the patient with a tumor without *RAS* mutation. The available data concerning the efficacy and safety of cetuximab or panitumumab in older patients with mCRC are derived from retrospective studies, pooled analyses, and small prospective trials. In a retrospective series of 54 patients older than 70 years treated with cetuximab + irinotecan, a response rate of 41% and a 4.21-month PFS in the non-mutated *KRAS* patients subgroup were reported (Fornaro et al. 2011). In 39% of cases, a decrease in the dose of irinotecan was necessary due to treatment-induced diarrhea. A large multicenter retrospective study suggested that the efficacy and safety profile of a combination of irinotecan and cetuximab in irinotecan pretreated patients aged >65 was similar to that in pretreated patients aged 18–65 years (Jehn et al. 2014). Nevertheless, the threshold of 65 years used in this

study resulted in a median age of 70 years in the elderly group, which made it impossible to draw conclusions for patients aged over 75. In a post hoc pooled analysis of the CRYSTAL and OPUS trials, which compared chemotherapy alone with chemotherapy + cetuximab, the age interaction test was not significant for the tumor response rate, PFS or OS. Nevertheless, cetuximab demonstrated no significant PFS improvement in the subgroup of patients over 70 but a higher toxicity rate especially for neutropenia and diarrhea (Folprecht et al. 2010). Analysis of subgroups of elderly patients treated in a trial that compared panitumumab monotherapy with best supportive care revealed no significant difference for toxicity or efficacy compared with younger patients (Van Cutsem et al. 2007). Nevertheless, another subgroup analysis of patients over 75 from a large phase III study that have compared FOLFOX + panitumumab to FOLFOX alone demonstrated that the favorable effects of the treatment combination were not seen in patients with poor PS or patients older than 75 years of age (Douillard et al. 2014). Several phase II studies dedicated to patients over 70 years suggested that in selected patients, cetuximab alone (Sastre et al. 2011) or in combination with capecitabine (Sastre et al. 2012) or panitumumab alone (Sastre et al. 2015) was effective. To date there are no prospective randomized trials exploring anti-EGFR antibody in the elderly mCRC population.

Regorafenib is an oral tyrosine kinase inhibitor that inhibits several receptors involved in angiogenesis, oncogenesis, and the tumor microenvironment. Data concerning regorafenib in elderly are still very scarce. A post hoc analysis of the CORRECT study evaluated treatment with regorafenib in patients aged 65 years compared with younger patients (Van Cutsem et al. 2013). The hazard ratio for overall survival (regorafenib/placebo) was 0.72 (95% CI, 0.56–0.91) in patients less than 65 years and 0.86 (95% CI, 0.61–1.19) in patients aged over 65 years ($p = 0.405$ interaction test). The median proportion of the planned dose really taken was 83.3% before 65 and 78.6% after 65. Most of the patients had side effects in relation to the treatment (<65, 93.8%; ≥65 years, 91.7%). The rate of grade ≥3 adverse effects related to regorafenib was 52% in patients <65 years, 57% in patients aged 65–74, and 66% in patients >75 years. Hypertension was more frequent in this last group than in younger patients.

No data are available regarding elderly patients over 75 for the treatment recently registered for mCRC.

In conclusion, choice of palliative chemotherapy in elderly patients remains controversial. Although doublet chemotherapy and targeted therapy did not demonstrate significant improvements in OS, an effort should be made to assess subgroups of patients who will benefit from these treatments. The benefit of chemotherapy should not focus on survival alone but must also consider patient autonomy and quality of life.

Cross-References

- ▶ Colorectal Cancer in Older Adults: Surgical Issues
- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Population Trends in Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management

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Colorectal Cancer in Older Adults: Surgical Issues

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Abstract

This chapter centers on what surgeons, patients, and hospital administrations want and need to know about surgical care for colorectal cancer in the older patients. From all angles, it is clear that older patients are unique and their colorectal cancer care should be individualized and approached in a multidisciplinary fashion. Evaluation of patient fitness to undergo surgery should be undertaken in the elective and emergent settings. If patients are deemed fit for treatment, they should be offered the appropriate treatment, regardless of their age. This includes proceeding with surgery and/or chemotherapy and utilizing minimally invasive techniques, when appropriate. In addition, quality of life should be a priority in the care of older patients and patient reported outcomes should be assessed and reported.

Keywords

Rectal cancer · Older patients · Outcomes · Quality of life · Tailored surgery

Introduction

Patients, surgeons, and institutions view colorectal care of the older patients through different lenses. However, the goals of care should be to enhance the patient's quality of life and treat the malignancy while maintaining the patient's quality of life. The patient's decision after multidisciplinary discussion as well as determination of their fitness to undergo treatment should be given priority in choosing a treatment modality. Treatment modalities should not be chosen solely based on the older patient's age.

What Do Surgeons Want To Know?

Role of Screening Tools in a Busy Surgical Practice

Every colorectal surgeon needs a fast and reliable preoperative evaluation of patients, especially when they are coming from both the elective and emergent settings. Several systems have been proposed and validated to evaluate patients in order to stratify operative risk and highlight possible areas amenable for prehabilitation. As reported in a previous chapter (Principles of Cancer Surgery in Older Adults), the overall message is that, regardless for the system of choice, it is essential to systematically assess older cancer patients to determine whether the patient is fit for surgery, which surgical plan is appropriate, and which adjustments may be needed before the procedure. As a rule of thumb, it is mandatory, regardless of the preferred system, to obtain information about three main domains: cognitive status (including history of delirium), independence/living situation, and sarcopenia, gait ability, and nutrition (Audisio et al. 2008; Fong et al. 2009; Huisman et al. 2014; Hempenius et al. 2015; Mohri et al. 2013).

Among the numerous and available tests, two deserve special attention since they seem to be well suited for common situations faced by a colorectal surgeon: the short amount of time available in a busy clinic and the need for quick decision in the emergency setting. These two instruments are the "Timed Up and Go" (TUG) test and the Triage Risk Screening Tool (TRST) in its Flemish version (fTRST).

The TUG is a tool that has been designed with the purpose of identifying frail older patients by quantifying their functional mobility and has been shown to be easy to administer and directly correlate with functional status (Podsiadlo and

Richardson 1991). The test is carried out by asking the patient to sit in a chair and when the timer goes off, the patient stands up and walks for 3 m, makes a 180° turns, and comes back to the chair. At the moment the patient is back in the chair, the final time is recorded. If a patient needs a walking device or a cane, this can be used during the test. The TUG has extensively been studied in community-dwelling older patients (Bischoff et al. 2003; Davis et al. 2011; Kim et al. 2010), and it was found to predict the risk of early death in oncogeriatric patients receiving chemotherapy (Soubeyran et al. 2012). The TUG was also investigated in cohorts of surgical patients and predicts long-term functional outcomes in patients undergoing hip surgery (Laflamme et al. 2012). In patients undergoing major cardiovascular or abdominal surgery, the TUG successfully predicted prolonged institutionalization and postoperative delirium (Brouquet et al. 2010; Robinson et al. 2011). In a prospective study among patients, >75 years old undergoing major elective abdominal surgery, multivariable analysis of the predictive value of a high TUG (>20 s) for postoperative delirium showed a hazard ratio of 4.8. A total of 47.6% of patients with a high TUG suffered from postoperative delirium, compared to only 18.5% of patients with a normal TUG (Brouquet et al. 2010). Robinson et al. found a 13 times higher risk of discharge to an institutional care facility, i.e., nursing home or rehabilitation center, for geriatric surgical patients with a high TUG (>15.0 s) (Robinson et al. 2011).

Data on the predictive value of the TUG in the oncogeriatric surgical population were recently published as part of the PRE-OP study (Huisman et al. 2014, 2015). In total, 362 patients were assessed in this study and the median age was 76 years. The majority of patients underwent major surgery ($n = 223$; 68.0%) and the most prevalent conditions were colorectal cancer and breast cancer. The study results showed that the TUG is a more useful screening tool than American Society of Anesthesiology (ASA) score or the more time-consuming Comprehensive Geriatric Assessment (CGA) in identifying those patients at higher risk of adverse outcome. This was also emphasized by the ability of TUG to predict the need for extended care postoperatively, as shown by the prolonged length of stay (LOS) and the increased number of specialists involved in the care of patients with an elevated TUG. The TUG seems to give an assessment of cognitive elementary abilities to follow simple orders, basic functional mobility, coordination and muscle strength in older patients which are reliable proxies for sarcopenia, considered as the ultimate predictor (Wagner et al. 2016).

An increasing number of older patients are seeking urgent surgical care because of unplanned emergent conditions (Desserud et al. 2016). Decision-making in the emergency setting is complex since a number of variables must be considered in order to tailor the surgical treatment. These include each patient's specific characteristics, the nature of the disease, and patient's wishes versus the pressing need to act proficiently in a short period of time (Launay-Savary et al. 2015). Frailty, not chronological age, is the most important risk factor associated with poor surgical outcomes even in the emergency setting (Farhat et al. 2012; Subramanian et al. 2010). It has been established that every older patient with cancer should undergo a specific geriatric assessment before every treatment (Extermann et al. 2005). Unfortunately, this is not always applicable in the busy emergency setting. To date, no concise frailty screening tool is available for emergency general surgery older patients. A recent cohort study describing the use of six short screening tools, (Vulnerable Elders Survey VES-13, fTRST, G8, Groningen Frailty Index (GFI), Rockwood/Balducci score) validated on oncogeriatric setting, has been reported with the aim to assess frailty before an emergent surgical procedure (Kenig et al. 2015). The authors concluded that the screening tools were adequate to investigate frailty also in the emergency setting. However, these screening tools were created for cancer patients, requiring an accurate knowledge of the patient's past medical history, which is not always available. A blood test is sometimes needed and they are still too time-consuming to be used routinely in the emergency room. Among the group of oncogeriatric-specific validated frailty screening

tools, there is a short, five-item questionnaire, which is very easy to perform: the fTRST (Kenis et al. 2006). The original TRST, designed in 2001 in the Emergency Department (ED), was a risk-stratification tool used to identify older patients at risk of recurrent trips to the ED, hospitalization, and nursing home admission (Mion et al. 2001; Meldon et al. 2003). The Flemish version fTRST is shorter and based only on five domains: presence of cognitive decline (2 points), living alone or no help from partner/family available (1 point), reduced mobility or falls in the past 6 months (1 point), hospitalized in the past 3 months (1 point), and polypharmacy (≥5 different medications) (1 point). A recent published recommendations update by the International Society of Surgical Oncology (SIOG) reported that the fTRST is an accurate instrument to identify oncogeriatric patients in need of a comprehensive geriatric assessment (Decoster et al. 2015) but no cutoff has been established in order to identify patients at higher risk for major complications after emergency general surgery. Recently, Zattoni et al. presented at the SIOG annual meeting the initial results of a prospective study including >70-year-old patients undergoing emergency, non-trauma surgery (Zattoni 2016). All patients underwent multimodal preoperative frailty assessment with fTRST, Charlson Age-Comorbidity Index (CACI), ASA score, and the Activity Daily Living (ADL) test. They prospectively enrolled 110 consecutive patients operated on under general anesthesia for emergency abdominal surgery. The vast majority of cases were related to small or large bowel primary diseases and the median age was 81. The postoperative 30-day mortality was 20.2% but the majority of death events (56%) occurred during the first postoperative week. Fourteen were recorded after major surgery (87.5%). A fTRST score ≥2 showed good sensitivity (93.7%) and specificity (41.3%) in detecting postoperative mortality (OR 10.5; 95% CI 1.31–84.8; $p = 0.027$). Logistic regression analysis showed a significant correlation between 30-day mortality and fTRST≥2, ASA≥4, while patients' age was not statistically relevant. Of the 63 patients who survived surgery, 17% developed severe functional loss. Scoring 2 or 3 at fTRST was highly related to functional deterioration. A regression model showed a significant correlation between a fTRST score ≥2 and the need for postoperative intensive care unit (ICU) admission, prolonged LOS, and need for long-term institutionalization.

Role of the Standard of Care in Older Fit Patients

Laparoscopy

The goals of minimally invasive surgery (MIS) are to obtain the same disease-related and functional outcomes as an open operation while decreasing the surgical stress and consequently the associated morbidity and mortality. Early studies showed that laparoscopy promoted improvements in return of bowel function, earlier oral intake, decreased opioid analgesia requirements, and decreased length of hospital stay, while improving cosmesis and patient satisfaction (Dunker et al. 1998).

Another goal of MIS is promotion of functional recovery. Return to active life, return to independent living or bowel/urinary control are particularly important in older patients, and reaching these goals often means the difference between an operation's success and failure (Frasson et al. 2008). Frasson et al. focused on functional recovery after laparoscopic surgery, analyzing a series of 535 patients with colorectal disease randomly assigned to laparoscopic ($n = 268$) or open ($n = 267$) resection. Within the two groups, the outcome of young patients was compared with those in patients ≥70 years. The authors demonstrated that laparoscopy reduced morbidity and LOS when compared to an open operation in the older patients group but less so in the young group (Frasson et al. 2008). In addition, laparoscopy in the older patients promotes a higher rate of postoperative independence at discharge and faster postoperative recovery. Stocchi et al. also demonstrated that independent status on admission (assessed in 37 patients undergoing laparoscopic-assisted colectomy and 38 undergoing open colectomy) was more frequently maintained at

discharge in those undergoing laparoscopic-assisted colectomy (95% vs. 76%, respectively, $p = 0.025$) (Stocchi et al. 2000).

Recently, Li Y et al. "settled" the debate of laparoscopic surgery versus open surgery in octogenarians by publishing a meta-analysis of 11 comparative studies pooling 1,066 laparoscopic and 1,034 open colorectal resections. The results demonstrated that laparoscopy is safe and carries a lower risk of infectious complications (both pulmonary and at the surgical site), shorter LOS, and a reduced incidence of postoperative ileus while maintaining the same cardiovascular risk as compared to open surgery. The authors concluded that laparoscopy is safe and feasible in the older patients population and has the additional benefit of faster return to productive lives (Li et al. 2016).

Given the expansion of robotic surgery in colorectal surgery, several authors examined the role of robotic surgery in the older patients' population. Ceccarelli et al. compared patients undergoing robotic surgery for a variety of indications including colorectal diseases in three age groups: $\leq$64, 65–79, and $\geq$80. They showed an increased conversion rate in the 65–79-year-old group, but no differences in morbidity or mortality between groups (Ceccarelli et al. 2017). The authors concluded that robotic surgery can be safe in properly selected older patients.

MIS is safe and feasible in properly selected older patients, and, in fact, is associated with faster functional recovery. Operative approach should be determined by the surgeon's expertise as well as the patient's cancer location and comorbidities.

Enhanced Recovery

Enhanced recovery or fast-track programs include some degree of preoperative patient education, selective use or no bowel preparation, no perioperative starvation (use of carbohydrate-loaded liquids), no use or early removal of the nasogastric tube and urinary catheter, tailored anesthesia and postoperative analgesia, and early mobilization with minimal fluid infusion. "Fast-track protocol" has been often used as a synonym of the enhanced recovery after surgery (ERAS) protocol, but the two entities are not the same. The ERAS protocol, promoted through the ERAS® society, refers to a well-designed but necessarily strict list of items that need to be entirely fulfilled in order to obtain the desired effect (Gustafsson et al. 2011). But adherence to the long list of tasks is not easy to achieve and, as demonstrated by several studies and surveys, despite increasing awareness of the importance of structured perioperative management, the implementation of this complex protocol has been slow (Segelman and Nygren 2014). Therefore, a patient-centered fast-track approach is likely more efficacious in the older population than a rigid set of ERAS protocols especially because the older population may not be able to follow a complex set of instructions and have great variability in the preoperative functional status. In addition, some of the items reported in the ERAS protocol such as the use of epidural anesthesia have been questioned, especially with the use of laparoscopy (Halabi et al. 2014), and the combination of antibiotics and mechanical bowel preparation has been reported to lower postoperative infections (Chen et al. 2016).

The literature suggests that older patients have an advantage in functional recovery if enrolled in a fast-track program. Baek et al. analyzed a group of 337 patients (87 over 70 years of age and 250 under 70 years of age) who underwent laparoscopic colorectal surgery with a perioperative fast-track program. No significant difference between age groups was observed for return of flatus, stool passage, progression of diet, complication rate (26% in the older patients vs. 32% in the young patients) or LOS (12 days for each group). There was no impact as well of comorbidities (70% in the older patients vs. 44.7% in the younger patients) and ASA score. Of note, the authors observed a rate of cardiopulmonary complications lower than expected, which they attributed to the use of a low-pressure pneumoperitoneum (8 mmHg). The only significant difference observed between the two groups was in the number of emergency room visits or readmissions (11.7% vs. 4% total, in older vs. younger patients) (Baek et al. 2013). Pawa et al. achieved similar global conclusions, with a median

LOS of 6 days in 558 patients <80 vs. 8 days in 130 patients ≥80 year ($P = 0.363$). There were no significant differences in 30-day readmission rates (8.6% in the whole population) (Pawa et al. 2012).

A second goal of fast-track protocols is to reduce stressors and to decrease the inflammatory response following surgery. Pursuing this aim, a recent systematic review by Watt et al. examined the impact on the magnitude of the systemic inflammatory response (SIR) for each ERAS component following colorectal surgery through objective markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). The review analyzed 19 studies including 1898 patients. With the exception of laparoscopic surgery, it did not show any effect of individual components of ERAS protocols to reduce the stress response following colorectal surgery (Watt et al. 2015).

Based on the current evidence, we conclude that older patients may more often benefit from laparoscopic surgery with a tailored patient-specific pre- and postoperative program than they would with a strict list of prescriptions as in ERAS. Early and progressive reintroduction of an oral diet, ambulation and physical therapy, early removal of drains and catheters, minimization of opioid analgesia, and individualized/limited fluid management are the components most likely to improve functional outcomes and recovery in older patients. In addition, preoperative and postoperative counseling and ongoing communication with the patient and his/her family is most effective in engaging the patient and meeting goals of recovery.

Adjuvant Chemotherapy in Older Patients with Stage III Colorectal Cancer

The benefit of adjuvant chemotherapy in Stage III colon cancer has been demonstrated and has become the standard of care in the adult population (National Comprehensive Cancer Network, Colon Cancer 2017). However, questions arise about whether older patients should be offered the same treatment as young patients. Bergquist et al. evaluated 8141 patients aged 80–89 who underwent surgery for Stage III colon cancer with curative intent. Fifty-seven percent of patients had surgery alone and 43% received postoperative chemotherapy. Patients who did receive chemotherapy were statistically significantly shown to be younger (82 years vs. 84 years), healthier (73% vs. 70% without comorbidities), and more likely to have advanced N2 disease (40% vs. 32%). In patients who received chemotherapy, the overall survival was prolonged (median 42.7 vs. 61.7 months; $p<0.001$). Of note, in 1315 patients deemed fit for chemotherapy who declined it, the overall survival was worse than in those who received chemotherapy (median 42 vs. 61 months; $p<0.001$). Multivariable analysis showed that surgery alone and refusal of chemotherapy were independently associated with increased mortality hazard (HR 1.83, HR1.45; $p < 0.001$) (Bergquist et al. 2016). Ko et al. analyzed 810 patients, 423 <70 years and 387 ≥70 years. The median age at diagnosis for the entire cohort was 69 years. Older patients had significantly more comorbidities than young patients (34% vs. 19% with ≥3 comorbidities; $p<0.001$). Young patients were more likely to undergo adjuvant chemotherapy (91% vs. 57%; $p<0.001$), more often with combination than monotherapy (74% vs. 32%; $p<0.001$). In comparison to younger patients who did not receive adjuvant chemotherapy in <10% of cases, older patients did not receive chemotherapy in 43% of cases because of age (45%), comorbidities (36%), or minimal benefit perceived by the medical oncologist (2%). In addition, advanced age was cited as the main reason to receive only monotherapy. However, multivariate analysis did not reveal any significant correlation between advanced age and worse outcome when using adjuvant chemotherapy. Treatment with either combination or monotherapy had same impact on cancer-specific survival in both age groups (Ko et al. 2016).

Chemotherapy in older patients with Stage III colon cancer should not be withheld based on age alone. Therapy should be tailored in a patient-centered multidisciplinary strategy to attempt a balance between improved survival and quality of life.

Undertreatment Versus Customized-Conservative Treatment in Older Patients with Rectal Cancer

Older patients' rectal cancer management is frequently influenced by many factors, leading to undertreatment and poorer outcome. This was first demonstrated by Chang et al. (2007) in a group of 21,390 patients identified from the Surveillance, Epidemiology, and End Results (SEER) database (1991–2002). The authors showed that rectal-cancer-specific survival rates decreased with increasing age. More recently, EUROCARE-5 study (2014) showed a global increase in survival for rectal cancer from 1999–2001 to 2005–2007 (52.1% vs. 57.6%) (De Angelis et al. 2014). Unfortunately, this did not apply to the older segment of the population. In UK, the National Cancer Intelligence Network reported the high rate of under treatment in surgery for older cancer patients (National Cancer Intelligence Network 2010). This is highlighted for colorectal cancer patients in who resection rate falls from 68% in the group of 64–74 years to 40% after 80 years, as do the use of multimodal treatments and radical resection in contrast of local excision.

Standard treatment for rectal cancer includes surgical resection with total mesorectal excision (TME) for early stage tumors (T1 N0 M0; T2 N0 M0). Locally advanced tumors (T3/4, N+) are treated with neoadjuvant chemoradiation followed by TME (National Comprehensive Cancer Network, Rectal Cancer 2017). However, a more tailored approach is appropriate in older patients to optimize workup and treatment. When judged as fit, they should follow standard of care as in younger adults with radical surgery and/or chemoradiotherapy. In those with comorbidities or refusing surgery, adjusted strategy should be discussed with the patient and the family.

The role for local resection in older patients is debated. A proctectomy indeed can yield high risk of poor functional outcome in the postoperative period in addition to the risk of definitive stoma (Kim et al. 2002; Paun et al. 2010). Age is the first item to consider according to the predictive nomogram for Low Anterior Resection Syndrome (LARS) (Pelicancancer.org 2017). In this light, local excision gives better functional results and decreases postoperative morbidity and mortality, especially for vulnerable or frail patients. There was also a renewal of interest for local excision with the launch of user-friendly and soft platforms. Since 1992, standardized transanal Endoscopic Microsurgery (TEM) has shown advantage over transanal excision with traditional instruments for which the surgeon often needs to combine operator' and speleologist' skills (Buess et al. 1985). Despite clear superiority (Christoforidis et al. 2009), the technique is spreading slowly in the surgical community because of the steep learning curve and the small number of eligible cases. There was a recent renewed interest for transanal endoscopic surgery after its first uses 30 years ago, due to increased knowledge on natural history of rectal cancer, increasing number of patients candidates for an organ-sparing approach, and development of easy to use soft platforms allowing Transanal Micro-Surgery techniques.

Several studies have tried to confirm the tailored approach. Several have selection biases, with poor experience and local excision being limited to patients with early stage or poor general conditions. More recently, the multicenter ACOSOG Z6041 trial evaluated organ preservation for T2 N0 distal rectal tumors treated with neoadjuvant chemoradiation and local excision (Garcia-Aguilar et al. 2015). High toxicity rates were encountered when oxaliplatin was included in the chemotherapy composition. However, long-term results were impressive with 3-year overall survival of 94.8% and a very low (4%) local recurrence rates. Return to normal bowel function and good quality of life were reported 1 year after surgery. Given the low (3%) lymph node positivity in ypT0-1, important data were published by Creavin et al. (2017) regarding standard local excision with TEM or Transanal Minimally Invasive Surgery (TAMIS) platform in patients having downstaged their tumor to cT0-1following neoadjuvant chemoradiation. Of note, node-positivity around 20% and 33% in

ypT2 and ypT3 tumors (Martin et al. 2012; Smith et al. 2010; Smith et al. 2012) makes TME mandatory for tumors ≥ypT2. In Creavin et al. experience, of 362 patients with rectal cancer, 60 (16.5%) had an organ-preserving strategy (10 with "watch and wait" and 50 by transanal excision). Fifteen patients were referred for salvage TME postlocal excision because of final pathological reports. There was no significant difference in overall survival or disease-free survival rate between radical surgery and organ preservation strategy (85.6% vs. 93.3%, $P = 0.414$, and 78.3% vs. 80%, $P = 0.846$, respectively). Tumor regrowth occurred in 4 out of 45 (8.9%) patients who had organ preservation. Despite the high interest for these results, a recent systematic review by Smith et al. (2017) warned against use of organ sparing techniques after chemoradiation, based on scattered residual tumor cells among radiation-induced fibrosis precluding the ability to reliably classify residual disease. Moreover, three studies have shown the difficulty to spot or identify these occult and scattered foci within the bowel wall (Hayden et al. 2012; Mandard et al. 1994; Perez et al. 2014). Of note, the systematic review by Garcia-Aguilar et al. (2015) describe at 3 years, only three local recurrences (4.0%) with disease-free and overall survival rates of 86.9% and 95.7%. With an 84-month median follow-up, Lezoche et al. (2008) report only two local recurrences (5.7%) and no difference in survival between local excision versus radical surgery incorporating TME (94%). Similarly but with only 17-month median follow-up, Verseveld et al. (2015) report four local recurrences (9%) in patients treated with conservative strategy while deemed fit for surgery including cT3. Although well-designed studies with standardization are still needed before adopting local excision as standard of care after neoadjuvant chemoradiation strategy, we consider this is a highly valuable option to discuss in some older patients unfit for major procedures or refusing surgery and loss of function.

In addition to organ preserving surgical strategies, there is new emphasis on "watch and wait" proposals after clinical complete response under neoadjuvant chemoradiation. Angelita Habr-Gama and her group investigated the possibility to skip surgery in patients developing a complete clinical response after chemoradiotherapy, showing similar 5-year disease-free and overall survival as compared with standard surgery (Habr-Gama et al. 2004). They extended these investigations to more advanced stages (cT2-4, cN1-2 low rectal) (Habr-Gama et al. 2013). Of 70 patients, 35 patients (51%) did not require any surgery and were in complete remission after 56 months of median follow-up. Although not conducted in an old population (mean age 60.2 ± 12.9), this strategy might be interesting for senior adults unfit-for-surgery. This was further evaluated by McLean Smith et al. (2015), using three age groups: 60 years with mild comorbidities, 80 years with minor comorbidities, and 80 years with significant comorbidities (Charlson score >3). Patients with a complete clinical response after chemoradiotherapy were followed by a watch-and-wait protocol or offered radical surgery (TME). Overall survival was similar in 60-year-old patients for both strategies, but in patients 80 years of age or those with significant comorbidities, watch and wait provided a 10.1% advantage over surgery, with no difference in disease-free survival or quality-adjusted life years. This suggests that watch and wait after a complete clinical response is a valid option in older patients limiting surgery-induced morbidity. Of note, same hypothesis has been explored at the Memorial Sloan Kettering Cancer Center group and a prospective study is ongoing.

Data from the international Watch and Wait database (IWWD) on behalf of the EUropean REgistry of Cancer CAre (EURECCA) have been presented in Krakow at the last meeting of the European Society of Surgical Oncology. The rate of local relapse was 29% at 3 years, 64% of patients recurring within 12 months. Local recurrence was very heterogeneous with only 60% of patients receiving a proper surveillance with the standard of care pelvic Magnetic Resonance Imaging (MRI). This calls for more controlled research before adopting such strategy in routine. However, they represent an important challenge for older patients to limit invasive

surgery and protect independence and quality of life.

Contact X-ray brachytherapy (CXB) is a last attractive strategy to mention. CXB is based on using 50 kVp Xrays with a short focus to skin distance (FSD). This noninvasive organ preserving technique was launched by Papillon (1975) in the 60s for T1 N0 rectal adenocarcinoma. Between 1980 and 2001, CXB has been used in several French centers in three different settings: adjuvant treatment after local excision for T1/N0 lesions in the case of high-risk pathological features (Gerard et al. 2000); for T2 and early T3 N0 tumors, mainly in older patients or frail patients, in combination with external beam radiotherapy to treat both the primary tumor and perirectal subclinical lymph nodes (Gerard et al. 2002; Papillon 1990); and treatment of distal locally advanced T3 N0-2 tumors when an abdominoperineal resection (APR) was indicated in order to increase the chances of a sphincter preserving procedure.

Frin et al. (2017) published their 12-years, 112-patients experience of using CXB with the above indications. In the first scenario, CXB was performed in case of T1 N0 (tumor <3 cm) treated after initial local excision if tumor fragmentation, vascular invasion, tumor budding, poor differentiation, R1 resection, or submucosal infiltration level of sm2 (according to the Kikuchi classification) was detected. At 5 years, the local recurrence rate was estimated at 4%. The overall 5-year survival rate was 94% with organ preservation in 26 of 27 patients (96%). In the case of T2 or early T3 (<4 cm) N0 tumors, a combination of CXB and CRT was proposed to achieve organ preservation as an option to avoid a standard TME surgery. A cCR was achieved in 43 patients (96%) with a small residual ulceration present at 1–6 months after treatment in 15 of them. Ulcerations were painless and healed spontaneously but two patients underwent an elective local excision (ypT0 and ypT1 R0 with few residual cells). The 5-year cumulative rate of local recurrence was 11%. The 5-year cumulative rate of distant metastases was 17%. The cancer-specific survival was 87% at 3 years and 76% at 5 years. To treat a distal locally advanced T3 N0-2 with the goal of avoiding an APR, the authors recommended CXB combined with CRT in order to shrink the tumor and increase the chance of a sphincter-saving surgery. A cCR was achieved at the end of irradiation in 15 patients (37%). An APR was performed in seven patients (18%) and 31 (82%) underwent a sphincter-saving surgery. Eight cases of ypT0 (21%) and 17 cases (44%) of ypT1, 2, and 3 with only few residual cells (Dworak TRG3) were observed. The overall survival rate was 84% at 3 years and 72% at 5 years.

The treatment of older patients with rectal cancer is evolving, but one cannot stress enough the importance of patient-centered multidisciplinary care to optimize oncologic, function, and quality-of-life outcomes in individual patients. When considering alternative treatment strategies, it is important to appreciate how some treatments, which are considered the standard of care for the general population (level 1 evidence), might not apply to senior cancer patients. As an example, TME has been established and validated on the general population of rectal cancer patients. However, considerable evidence has been gathered to prove the opposite is true for older rectal cancer patients, where the increased operative mortality and morbidity exceeds the survival advantage (Rutten et al. 2008). In short, when considering either alternative or standard treatment pathways, patient selection seems again to be the key step in order to offer feasible solutions without under treating our older patients (Ugolini et al. 2014).

What Do Patients Want to Know?

The Role of Patient-Reported Outcome Measures

Effectiveness of any oncologic treatment has been historically measured by several indicators in order to define patient survival after (or hopefully because of) the treatment. Overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS) 5 years from the diagnosis have long been considered the best indicators to define the ability of a given treatment to stop or prevent cancer progression. Several

of the most important studies in colorectal cancer surgery treatment have used that indicator to suggest superiority of one treatment over another (Bonjer et al. 2015; Sauer et al. 2004). Unfortunately, 5-year DFS has only a limited value for 80-year-old patients undergoing colorectal surgery for an obstructing malignancy. The only "historically-used" outcome that has been shown to be of interest in this group of patients is mortality or OS. Progress in the care of older patients affected by cancer has been slow and halting, partly because measurement of outcomes that matter to patients, aside from survival, remain limited.

Even with higher rate among older cancer patients, death is a rare event. Many physicians, surgeons in particular, have the tendency of stop measuring mortality 1–3 months after surgery and so these data fall under the radar. Mortality is also a rare occurrence right after elective colorectal surgery, and it fails to differentiate excellent from merely competent providers. In one of the most innovative papers about this topic, Porter et al. have summarized the reason why the scientific community should undertake a more challenging (but also more efficacious, in the long run) outcome-measuring system: the patient-reported outcome measure (PROM) (Porter et al. 2016). Authors defined four reasons why PROM studies are critical in the modern health care system that must be centered on outcomes that matter to patients. First, hospital administrations and health-care-management specialists have often reduced the "quality" of care to detecting the system's compliance with evidence-based practice guidelines rather than as improvement in pure patients' outcomes. Secondly, what generally matters to patients are outcomes that encompass the whole cycle of care, more than a single phase of the process (e.g., surgery, chemotherapy, etc.). This includes the global health status achieved during and after the care. Data such as functional status and quality of life are rarely reported at the end of the process. Patient's time, the burden of having a complication, and the suffering involved in getting the care are usually not considered when discussing/deciding about the overall benefits of a treatment strategy and frequently the amount of time those benefits will last is ignored (e.g., time until recurrence). Third, efforts at outcomes measurement have been overwhelmingly focused on disease-related status (e.g., survival and other outcomes that are readily captured by laboratory or radiological tests), while functional status is often left out, even though improving functional status is why patients seek care. These omissions reflect clinicians' inclination to focus on readily accessible data, as well as the fact that many outcome measures developed to date have emerged from controlled clinical trials, which often have a single primary clinical end point. It should be acknowledged that focusing on functional results is extremely demanding, as shown, for example, by the limited amount of good-quality data about urinary and sexual dysfunction after rectal resections. The challenge is complex because function is sometimes subjective and because patient perspectives are altered depending on a number of variables that may or may not reflect the level of the care delivered. Lastly, progress on outcomes measurement has been slowed dramatically by the lack of standardization of recording and stratification.

The role of providers, payers, patient-advocacy groups, and regulators is crucial to create a process to agree on a minimum sufficient set of outcomes for each important medical condition. From this perspective, the role of The International Consortium for Health Outcomes Measurement (ICHOM) has been crucial (ichom.org 2017). This international group of about 300 specialists focused on the most frequent medical conditions that, together with patient representatives, have defined the minimum standard outcome sets and risk factors using a structured process. ICHOM has approved or is in the final stages of approval of more than 20 sets covering about 45% of disease burden in the USA and other high-income countries, with many more to come. The international nature of the effort has allowed participants to see that patients with a given condition have the same or similar needs everywhere. ICHOM working groups understood that their role is not to devise new outcome measures but to agree on which

well-validated ones, including patient-reported measures, everyone should use. These standards are putting providers, payers, patients, and information technology vendors on a common path for tracking what needs to be tracked and making implementation of outcome measurement easier and more efficient. Aiming for the same targets, the GOSAFE (Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery) study has been recently launched by the European Society of Surgical Oncology in collaboration with the International Society of Geriatric Oncology (@GOSAFEstudy). The GO SAFE study is a prospective international collaborative high-quality registry aiming to gain knowledge about postoperative outcomes in older cancer patients with a particular emphasis on QoL and FR. The target is to obtain meaningful data to assist clinicians in tailoring the care to avoid under/overtreatment and providing robust data to identify new strategies to improve functional outcomes in older cancer patients. The same way Porter et al. (2016) concluded their manuscript we also predict that "*a time will soon come when it will be hard to believe that measurement of outcomes that mattered to patients was rare in 2016 – and organizations that measured them each did it in their own way.*"

What Do Hospital Administrations Want to Know?

Costs and Perception of Surgical Oncology Versus Medical Oncology

In September 2012, the Royal College of Physicians released its annual report on "Hospitals on the edge? – the time for action" (rcplondon.ac.uk 2017). The College realized that the reality of care in the UK hospitals has changed considerably over the last 10 years. Data showed an increasing number of patients seeking care in the NHS are older and frail, and around 25% of inpatients have a diagnosis of dementia. Nearly two-thirds (65%) of people admitted to hospital are over 65 years old and they occupy more than 51,000 acute-care beds at any one time, accounting for 70% of bed days (Cornwell et al. 2012; Imison et al. 2012; Hospital Episode Statistics 2017). People over 85 years old account for 25% of bed days, increased from 22% over the past 10 years. This equates to more than five bed days per annum, compared to only one-fifth of a bed day each year for those under 65. People over 85 years tend to spend around 8 days longer in hospital than those under 65 years, 11 days compared to 3. This becomes a larger burden for health care sustainability if we consider the cost related to cancer care, on top of hospitals beds' occupancy. The US Department of health, through the Agency for Healthcare Research and Quality (AHRQ) and the Medical Expenditure Panel Survey (MEPS), reported that cancer care is the first source of expenditures with $25,000 per person (trauma-related disorders is second with about $20,000/person) (meps.ahrq.gov 2017). It has been also unfortunately showed that costs increase proportionally when cancer is associated with comorbidities, which is quite a common condition in older patients. The HealthCore 2002–2005 claims data set reported that total cost rises from $31,000 for "healthy"-cancer patients to $46,000 in the presence of one comorbidity and is reported to increase dramatically up to about $65,000 per patient in cases where 3+ comorbidities are documented. While the increase in cost is understandable given the fact that more complicated conditions require higher expenses to be treated/managed, it must be noted that there is currently a disproportion of funds allocation for cancer treatment modalities. This is particularly relevant if we consider that of hypothetical 5 Euros for cancer treatment, 3.5 Euros are used for the chemotherapy drugs, and 1.5 Euros for the rest of the cancer care (including surgery and radiation therapy).

The misbalance between these two sides of cancer care has been recently reported by a powerful editorial in *Cancerworld*, the journal reporting opinion leaders' thoughts on medical and surgical oncology across Europe. Wagstaff (2016) reported first a widely cited analysis of cancer research stories published between 1998 and 2006 on the BBC website, chosen by the

researchers as "an ideal surrogate... for overall media impact," finding that stories about cancer drugs dominated, accounting for around 20% of all coverage (Lewison et al. 2008). Stories about research on any other modality of treatment were so few and far between that they didn't even get a mention in the report. Other major research topics, in order of frequency, were stories on lifestyle, genetics, food and drink, and work-related risk factors. It's surprising how surgery has not given any attention, given the fact that the vast majority of the most common solid tumors (e.g., breast and colorectal) are mainly cured with surgery. The same article described a peculiar reason to explain why medical management grabs so much more attention than surgery by reporting an interesting paper published in the Journal of the European Molecular Biology Organization. Sullivan et al. (2010) indeed brought together a body of evidence to show that we are all hard-wired, through evolution, to seek medication when we are not feeling well, and that we share this trait with much of the animal world. Significantly, it linked this trait to the placebo effect, the real biological effect (hence the evolutionary benefit) that has been demonstrated to arise simply from our seemingly irrational belief in the efficacy of an ingested medicine. Irrational or not, it's a common misunderstanding that efforts in cancer research and basic science should have their main focus on ridding a patient of the need for surgery while almost nobody realizes that research should be focused on improving the quality of surgery since the majority of are cured by surgery and only around 5% or 6% by medical oncology.

While considering the disproportion of collective awareness and funds allocated for medical vs. surgical care, everyone who carries responsibilities for any hospital administration should explore the Memorial Sloan Kettering Cancer Center colorectal cancer nomogram (mskcc.org/nomograms 2017) to determine the predicted impact of adjuvant chemotherapy in the group of patients that is currently receiving it: older patients 70 year and older (Weiser et al. 2008). For example, per the nomogram, for a 70-year-old male with T3, N1 colon cancer with lymphovascular invasion and perineural invasion, the 5 year disease-free survival only increases minimally from 48% to 51% with the addition of chemotherapy while the 10 year disease-free survival increases from 36% to 39% (mskcc.org/nomograms 2017). This nomogram can help counsel patients further about the risks and benefits of undergoing adjuvant chemotherapy based on their characteristics and the characteristics of the tumor.

What Is the Value of Health Care: Outcomes That Matter to Patients/Cost per Patient Ratio

"Achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent" (Porter and Teisberg 2006). This simple but powerful statement by a Harvard Business School group of authors is the key message of this chapter. "If value improves, patients, payers, providers, and suppliers can all benefit while the economic sustainability of the health care system increases," they continued. Unfortunately, value in health care remains largely unmeasured and misunderstood. The process carries intrinsic complexity (increased by the single patient's complexity as for older patients cancer patients) but also because providers tend to measure only what they can directly control in a particular intervention and what is easily measured, rather than what matters for patients. For example, current clinical-outcomes-measure strategies often cover either a miniscule part of a process (e.g., intraoperative blood loss, too narrow to be relevant to patients who are managed in a multidisciplinary fashion) or outcomes of a whole hospital, such as infection rates (too broad to be relevant to individual patients). Rigorous, disciplined measurement and improvement of the awareness of the true meaning of clinical "value," instead is the best way to drive progress of the healthcare system. Since value is defined as outcomes relative to costs, it incorporates efficiency. Cost reduction without regard to the outcomes achieved is dangerous and self-defeating, leading

to false "savings" and potentially limiting effective care (Porter 2010).

In order to identify the proper unit for measuring value, administrations should encompass all services or activities that jointly determine success in meeting a set of patient needs. Examining the rectal cancer case, for example, true value for patients cannot be achieved without measuring the cumulative efforts that produce a high standard of care. The system starts with preoperative staging/imaging (underlining the key role of dedicated MRI specialist), to the multidisciplinary management by radiation and medical oncologists, to the pivotal role of dedicated rectal-cancer surgeons and their teams, and moving forward, the crucial value of specialized pathologists able to define tumor regression grade and circumferential margin status in order to guide the need for further treatments. Altogether, the system generates value for the single patient but if one step of the ladder is analyzed independently you may obtain a misleading perception.

Porter (2010) identified two key elements that should drive the measurement of outcomes that matter to patients. First, "the value comes from the sum of combined efforts from health care providers over the full cycle of care." The benefits of any one intervention for the ultimate outcome will depend on the effectiveness of other interventions throughout the care cycle. This is not just the definition of a "care cycle" but should be the spirit that characterizes every true multidisciplinary system considered devoted to cancer care. Second, "value for patients is often revealed only over time and is manifested in longer-term outcomes such as sustainable recovery, need for ongoing interventions, or occurrences of treatment-induced illnesses" (Institute of Medicine 2006). The only way to accurately measure value, then, is to track patient outcomes and costs longitudinally.

This approach is diametrically opposed to the one often used by hospital administrations that tends to dissect the process in microscopic segments (e.g., cost of laparoscopic energy devices in the operating room) in order to apparently govern the system expenses. Unfortunately, this way of approaching the problem doesn't allow managers to capture either the economic value (the use of laparoscopic energy devices may or may not reduce surgery time and may or may not reduce postoperative complications/length of stay) or the patients' true benefit (faster recovery after surgery using "expensive" laparoscopic devices) of a given surgical practice. Outcome measurement should include the health circumstances most relevant to patients addressing a period long enough to comprehend the ultimate results of care.

Today, health care organizations measure and accumulate costs around departments, physician specialties, discrete service areas, and line items such as drugs and supplies as a reflection of the organization and financing of care. Costs, like outcomes, should instead be measured around the patient. Measuring the total costs over a patient's entire care cycle and weighing them against outcomes will enable truly structural cost reduction, through steps such as reallocation of spending among types of services, elimination of non–value-adding services, better use of capacity, shortening of cycle time, provision of services in the appropriate settings, and so on (Porter 2008).

Outcome measurement should then include sufficient measurement of risk factors or initial conditions to allow for risk adjustment as in the case of older cancer patients. Measuring, reporting, and comparing outcomes are perhaps the most important steps toward rapidly improving outcomes and making good choices about reducing costs. The role of clinicians in this process is to show hospital administrations that good, patient-centered clinical practice is effective because it produces outcomes that matter to patients and it's ultimately able to control expenses because it can prioritize what is essential and reduce what is of little value for oncologic patients.

There is probably no better way than reporting the Royal College of Physicians 2012 annual report (rcplondon.ac.uk 2017) to summarize a practical vision of what it means to promote the true value for health care among professionals and administrations. As the College highlights, this virtuous process should be implemented through three simple steps:

1. Rebuild awareness that patients' dignity is the center of our profession
2. Redesign services to improve patients' care
3. Reconsider the way medical education is delivered and physicians are trained in the modern era

> We must promote dignity and patient-centered care. We must make sure patients are at the heart of service design and clinical practice. Hospitals must be a safe place in which all patients are treated with dignity and respect, including those with dementia. All health professionals have a duty to ensure patient needs are met, working together as a team to deliver the best possible care [. . .].
>
> We must redesign services. We must make difficult decisions about the design of services where this will improve patient care. In some areas, this will require service reconfiguration. Decisions about service redesign must be clinically led and clinicians must be prepared to challenge the way services – including their own service – are organized. [. . .] We must change the way we organize hospital care. We must reorganize hospital care so that patients have access to efficient, high-quality, expert care regardless of their age or day of the week. [. . .] We must consider whether the way we educate, train and deploy physicians ensures the right balance of general and specialist skills to deliver expert, holistic care for current and future patients. It is vital that all medical professionals have the skills and knowledge they need to care for older patients with complex conditions, frailty and dementia. (rcplondon.ac.uk 2017)

Conclusions

Cancer care in the older patients should be patient-focused, multidisciplinary, and take into account patient, surgeon, and institution factors. In striving for patient-centered outcomes rather than surgeon- or institution-driven outcomes, patients stand to gain quality of life, and the chance to meet their goals of care.

Summary

Colorectal cancer care cannot be dictated by chronological age alone. Regardless of the system of choice, it is essential to systematically assess older cancer patients to determine whether the patient is fit for surgery, which surgical plan is appropriate, and which adjustments may be needed before the procedure. Main domains that should be accessed before colorectal surgery are: cognitive status (including history of delirium), independence/living situation, sarcopenia, gait ability, and nutrition. Minimally invasive colorectal surgery is safe and feasible in properly selected older patients, and, in fact, is associated with faster functional recovery. Perioperative enhanced recovery protocols can be safely adopted and are beneficial in senior adults with colorectal cancer undergoing surgery. Rectal cancer management is changing; in addition to organ preserving surgical strategies, there is new emphasis on "watch and wait" protocols after clinical complete response following neoadjuvant chemoradiation. Both strategies could be of tremendous benefit for older rectal cancer patients especially in vulnerable or frail individuals. In order to better understand the value of different treatment strategies, data such as functional status and quality of life should be routinely reported at the end of the process. Achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent. Costs, like outcomes, should be measured around the patient. Measuring the total costs over a patient's entire care cycle and weighing them against outcomes will enable truly structural cost reduction in colorectal cancer care.

Cross-References

- ▶ Frailty in Cancer Patients
- ▶ Geriatric Screening in Cancer Patients
- ▶ Lung Cancer in Older Adults: Local Treatment
- ▶ Multidisciplinary Management of Liver, Pancreatic, and Gastric Malignancies in Older Adults
- ▶ Predictive Tools for Older Cancer Patient Management
- ▶ Principles of Cancer Surgery in Older Adults

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45 Multidisciplinary Management of Liver, Pancreatic, and Gastric Malignancies in Older Adults

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Abstract

Liver, pancreatic, and gastric cancers are aggressive and common malignancies and their incidence is increased in the elderly. Treatment requires a multidisciplinary approach involving multiple specialties including gastroenterology, surgery, radiation oncology, interventional radiology, and medical oncology. Appropriate management is limited by inherent biases among clinicians and the fact that very few clinical trials enroll elderly patients. It is well documented across multiple malignancies that elderly patients often receive substandard care, are denied potentially curative surgery, and are less likely to be treated with standard of care chemo- and radiation-therapies. However, it is clear that chronological age should not be used as the sole determinant when formulating a treatment strategy. Various tools included within a Comprehensive Geriatric Assessment are available and can aid in the decision-making process, when considering the best treatment for patients with advanced age.

Mounting data support the argument that elderly patients derive somewhat similar benefit from treatment compared with younger patients. Surgical complications and toxicities with chemotherapy may be higher in elderly population because of associated comorbidities, diminished functional status, and altered pharmacokinetic profiles. Increased clinical trial accrual of elderly patients is needed and can help provide data to guide management of these complex patients. In the following chapter, we evaluate the multidisciplinary management of liver, pancreatic, and gastric cancer in the elderly with a focus on evidence-based, patient-centered treatment strategies.

Keywords

Hepatocellular carcinoma · Cholangiocarcinoma · Colorectal liver metastases · Pancreatic adenocarcinoma · Gastric cancer

Introduction and Background

Tumors of the liver, pancreas, and stomach are common in elderly patients and are associated with high morbidity and mortality. Healthcare providers frequently struggle with how to best manage the elderly, often resulting in substandard care. Most of the available data support a more aggressive treatment approach that puts less emphasis on chronologic age and more on patient function, comorbidities, and quality of life. It is clear that a multidisciplinary treatment approach is necessary, especially in the very elderly patient with multiple comorbidities, advanced local or systemic disease, and/or a complex social situation. It is crucial that patients are given the opportunity to voice their goals and values so that an appropriate treatment plan is formulated. Many elderly patients will require transitional care placement after a complex operation, and in some cases, they may experience increased complications rates. Similarly, aggressive chemotherapy regimens might not be well

Table 1 Selected studies of liver resection in young versus elderly patients for mixed indications

Reference	Number of patients by age	Perioperative mortality (%)	Perioperative complications (%)	5-year survival (%)	Comments
Cescon et al. 2003	≥70 y ($n = 23$) <70 y ($n = 99$)	0 2	39.1 32.3	64.2 53.9	Survival is 3-year. No significant differences
Menon et al. 2006 (Cescon et al. 2003)	≥70 y (N = 127) <70 y ($n = 390$)	7.9 5.4	31 33	–	No significant differences
Shirabe et al. 2009	≥ 80 y ($n = 43$) < 80 y ($n = 307$)	0 0.3	26 22	–	No significant differences
Reddy et al. 2011	≥75 y ($n = 423$) 65–74 y ($n = 2261$) 50–64 y ($n = 1703$) ≤50 y ($n = 883$)	≥50 y 7.7 <50 y 1.5	- -	- -	Analysis based on age as continuous variable. Each 1-year and 10-year increase in age associated with 1.036 and 1.426 odds ratio of mortality
Schiergens et al. 2016	18–90 y ($n = 763$) examined age as continuous variable	4/7	43	–	Age had no effect on long-term survival within the first 3 years of surgery

tolerated. Patients must be thoroughly counseled regarding the risks and benefits of various approaches so that they can make the most informed decision possible. Whenever possible, we recommend treatment at high-volume centers. Several tools are available to assist clinicians with the management of elderly patients, including the Comprehensive Geriatric Assessment (CGA), which can help streamline care and guide clinicians in the management for these complex patients.

Liver Malignancies

In contrast to most malignancies, the incidence of liver cancer is increasing at a staggering rate of 3–4% per year, with an associated nearly 3% increase in mortality (Siegel et al. 2017). The burden of this increase is realized disproportionately by the elderly. The MacArthur Foundation predicts the number of patients older than 65 will triple by 2050 (Olshansky et al. 2009). Accordingly, physicians are treating a rapidly increasing number of geriatric patients with hepatobiliary cancers. Significant disparities have been documented in the geriatric population, with many patients receiving substandard cancer care based on their age. In some, but not all cases, additional comorbidities present in the elderly will determine overall survival. However, life expectancy is often underestimated by health care professionals when assessing elderly patients with comorbidities (Wirth and Sieber 2012). This may lead to unacceptable denial of appropriate medical and surgical therapy.

Liver Resection and Special Considerations

Liver resection remains the best option for patients with potentially curable primary and metastatic liver tumors. Traditionally, advanced age was considered a contraindication to major hepatic resection. Many elderly patients present with poor cardiopulmonary, renal, and hepatic reserve, often in the setting of poor nutritional status and significant physical and mental frailty. However, there is increasing worldwide experience to support hepatic resection in appropriately selected elderly patients with primary and secondary liver tumors. Over time, it has become quite clear that major hepatic resection is safe and feasible in elderly patients, and chronologic age alone should not determine surgical candidacy (Table 1).

Technical aspects of surgery, including liver ultrasound, surgical devices for parenchymal transection, and improved anesthetic care, have been refined over recent decades and have led to low mortality rates, typically less than 3% in well-selected patients, and when performed at high-volume institutions. Increased experience with portal vein embolization and ablative strategies has opened doors for patients with increasing burdens of disease, who would otherwise be considered unresectable. A multidisciplinary approach with coordination of care between the surgeon, oncologist, primary care physician or geriatrician, anesthesiologist, and often interventional radiologist is crucial for successful management of these patients.

The feasibility of hepatic resection is largely determined by the size and underlying function of the future liver remnant – the liver parenchyma to remain after surgery. Postoperative liver failure is a rare but often fatal complication, with highly variable rates depending on the series (Aldrighetti et al. 2006; Menon et al. 2006). Physiologic changes within the aging liver may account for an increased incidence of postoperative hepatic failure demonstrated in some series. Hepatic blood flow is decreased in the elderly, and average liver size decreases from 2.5% total body mass to 1.5% total body mass in the octogenarian. The number of hepatocytes appears to decrease, with a concomitant hypertrophy of those that remain. Under normal circumstances, liver function is not noticeably impaired, although clotting factors and other liver proteins may be produced in lower numbers. In the setting of hepatic stress such as surgery or hepatotoxic chemotherapy, these effects may become more apparent (Aalami et al. 2003). The effects of chronic liver injury over the course of a lifetime are also a concern, especially given increasing prevalence of obesity and diabetes in the aging population. Animal studies have also reported decreased capacity for liver regeneration in older animals (Schapiro et al. 1982). However, most human series suggest little difference in the rate of hepatic regeneration following resection in old and young patients when compared using pre- and postoperative volumetric analysis (Kit Wan Chiu and Fong 2011). Liver regeneration is certainly impaired in patients with diabetes, nonalcoholic fatty liver disease, and cirrhosis, and resection should be undertaken in these patients with extreme caution.

Comorbidities and frailty associated with elderly populations can make the decision when to operate difficult. First and foremost, it is crucial that those caring for the patient have an understanding of the patients overall values and healthcare goals, especially as they relate to expected and possible treatment outcomes. Some patients will value quality of life over all else, while others may have very specific future events, such as a grandchild's wedding or graduation, that they aim to attend. Many elderly patients that undergo major hepatic resection will require placement in a transitional care facility for an uncertain amount of time after discharge from the hospital. This must be clear to the patient preoperatively. Similarly, clinicians tend to focus on perioperative mortality and discrete complications such as liver failure, sepsis, and bleeding, but the higher than average risk of postoperative functional and cognitive decline should also be addressed explicitly as they are often considered even more important by the elderly, and have a significant effect on both quality of life and survival (Hofman et al. 2015). As with other surgical procedures, preoperative evaluation should include a multidisciplinary evaluation to assess fitness for surgery. Comprehensive assessments with tools such as the preoperative assessment of cancer in the elderly (PACE – a comprehensive geriatric assessment model) examine general health, specific and relevant to the geriatric population, through a series of validated scales and tests with the goal of identifying modifiable risk factors and predicting postoperative morbidity and mortality (Kim et al. 2013a; Pope et al. 2006). Although liver specific assessment tools are not currently available, the use of this and other similar screening tools can help identify patients at high risk of adverse events, and most importantly, guide providers regarding specific deficits that can be optimized before, during, or after surgery.

Recent analysis of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database demonstrated

increased mortality in elderly patients across all gastrointestinal oncologic operations, with these findings most pronounced after hepatectomy. In this study, 30-day mortality increased from 3.6% in patients younger than 65 years, to 5.7% in patients 65–74 and 7.9% in patients 75–84 years old. Patients older than 85 years of age had a five-fold increase in mortality when compared with patients less than 65 years old (Yeo et al. 2016). Similar results were published in a multi-institutional analysis of patients undergoing major liver resection at Duke University and the University of Pittsburgh from 2002 to 2009. In this study, a 1.5% mortality rate was reported in patients below the age of 50, versus 7.7% in patients over age 50 (Reddy et al. 2011). Similarly, a population-level study evaluating outcomes after hepatectomy in patients with colorectal liver metastasis also found that older patients were significantly more likely to require post-acute care needs following discharge; 18.3% of those $\geq$75 years old patients required postdischarge care at another institution (i.e., rehab, skilled nursing facilities, among others) as compared to only 2.1% of those <65 years old (p <0.001) (Orcutt et al. 2012). The difference in these outcomes is not driven by age alone and should not be interpreted as a reason to withhold surgery for geriatric patients. Instead, they underscore the importance of proper patient selection as well as an opportunity to improve upon and streamline current guidelines for perioperative care in the elderly, with a special focus on the quality of recovery. Specific perioperative system interventions such as enhanced recovery after surgery (ERAS) protocols, geared at improving the quality and experience of surgery during the whole perioperative period, can have a meaningful impact for the elderly and should be considered as a model to optimize care for this population.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death in men and the sixth most common in women worldwide. It differs from other liver tumors by the increased prevalence of chronic liver disease and associated cirrhosis. Malignant transformation often occurs in the setting of chronic hepatic inflammation and injury, with the peak age of HCC incidence being variable worldwide. This is explained by variability in etiologic factors, including viral hepatitis, alcoholic cirrhosis, and nonalcoholic steatohepatitis (NASH) in different parts of the world. Specifically, patients in the developing world are more likely to develop hepatitis B virus (HBV) related HCC and present at an earlier age. In western countries, HCC is more likely related to hepatitis C virus (HCV), alcoholic cirrhosis, and nonalcoholic steatohepatitis (NASH), and median age at presentation is over 60 years (McGlynn and London 2005). Furthermore, as treatment options for HBV and HVC become increasingly available, it is postulated that the peak incidence of HCC will be even further delayed.

Diagnosis

In the majority of patients, HCC causes no additional symptoms besides those associated with chronic liver disease. As the tumor grows, patients may develop pain, distention, weight loss, fatigue, and anorexia. Hepatic decompensation in a previously well-compensated cirrhotic may be the first sign of malignancy. Depending on tumor location, the patient may present with invasion or obstruction of the biliary tree, portal vein, hepatic artery, or inferior vena cava. Extrahepatic spread is rare, with only about 5–15% of patient with metastases at presentation. The most common sites are lung, intra-abdominal lymph nodes, bone, and adrenals (Uka et al. 2007).

Workup consists of thorough history and physical exam with focus on the presence and extent of chronic liver disease. Laboratory studies including CBC, coagulation studies, hepatitis serologies, AFP, and CEA are needed. Cross-sectional imaging with multidetector row CT or MRI with liver protocols is helpful in distinguishing HCC from other benign or malignant tumors of the liver. Furthermore, it is necessary to determine the extent of intrahepatic tumor burden and assess local resectability. It is important to note that perihepatic adenopathy

should not be assumed to represent extrahepatic spread since many cirrhotics harbor benign nodal enlargement, particularly in the setting of viral infections.

The best strategy for early diagnosis of HCC in high-risk patients is close follow-up with ultrasound at 6-month intervals. Unfortunately, most patients at high-risk, particularly elderly patients, do not undergo recommended screening (Davila et al. 2010). Yan et al. recently published a large series using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population based cancer registry from 2003 to 2011; patients age 70 years or older presented with more advanced disease, were less likely to fall within Milan criteria at diagnosis, were less likely to receive any HCC treatment, and had significantly worse long-term survival (Yan et al. 2017). There is a perception, often incorrect, that elderly patients may not benefit from treatment and may suffer undue harm from complications and toxicity. However, there is clear evidence to suggest that treatments for HCC in elderly patients are as effective as in younger patients and that when appropriate treatment is provided, outcome is predicted by cancer stage, not age (Mirici-Cappa et al. 2010).

Resection

Based on different US and international guidelines, it is agreed that resection should be first line of treatment for patients with limited liver tumors (e.g., solitary lesions) and well-preserved liver function (Heimbach et al. 2018). The significance of chronic liver disease in patients with HCC cannot be overstated, and the surgeon must be experienced in the simultaneous management of chronic liver disease and HCC. Perioperative mortality after liver resection in cirrhotic patients is expected to be 2–10% and may be slightly higher in the elderly. That said, several reports indicate that elderly patients with HCC present with less cirrhosis than their younger counterparts, possibly because patients with cirrhosis die at a younger age (Nakamuta et al. 2005). Multifocal HCC also appears to be less common in the elderly. Proper patient selection is paramount and a thorough understanding of the patients overall fitness, hepatic reserve, and the presence of portal hypertension must be obtained.

Multiple contemporary studies have examined outcomes following surgical resection for elderly patients with HCC and reported that age is not an independent determinant of prognosis (Table 2). These studies are generally limited by small sample sizes and all are

Table 2 Selected studies of liver resection in young versus elderly patients with hepatocellular carcinoma

Reference	Number of patients by age	Perioperative mortality (%)	Perioperative complications (%)	5-year survival (%)	Comments
Kondo et al. 2008	≥70 y ($n = 109$) <70 y ($n = 210$)	3.7 2.9	41.3 43.8	- -	No significant differences
Oishi et al. 2009	≥75 y ($n = 64$) <75 y ($n = 502$)	0 0.4	19 22	58 64	No significant differences
Huang et al. 2009	≥70 y ($n = 67$) <70 y ($n = 268$)	1.5 1.1	9 4.5	54.6 29.9	No significant differences
Su et al. 2012	≥55 y ($n = 700$) <55 y ($n = 375$)	- -	- -	51.4 58.9	No significant differences
Sato et al. 2012	≥80 y ($n = 423$) 70–79 y ($n = 2261$) 60–69 ($n = 1703$) ≤59 ($n = 883$)	2.6* 3.36** 2.35* 1.13	- - - -	- - - -	*$p < 0.05$ **$p < 0.005$ when compared with age ≤59
Kishida et al. 2015	≥75 y ($n = 22$) <75 y ($n = 82$)	9 2	59 28	25 33	Significant increase in Clavien-Dindo grade 3a or higher complications in the elderly: 48 versus 15% ($p = 0.006$)

retrospective in nature. Furthermore, most of these studies were conducted in Asian populations and should be applied to Western patients with caution. Despite these limitations, they do provide mounting support for the safety and efficacy of liver resection for HCC in the well-selected elderly population. Unfortunately, analysis of patient-centered and transitional outcomes, such as need for prolonged inpatient rehabilitation, is seldom included.

Transplant

Unfortunately, only 5–15% of patients with HCC present with adequate liver reserve to tolerate curative resection (Bismuth et al. 1999). Liver transplant is the treatment of choice in patients with advanced cirrhosis and HCC but is often not considered for patients older than 65–70 years old. Some studies have demonstrated equivalent outcomes with respect to perioperative and long-term morbidity, mortality, and rejection in elderly patients, while others have raised concerns (Nishikawa et al. 2013). The concern regarding substandard outcomes in the elderly and the limited number of organs available are both important considerations that have led to a limited role of liver transplantation for those over 70 years old. Further, it is clear that elderly patients with associated comorbidities are not candidates for transplant. Despite this, there is an increasing trend at high volume centers to evaluate the elderly using the same selection criteria as is used for younger patients (Taner et al. 2012), and for well-selected elderly patients this may be a treatment option to be evaluated on a case-by-case basis.

Ablation

Experience with potentially curative ablative strategies, including radiofrequency (RFA) and microwave ablation (MWA), has greatly expanded in recent years. Ethanol ablation and cryoablation, which were once commonly employed, have fallen out of favor given increased efficacy and efficiency of RFA and MWA. Tumor ablation can be performed percutaneously, typically by an interventional radiologist, or during an open or laparoscopic surgical procedure. Tumor ablation is an excellent option for elderly patients with medical comorbidities and/or cirrhosis that would render them poor candidates for resection. In fact, in contrast to resection, technical aspects of RFA are enhanced by a cirrhotic parenchyma because of the "oven effect," whereby the stiff cirrhotic liver traps the heat generated by ablation within the tumor. RFA is currently considered the standard of care for small unresectable HCC (Bruix et al. 2011), and there are randomized data to support equivalence between RFA and resection for small tumors, typically <3 cm (Huang et al. 2010; Chen et al. 2006; Lü et al. 2006). Ablative strategies are typically used for up to three lesions of small size and can also be employed in combination with resection or embolization.

Hepatic Arterial Embolization

Transarterial embolization, with or without chemotherapy, capitalizes on the fact that the blood supply for HCC is preferentially derived from the hepatic artery rather than the portal vein. It is a viable option for intermediate size or multifocal HCC that is deemed unresectable but is without vascular invasion or extrahepatic spread in patients with relatively preserved hepatic function. A recent meta-analysis demonstrated similar 5-year survival in elderly and nonelderly patients treated with transarterial chemoembolization (TACE) suggesting this is a safe and effective treatment modality (Hung and Guy 2015). Complications were similar and included liver failure, abscess, peptic ulcers, and renal impairment. Radioembolization with Yttrium-90 (Y-90) labeled glass (TheraSphere) or resin (SIR-Spheres) has also gained traction as a liver-directed therapy and an alternative to TACE. A recent series from Italy reported radioembolization is as well tolerated and effective for elderly patients as it is for older patients with HCC (Golfieri et al. 2013). Complication rates may also be less compared with TACE in certain circumstances, including portal vein thrombosis (Tsai et al. 2010).

Systemic Therapy – Sorafenib

The SHARP trial demonstrated a modest survival benefit in patient with advanced HCC

(unresectable or metastatic) treated with sorafenib (Llovet et al. 2008), a multitargeted tyrosine kinase inhibitor. The use of sorafenib in the elderly has been evaluated largely by way of retrospective data. No significant differences in overall survival, tumor response, and frequency, and severity of drug-related adverse events have been identified in the elderly, including very elderly patients age >80 years (Jo et al. 2014). Cytotoxic chemotherapy is not typically recommended for patients with HCC and use has largely been limited by hepatic reserve, the presence of cirrhosis, and possibly the fact that HCC is relatively chemo-refractory. Neoadjuvant and adjuvant systemic therapies, including sorafenib, have not proven beneficial in patients treated with resection or ablation and are not generally recommended outside of a clinical trial.

Cholangiocarcinoma

After HCC, cholangiocarcinoma is the second most common primary hepatic malignancy and accounts for about 3% of GI malignancies. The incidence is nearly two-fold higher in the elderly (Khan et al. 2008). Resection is the treatment of choice for patients with non-metastatic intrahepatic cholangiocarcinoma with reported 5-year survival of 30–35% with R0 resections (de Jong et al. 2011). In patients with unresectable/metastatic disease, or those that undergo R1 resection, there are essentially no survivors at 5 years. Data from a recent large retrospective multinational cohort (Vitale et al. 2016), which is the only study to specifically examine management of intrahepatic cholangiocarcinoma in the elderly, found that older patients were more likely to suffer severe postoperative complications after resection and were less likely to be treated with adjuvant systemic therapy. However, there was no difference in disease free or overall survival. Once again, disease characteristics and not age were predictive of long-term outcomes. For patients with unresectable/metastatic disease, the preferred systemic chemotherapy is with combination gemcitabine and cisplatin based on the ABC-02 trial (Valle et al. 2010). The role of systemic therapy in the neoadjuvant or adjuvant setting is not well defined. Transarterial therapy, in particular radioembolization, for patients with intrahepatic cholangiocarcinoma is of significant benefit and may be an alternative to the more toxic systemic therapy, for patients with unresectable, not-metastatic disease. Its favorable toxicity profile may be a more reasonable alternative for elderly frail patients specifically.

Colorectal Liver Metastasis

An estimated 30–50% of patients with colorectal liver cancer either present with or develop liver metastases at some point during their course. Optimal care of elderly patients with colorectal cancer liver metastases (CRC LM) is complex and requires a multidisciplinary team approach. Although the majority of patients diagnosed with CRC LM are 65–85 years old, elderly patients are underrepresented in clinical trials and population-based studies. Furthermore, improvement in outcomes has lagged when compared with younger populations. Cancer specific survival is significantly worse in the elderly, and this is at least partially driven by treatment (Anaya et al. 2011). There is mounting evidence to support that appropriately selected elderly patients with CRC LM benefit from standard of care treatment and, when treated aggressively, have long-term outcomes similar to younger populations (Leporrier et al. 2006). Unfortunately, age remains an independent predictor that a patient will be treated symptomatically, and not with the intent of improving survival (Kopetz et al. 2009).

Resection

Surgery remains the only curative option for patients with colorectal cancer liver metastases (CRC LM), and approximately 10–20% of patients present with surgically resectable disease (Simmonds et al. 2006). After 5 years, at least 30% of patients that undergo metastasectomy are alive, with approximately two-thirds of them without evidence of disease versus less than 5% of

Table 3 Selected studies of liver resection in young versus elderly patients with colorectal Cancer liver metastases

Reference	Number of patients by age	Perioperative mortality (%)	Perioperative complications (%)	5-year survival (%)	Comments
Brunken et al. 1998	>70 y ($n = 25$) <70 y ($n = 141$)	4 2	28 26	47 36	No significant differences
Nagano et al. 2005	≥70 y ($n = 62$) <70 y ($n = 150$)	0 0.49	19.7 23.3	34* 53	Significant difference in overall 5-year survival.
Mann et al. 2008	≥70 y ($n = 49$) <70 y ($n = 142$)	0/4 2/3	30 19	31 43	Mortality = 30/60 days. No significant differences
Di Benedetto et al. 2011	≥70 y ($n = 32$) <70 y ($n = 32$)	3 0	28.1 34.4	33.3 28.	60-day mortality, not significant
Orcutt et al. 2012	≥75 y ($n = 483$) 65–74 y ($n = 992$) <65 y ($n = 2551$)	3.3* 2.2 1.3	- - -	- - -	*Age significant independent predictor in-hospital mortality. Nonhome disposition: was 18.3%, 6.1%, and 2.1% in oldest, old, and young groups, respectively
Cook et al. 2012	≥75 y ($n = 151$) <75 y ($n = 1292$)	7.3* 1.3	32.5* 21.2	37 38.2	*Age significant predictor of complications and 90-day mortality. No difference in 5 year survival.
Booth et al. 2015	≥75 y ($n = 186$) 65–74 y ($n = 414$) <65 y ($n = 710$)	5/8 3/5 2/3	- - -	28 44 49	Mortality = 30/90 days

patients treated with best supportive care and 5-FU based chemotherapy (Manfredi et al. 2006; Mazzoni et al. 2007). A 2012 report by Orcutt et al. used the United States National Inpatient Sample to evaluate short-term outcomes in elderly patients that underwent resection for CRC LM and reported a 1.3% mortality rate in patients younger than 65, 2.2% in patients 65–74, and 3.3% in patients 75 and older. This study also highlighted the significantly increased need for placement in transitional care facilities in elderly patients undergoing liver resection (Orcutt et al. 2012).

It is not surprising that several studies have demonstrated slightly increased perioperative mortality in elderly patients that undergo hepatectomy for CRC LM (Table 3). Despite this finding, perioperative mortality is still low and within acceptable ranges and we believe that liver resection should still be the treatment of choice for appropriately selected patients. A number of prediction tools have been reported to guide treatment options in the elderly. Mazzoni et al. formulated a clinical risk score to predict overall survival in elderly patients with CRC LM treated with liver resection. The authors concluded that a clinical risk score of 3 or more should be a contraindication to surgery and advised RFA or TACE depending on the clinical scenario (Table 4) (Mazzoni et al. 2007). Although tools such as this can potentially help in decision-making, this model still warrants external validation.

Table 4 Clinical risk score to predict overall survival in elderly patients with CRC LM treated with liver resection. (Mazzoni et al. 2007)

Risk Factor	Points
Node-positive primary tumor 1	1
Disease-free interval <12 months 1	1
Number of metastases >1 1	1
Tumor size >5 cm 1	1
Preoperative CEA >100 ng/mL 1	1
Score	*Predicted median overall survival (months)*
0–2	30–46
3–4	20–23
5	12

Although for the most part indications for liver resection should not be based on age alone, there are specific circumstances with extensive resections in which older patients, even those fit and with limited comorbidities, may not do as well. Specifically, major operations such as the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPSS) though most applicable for patients with CRCLM have been shown to have significantly higher mortality rates in older patients and as such, it is generally considered contraindicated for this population (Oldhafer et al. 2016). Additional data are needed in the elderly with respect to combined resection of liver metastases and the primary tumor, though this has been shown to be safe in the general patient population with low-moderate volume disease.

Chemotherapy

The available data suggest similar cytotoxic efficacy of chemotherapy in young and old patients, with variably increased toxicity in the elderly. The optimal approach in patients with resectable CRC LM remains somewhat unclear, especially for the elderly. Perioperative chemotherapy is the current approach for most patients outside of a clinical trial. A phase III EORTC trial in which perioperative FOLFOX (3 months before and 3 months after surgery) administration led to a 7.3% improvement in progression free survival at 3-years, but no difference at 5-years. There was no difference in overall survival at 5 years, but the study was not powered to detect this endpoint. Perioperative morbidity increased from 16% to 25% in patients treated with chemotherapy (Nordlinger et al. 2013). Current NCCN guidelines recommend 6 months of an active systemic regimen administered perioperatively in patients with resectable disease (Benson et al. 2017). 5-Fluorouracil/leucovorin alone or 20% dose-reduced FOLFOX are reasonable approaches in elderly patients with poor reserve that may not be able to tolerate full dose oxaliplatin (Sanoff and Goldberg 2013). A recent Italian multicenter analysis demonstrated a treatment benefit in patients over 80 years old with metastatic CRC (not limited to liver), reporting a 2-year overall survival of 34.8% in patients treated with chemotherapy versus 17.6% in those not treated (Grande et al. 2016). The optimal timing of chemotherapy for patients with CRC LM remains a topic of debate.

In patients that are poor candidates for, or decide against resection with or without systemic therapy, additional alternatives include tumor ablation and hepatic arterial directed therapy.

Neoadjuvant Therapy

Neoadjuvant chemotherapy is sometimes appealing, especially in high-risk patients with synchronous or large volume metastases as an in vivo test of tumor biology and the patient's response to treatment. In addition it allows for early treatment of any micrometastatic foci of disease and ensures that patients actually receive systemic treatment. However, chemotherapy-induced hepatotoxicity with steatosis and noncirrhotic portal hypertension have been associated with increased

postoperative complications and limit the utility of upfront systemic treatment in patients with clearly resectable disease (Zorzi et al. 2007). This is even more relevant in elderly patients that may already have compromised hepatic function. Finally, complications related to chemotherapy sometimes worsen an already borderline patient's performance status, such that surgery is no longer an option.

Conversion Therapy

Conversion therapy is administered with the goal of converting a patient with borderline or unresectable disease into a surgical candidate. The optimal regimen has not been determined. Both FOLFOX and FOLFIRI have been demonstrated to achieve resectability in 12.5–40% of patients (Ychou et al. 2013). The addition of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, should be decided on a case by case basis and is only appropriate for the most fit elderly patients with borderline/unresectable CRC LM, but modest improvement in tumor control needs to be weighed against treatment toxicities including stroke and arterial thromboembolic events, and bowel perforation. If used in the neoadjuvant setting, it should be held at least 4–8 weeks prior to resection to minimize effects on wound healing and perioperative complications (Gruenberger et al. 2008). In exceptionally fit elderly patients with wild-type KRAS and BRAF tumors, the EGFR inhibitors cetuximab or panitumumab plus FOLFIRI may be considered if curative resection seems possible. In all cases, patients should be re-scanned at least every 2 months and duration of systemic treatment should be limited if the patient becomes a surgical candidate.

Adjuvant Therapy

Although no clear survival advantage has been demonstrated compared with observation alone in patients that undergo R0 resection, the standard of care is to administer systemic therapy for a period of 6 months. If no therapy was administered in the neoadjuvant setting, it is administered postoperatively. Given the lack of conclusive evidence in elderly patients with resected disease, it is important to consider the patients' health-related goals and performance status so that an informed decision can be made. FOLFOX or XELOX are the preferred regimens, as there is no evidence to support the use of irinotecan, cetuximab, or bevacizumab in patients with no evidence of disease after resection of primary colorectal cancer with metastases to the liver.

Pancreatic Cancer

Pancreatic ductal adenocarcinoma accounts for 90% of the tumors in the pancreas. Pancreatic adenocarcinoma is the fourth most common cause of cancer deaths in the United States with estimated 43,090 deaths and 53,670 new cases in 2016 (Siegel et al. 2017). It is expected that pancreatic cancer will become the most common cause of cancer-related death in the next decade (Rahib et al. 2014). The median age at diagnosis is 72 years for pancreatic cancer and is the highest of all cancers (Olson and Kurtz 2013). The strongest risk factor for pancreatic cancer is age. The risk for pancreatic cancer increases from only 73.4 per 100,000 in those aged 50–54 years to 104 per 100,000 for those aged 75–79 years. There are gender-specific differences as well with men having higher risk than women (13.5 vs. 10.8 per 100, 000) (Olson and Kurtz 2013). In terms of race, the incidence rate is highest among African Americans followed by whites, Hispanics, and Asians. Because of age distribution in United States among different races, the majority of patients with pancreatic cancer are whites.

Despite the fact that pancreatic cancer is a disease predominantly of older patients, there are limited data available on how to treat older patients. Most of the data are derived from small retrospective series. Even though the median age of diagnosis of pancreatic cancer is 72 years, the median age of patients enrolled in clinical trials is almost a decade younger. Further, some trials have excluded very elderly patients from enrolling in the clinical trials (Conroy et al. 2011). Similar bias is observed in surgical resection of pancreatic cancers where older patients are less

likely to undergo curative surgery. One study comparing the pathologic features of pancreatic cancer in elderly *and* younger patients did not find any differences in the grade, location, or incidence of the local spread, although elderly patients developed fewer hematogenous metastases (Kamisawa et al. 1998). Some reports have suggested that older patients present more diploid tumors or with p53 mutations, which are associated with a worse prognosis (Sato et al. 1997).

Both genetic and epidemiologic risk factors are associated with development of pancreatic cancer. Cigarette smoking remains the strongest environmental risk factor with almost a two-fold increased risk among current smokers compared to nonsmokers (Lynch et al. 2009; Iodice et al. 2008). Other environmental risk factors associated with pancreatic cancers include diabetes, obesity, pancreatitis, heavy alcohol use, and allergies (Calle et al. 2003; Ben et al. 2011; Olson 2012; Lucenteforte et al. 2012; Turner et al. 2006). A family history of pancreatic cancer is observed in 5–10% of patients with pancreatic cancers. Mutations in BRCA gene, especially BRCA2 and PALB2, are associated with increased risk of pancreatic cancers. Other known associated genetic conditions include hereditary nonpolyposis colon cancer (Lynch Syndrome), familial atypical multiple mole melanoma syndrome (FAMMM), Peutz–Jeghers syndrome, familial adenomatous polyposis, and hereditary pancreatitis (Olson and Kurtz 2013).

Staging

Accurate staging is required for patients with pancreatic cancer for selecting appropriate treatment strategies. Staging work-up includes measurement of tumor markers (CA19–9 and CEA), endoscopic ultrasound, and cross-sectional imaging (CT or MRI). In addition, laparoscopy and/or positron emission tomography (PET) scan may help detect metastases in additional patients initially considered to have early stage disease and thus prevent futile pancreatic resection.

There are two types of staging system typically used for prognosis and treatment: TNM staging by American Joint Committee on Cancer (AJCC) and clinical classification system based on imaging studies (Edge et al. 2009). TNM staging is based on tumor size, involvement of blood vessels and lymph nodes, and presence of metastatic disease. More frequently, the clinical classification system is utilized for making treatment recommendations. The clinical classification system divides the patients into following four groups: Resectable, Borderline resectable (Table 5), Locally advanced, and Metastatic disease. The classification of nonmetastatic pancreatic cancer into different groups is based on degree of involvement of blood vessels and the definitions are not uniform (Mahipal et al. 2015). Moreover, individual institutions may utilize their own criteria for determining resectability. At the time of staging, approximately 50–55% of the patients present with metastatic disease, 20% with

Table 5 Common definitions of borderline resectable pancreatic cancer

Blood vessel	NCCN (Tempero et al. 2014)	AHPBA/Consensus (Vauthey and Dixon 2009)	MD Anderson (Katz et al. 2008)
Celiac axis	Distortion of narrowing of the vessel wall, and/or reconstructible occlusion	Uninvolved	Short segment occlusion/ reconstructible
Superior mesenteric artery	Tumor-vessel interface $\geq$180 degrees of the circumference of the vessel wall	Abutment	Abutment
Hepatic artery	Reconstructible short segment interface between tumor and vessel	Abutment or short segment encasement	Abutment or short segment encasement
Superior mesenteric vein/portal vein	Distortion or narrowing of the vessel wall, and/or reconstructible occlusion	Abutment, impingement, encasement of the SMV/PV or short segment occlusion	Short segment occlusion/ reconstructible

resectable disease, and 20–25% with locally advanced stage (Stathis and Moore 2010).

Surgical Resection in Elderly Patients

Pancreatic cancer is an aggressive malignancy associated with poor prognosis. Despite recent advances for the treatment of pancreatic cancer, the 5-year survival rate remains approximately 6% (Siegel et al. 2016). Surgical resection with negative microscopic margins remains the only curative option. Even among patients who undergo potentially curative resection, the 5-year survival is only 20%. With the improvements in modern surgical techniques and adjuvant chemotherapeutic regimens, the median survival in clinical trials has increased to 28 months. Notably, the perioperative morbidity and mortality has substantially decreased, especially at high volume centers, making surgical resections feasible for higher proportion of patients. It is of utmost importance to select patients for surgical resection after appropriate staging, as there is no survival benefit of surgery for patients with metastatic disease.

Typically, upfront surgical resection is recommended for patients with resectable pancreatic cancer and neoadjuvant therapy for patients with borderline and locally advanced disease. At some centers, neoadjuvant therapy is routinely delivered even for patients with resectable disease. The probability of effective down-staging followed by surgical resection with negative margins is much lower for patients with locally advanced disease compared with resectable disease.

Prior to 1990, pancreaticoduodenectomy (PD) for pancreatic cancer was rarely performed in patients older than 70 years of age because of high mortality and morbidity rates (Gudjonsson 1987). Overall, the mortality after pancreatic resection was as high as 20% on average prior to 1984. In recent series, the mortality rate is less than 4% on average (Gudjonsson 2016). More importantly, both mortality and postoperative complications have significantly decreased at high volume centers (Scurtu et al. 2006). This has led to feasibility of potentially curable surgical resection for pancreatic cancer among older patients. Multiple studies have demonstrated that PD can be performed safely in patients older than 70 years of age (Scurtu et al. 2006; DiCarlo et al. 1998; Vickers et al. 1996). Some studies have demonstrated safety even in patients older than 80 years of age (Teague et al. 2015).

Older patients have similar postoperative mortality after PD as younger patients (Sohn et al. 1998; Makary et al. 2006). Some studies have demonstrated that elderly patients may have higher operative risks after PD. Some intraoperative factors like blood loss, transfusion requirements, and operative length seems to be similar across different age groups (Sohn et al. 1998). Elderly patients may have a more complicated postoperative period with some studies showing longer postoperative stay (Scurtu et al. 2006; Sohn et al. 1998). Some complications like delayed gastric emptying seems to be more common in patients >80 years of age (Finlayson et al. 2007). The proportion of patients being discharged to nursing home after the surgical resection was higher in older patients with 10.6% in the age group 60–65 years and 36.7% with ages ≥80 years were unable to be discharged home (Finlayson et al. 2007).

Surgical resection has demonstrated to increase the survival in patients with pancreatic cancer regardless of age. However, elderly patients are much less likely to undergo surgical resection than younger patients. In a population-based study, patients ≥85 years of age are 94% less likely than patients <70 years of age to undergo pancreatic resection (Riall et al. 2011). Since the benefit of surgery does not necessarily diminish with age, older patients with resectable pancreatic cancer should be considered for surgical resection. There are some tools available to assess elderly patients. Elderly patients should undergo comprehensive geriatric assessment (CGA). CGA is a multidimensional, interdisciplinary diagnostic process that focuses on the determination of medical, psychosocial, and functional capabilities in older people to develop an integrated treatment plan. CGA has been shown to improve overall survival, quality of

life, and physical functioning in the nononcologic geriatric population. Several recent reports have strongly suggested that different components of comprehensive geriatric assessment can be useful in oncology to predict early death, functional decline, toxicity, and overall survival (Puts et al. 2014; Hurria et al. 2011). As part of geriatric assessment functional status, comorbidities, cognition, mental health status and support, fatigue, and polypharmacy are assessed (Higuera et al. 2016). The Charlson age comorbidity index (CACI) is another tool that assesses the comorbidity in standardized fashion to predict the postoperative mortality of patients undergoing surgery. CACI is a statistically validated tool that assigns different weights to patient's comorbidities and can be adjusted for age of the patients. In a study of 379 patients with pancreatic cancer undergoing surgery, high CACI score of more than 4 was associated with significant poor survival (Asano et al. 2017). With the help of these validated tools, patients can be better selected for pancreatic resection and age alone should not be used as a discriminating factor to exclude patients from potentially curative surgery.

Chemotherapy in Elderly Patients

Metastatic Disease

Until few years ago, single agent gemcitabine had remained the mainstay treatment of patients with pancreatic cancer. This was based on a phase III multicenter randomized trial which assigned patients to either treatment with gemcitabine at a dose of 1000 mg/m2 for 7 weeks followed by 1 week of rest and then weekly for 3 weeks on and 1 week off or 5-fluorouracil (5-FU) 600 mg/m^2 given weekly on the same schedule (Burris et al. 1997). The median survival was 5.6 months in gemcitabine arm as compared to 4.4 months in 5-FU arm. There were no specific concerns about using single agent gemcitabine in elderly patients. Multiple randomized trials evaluating combination gemcitabine with a novel agent failed to demonstrate any significant clinical benefit. Combination of gemcitabine and erlotinib provided modest benefit with median survival of 6.2 months in the combination arm compared to 5.9 months with single agent gemcitabine (Moore et al. 2007). Erlotinib containing arm had higher incidence of rash, diarrhea, stomatitis, and infection. Gemcitabine and erlotinib has fallen out of favor in the clinical practice.

More recently, the combination of gemcitabine and nab-paclitaxel (albumin bound paclitaxel) was compared to gemcitabine in a large randomized phase III trial of 861 patients (Von Hoff et al. 2013). This study was conducted in both USA and Europe. The median age was 63 years (Range: 27–88 years). Patients with Karnofsky performance score (KPS) of 70 or higher were included in this trial. The median survival in the combination arm of gemcitabine and nab-paclitaxel was significantly higher than single agent gemcitabine arm (8.7 versus 6.6 months ($P < 0.001$). Gemcitabine plus nab-paclitaxel was associated with increase rates of neutropenia, leukopenia, fatigue, peripheral neuropathy, and diarrhea. Higher proportion of patients experienced grade 3 or higher treatment-related, treatment-emergent adverse events in the nab-paclitaxel plus gemcitabine arm (77%) than in the gemcitabine-alone arm (51%). Forty two percent of the patients were $\geq$65 years of age and significant survival benefit was observed in this subgroup as well (Goldstein et al. 2015). However, the median survival was shorter in both arms in older patients compared to younger patients. In the subgroup analysis, patients with KPS score of 70–80 also derived significant benefit with combination treatment. Overall, patients with better performance status had better survival.

In a randomized phase 3 trial conducted in Europe, single agent gemcitabine was compared to combination chemotherapy of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX) (Conroy et al. 2011). Only patients with Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 were included in this trial to select for patients who can better tolerate this intensive chemotherapy. Patients >75 years of age were excluded from this trial, thus limiting the generalization of these results to very elderly patients. The median age in this trial was 61 years, almost a decade

lower than the median age of pancreatic cancer patients in actual practice. The median survival was 11.1 months in the FOLFIRINOX group compared to 6.8 months in gemcitabine group (P <0.0001). Higher objective responses were seen in the FOLFIRINOX group (31.6% versus 9.4%). Incidences of grade 3 or 4 neutropenia (45.7% versus 21%), febrile neutropenia (5.4% versus 1.2%), thrombocytopenia (9.1% versus 3.6%), diarrhea (11.4% versus 1.2%), and sensory neuropathy (9% versus 0%) were significantly higher in the FOLFIRINOX group, whereas the incidence of grade 3 or 4 elevated alanine aminotransferase levels was significantly higher in the gemcitabine group. The quality of life at 6 months was better for patients receiving FOLFIRINOX likely due to better control of tumor growth. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive decrease in the scores on the Global Health Status and Quality of Life scale versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P <0.001). Thus, FOLFIRINOX therapy resulted in almost doubling of median survival at the expense of increase toxicities. However, this trial excluded older patients and patients with marginal performance status. Thus, it is not clear if FOLFIRINOX chemotherapy would provide benefit for elderly patients. Different dose modifications have been proposed to reduce the toxicity profile of FOLFIRINOX while maintaining the efficacy of the regimen. 5-Fluorouracil bolus is commonly omitted. Prophylactic G-CSF can be added as well. In a retrospective series from Memorial-Sloan Kettering Cancer Center, all patients were dose reduced to 80% of the standard dose from the beginning without compromising efficacy (Lowery et al. 2012). Other modifications include reducing the dose of irinotecan only and omitting bolus 5-fluorouracil (Conroy et al. 2013). The outcomes of these modifications of FOLFIRINOX chemotherapy in elderly patients with pancreatic cancer remain unclear. We typically do not use age as a cutoff for administering FOLFIRINOX. However, it is preferred in patients with excellent performance status with limited comorbidities, in the palliative setting. Gemcitabine and nab-paclitaxel combination was evaluated in more representative population of pancreatic cancer with significant proportion of older patients in the clinical trial. Single agent gemcitabine is reserved for patients with borderline performance status.

Adjuvant Treatment

Adjuvant chemotherapy after surgical resection for pancreatic cancer has been demonstrated to improve survival. In the CONKO-001 trial, a phase III multicenter randomized trial, efficacy, and toxicity of gemcitabine was evaluated as an adjuvant treatment (Oettle et al. 2013). The disease-free survival (DFS) was significantly prolonged in the gemcitabine group compared to observation group (13.4 vs. 6.7 months, P <0.001). The long-term survivors were almost doubled with 5-year survival of 20.7% in the treatment group compared to 10.4% in the observation group. Median age was 62 years with 62% of the patients were more than 65 years of age. Patients older than 65 years had slightly lower survival than younger patients, but older patients also derived similar benefit from adjuvant chemotherapy. In a large randomized trial of 1088 patients, The European Study Group for Pancreatic Cancer (ESPAC)-3 trial, 5-fluorouracil was compared to gemcitabine as an adjuvant therapy after pancreatic resection (Neoptolemos et al. 2010). No significant differences in overall survival were reported. In this study, age was not found to be of prognostic significance again, suggesting that elderly patients should not be excluded from receiving adjuvant therapy.

More recently, addition of capecitabine to gemcitabine as an adjuvant therapy was evaluated in ESPAC-4 trial. Seven hundred and twenty two patients were randomized to receive gemcitabine plus capecitabine combination or single agent gemcitabine. The median survival was 28 months in the combination group compared to 25.5 months in the gemcitabine arm. The combination arm has higher incidences of grade 3 or 4 diarrhea, infection, neutropenia, and hand-foot syndrome. The median age was 65 years. As with previous trials, age was not significantly associated with prognosis or

treatment benefit. Thus, gemcitabine plus capecitabine combination has now become standard of care treatment, but the combination treatment does have additional toxicities.

Despite the survival benefit reported with chemotherapy, adjuvant treatment is underutilized in elderly patients. Several large retrospective series have demonstrated that adjuvant therapy is less frequently administered to older patients. In a retrospective study using Surveillance, Epidemiology, and End Results (SEER)-linked Medicare data of patients >65 years of age, only 11% of the patients underwent resection and adjuvant chemotherapy (Parmar et al. 2014). The median age was 77 years in this study. Among patients who underwent resection, over half of the patients did not receive any adjuvant therapy. Younger patients were much more likely to receive chemotherapy. In another study, only 30% of the patients older than 70 years of age received adjuvant chemotherapy compared to 52% of the patients younger than 70 years (Nagrial et al. 2014). Older patients who received chemotherapy had much better survival with median survival of 21.8 months compared to 13.1 months for those who did not receive chemotherapy. Interestingly, among patients who received chemotherapy, the mean numbers of cycles administered were similar across different age groups suggesting that older patients are equally likely to complete treatment. Moreover, there is a perception that elderly patients are likely to die from non-cancer related deaths and thus may derive only limited benefit from adjuvant treatment. However, the predominant cause of deaths in both younger and older age group was pancreatic cancer and there were no significant differences between the two groups. Adjuvant therapy is the only actionable variable associated with improved survival in elderly resected pancreatic cancer patients.

Based on the above data, elderly patients should be considered for receiving adjuvant therapy. Current standard of care adjuvant therapies would include combination of gemcitabine plus capecitabine or single agent gemcitabine. Fluoropyrimidine-based chemotherapy is rarely administered in adjuvant setting in clinical practice. The role of chemoradiation therapy remains controversial. Age should not be used as a single determinant for excluding patients from receiving adjuvant therapy.

Neoadjuvant Treatment

Patients with borderline resectable and locally advanced pancreatic cancer have vascular involvement that limits the feasibility of upfront margin-negative resection **(**Table 5**)**. The definitions for these stages are not uniform and continue to evolve (Mahipal et al. 2015). With better imaging tools, patients can be more accurately staged into these subgroups. Technically, patients with locally advanced pancreatic cancer are surgically unresectable. However, with recent advancements in neoadjuvant therapy, higher response rates are observed and small proportion of patients with locally advanced disease are able to undergo surgical resection.

Patients with borderline resectable pancreatic cancer receive neoadjuvant therapy that could involve chemotherapy, radiation therapy, or combination of both. There is no standard of care for the type of neoadjuvant therapy in this patient population. The treatment regimens are usually reported from a single institution experience and are largely retrospective in nature. Only few small prospective trials have been reported and elderly patients were underrepresented in these studies (Landry et al. 2010; Kim et al. 2013b). After neoadjuvant therapy, depending on the case series, approximately 50% of the patients are able to undergo resection (Mahipal et al. 2015). There are only few reports regarding surgical resection for patients with locally advanced pancreatic cancer. Higher response rates are observed with regimens like FOLFIRINOX which has increased the likelihood of possible resection with negative margins (Hackert et al. 2016). At some centers, neoadjuvant treatment is recommended even for patients with resectable pancreatic cancer.

Only a few studies have evaluated the role of neoadjuvant therapy in elderly patients. Miura et al. reported the outcomes of neoadjuvant therapy in resectable and borderline resectable pancreatic cancer patients with ages ≥75 years (Miura et al. 2015). Similar rates of completion

of neoadjuvant therapy were observed in older and younger patients (67% vs. 73%). Older patients did have higher CACI score than younger patients. Among patients who completed neoadjuvant therapy, there were no statistically significant differences in survival. Postoperatively, older patients had a similar median duration of hospital stay compared with younger patients; however, older patients were more likely to be discharged to a skilled nursing or rehabilitation center. Older patients who completed neoadjuvant therapy experienced a survival benefit compared with those who did not complete all intended therapy. The reasons for noncompletion of neoadjuvant therapy were different in two age groups. In older patients, comorbidities and worsening performance status were most common reasons while development of metastatic disease was the predominant cause of early termination of therapy.

Neoadjuvant therapy not only helps in downstaging the tumors but also helps in excluding patients from surgical resection who will rapidly progress or soon develop metastatic disease. This approach is particularly appealing for elderly patients. The relative toxicities of neoadjuvant therapy may accentuate underlying medical comorbidities and provide for a more accurate assessment of both performance status and physiologic reserve. Further, some patients are unable to receive adjuvant therapy due to postoperative complications. Thus, for elderly patients with localized pancreatic cancer, neoadjuvant treatment can be a preferred approach.

Elderly Patients and Clinical Trials

Despite the fact that cancer disproportionately affects the elderly, most participants of clinical cancer trials are relatively young. This misrepresentation greatly affects the oncology treatment of the elderly population. It is difficult to generalize the results of pancreatic cancer trials to elderly population if there is only small proportion of elderly patients enrolled. The barriers for enrollment of patients in the trial could include patient related factors including logistics issue, lack of autonomy, and complex pharmacologic and pharmacodynamic changes; physician-related barriers including perception, cultural issue, and lack of evidence; and trial-related barriers including strict inclusion criteria and lack of proper methods for evaluating functional status (Denson and Mahipal 2014). Some of these issues can be tackled by developing geriatric focused trials, improving communication, educating clinical trialists, and using tools like CGA for functional assessment.

Age should not be the sole determinant for developing treatment plan for patients with pancreatic cancer. Pancreatic cancer is an aggressive malignancy and requires multidisciplinary approach for therapy. Clinical stage, functional status, comorbidities, and toxicities of the therapy need to be taken into account for choosing the best treatment option. Participation in the clinical trials should be encouraged especially for elderly patients. Geriatric assessment can help in decision-making process for older patients.

Gastric Cancer

Gastric cancer will have accounted for an estimated 26,370 cases and 10,730 deaths in 2016, with significantly higher incidence and mortality found in men compared to women (Siegel et al. 2016). The 5-year overall survival rate has improved significantly over the last 40 years, almost doubling during that time, but remains low at around 30%. Gastric cancer in elderly patients occurs with clinical and pathological characteristics distinct from those found in younger patients.

Gastric cancer is much more prevalent in older populations, with the highest incidence in patients who are $\geq$80 years. The disease is relatively uncommon in patients younger than 40, while the incidence increases with age after 40 years (Herszenyi and Tulassay 2010). Elderly patients also present with more advanced disease based on TNM stage compared to younger patients (Liang et al. 2013; Lim et al. 2013). In terms of pathological characteristics, gastric cancer in elderly

patients is more common in the lower third of the stomach; additionally, well and moderately differentiated adenocarcinoma are more common in this patient population compared to younger patients (Lim et al. 2013). In a meta-analysis including evaluation of nine retrospective clinical studies, Kong et al. found a lower male-to-female ratio in elderly patients compared to younger ones, more metastases in the peritoneum, and more diffuse type gastric cancer, but less vascular invasion (Kong et al. 2012).

Elderly patients also present with a higher number of co-morbidities compared to younger patients (Lim et al. 2013), which warrants concern regarding their ability to tolerate treatments associated with high toxicity and morbidity.

Surgery

The only potentially curative treatment for gastric cancer is resection (Saif et al. 2010; Jackson et al. 2009). However, there is concern among many providers that elderly patients, who usually present with more co-morbidities, are unable to tolerate invasive surgery without significant morbidity and mortality (Saif et al. 2010). Several studies have sought to investigate complications and outcomes in elderly populations to determine the safety and efficacy of surgical resection. Much debate has focused on the extent of resection, in particular with regards to the degree of lymph node removal (Randle et al. 2016). Standardized limited lymphadenectomy (D1) and standardized extended lymphadenectomy (D2) are the most common lymph node dissections accompanying gastrectomy **(**Table 6**).** In a D1 lymphadenectomy, the portion of the stomach invaded by tumor is removed including the greater and lesser omentum, while the spleen and pancreas are left intact unless involved by the cancer (Hartgrink et al. 2004). A D2 lymphadenectomy entails removal of the omental bursa with the front leaf of the transverse mesocolon, with the vascular pedicles of the stomach cleared (Hartgrink et al. 2004). N1 lymph nodes are classified as the perigastric lymph node stations along the lesser and greater curvature while N2 lymph nodes are those along the left gastric artery, common hepatic artery, celiac artery, and splenic artery (Hartgrink et al. 2004).

The Dutch D1D2 randomized trial prospectively evaluated outcomes in 711 patients younger than 85 years who received D2 lymphadenectomy vs. D1 lymphadenectomy for gastric adenocarcinoma (Songun et al. 2010). In their 15-year follow-up, they reported significantly lower gastric-cancer-related death (37% vs. 48%) as well as lower local recurrence (12% vs. 22%) and regional recurrence (13% vs. 19%) in the group that received D2 lymphadenectomy (Songun et al. 2010). However, D2 lymphadenectomy was also associated with significantly higher complication rate (43% vs. 25%; $p < 0.0001$), greater operative mortality (10% vs. 4%; $p = 0.004$), and higher reoperation (18% vs. 8%; $p = 0.00016$) – data that may indicate concern for extended lymphadenectomy for elderly patients, in whom complications are more poorly tolerated (Songun et al. 2010).

Since then, a number of other investigators have studied D2 resections, demonstrating both its safety and efficacy (Rausei et al. 2016; An et al. 2011). For example, a multi-institutional study comparing outcomes after D1 and D2 lymphadenectomy in 461 patients with gastric cancer found similar morbidity between both resections ($P = 0.85$), but lower mortality

Table 6 Limited vs. extended lymphadenectomy characteristics

Lymphadenectomy type	Extent of resection	Assigned lymph node stations
D1 limited lymphadenectomy	Portion of stomach invaded by tumor including the greater and lesser omentum; spleen and pancreas only if involved	Perigastric lymph node stations along lesser and greater curvature of stomach
D2 extended lymphadenectomy	D1 + anterior leaf of transverse mesocolon with vascular pedicles of stomach cleared	D1 + lymph nodes along left gastric, common hepatic, celiac, and splenic arteries

associated with D2 lymph node dissection (0.9% vs. 1.3%, $P = 0.004$) (Randle et al. 2016). Moreover, patients who underwent D2 lymphadenectomy also experienced significantly higher median overall survival for stages I–III, even after adjustment for other confounders (HR 1.5, 95%CI 1.1–2.0, $P = 0.008$) (Randle et al. 2016). Data from these studies and more have resulted in D2 lymphadenectomy – including some technical modifications – becoming standard treatment for patients undergoing resection for gastric cancer (Rausei et al. 2016; An et al. 2011).

Extent of Resection in the Elderly

Although gastrectomy with D2 lymphadenectomy is standard for resectable gastric cancer, there is concern regarding its safety in the older population (Rausei et al. 2016; An et al. 2011), which often results in elderly patients receiving D1 lymphadenectomy instead. Many studies have examined the safety and efficacy of extended lymphadenectomy specifically in the context of elderly populations with gastric cancer, with mixed results.

Emir et al. reported retrospective outcomes in 53 gastric cancer patients older than 70 years who received either D1 or D2 lymphadenectomy ($n = 28$, 52% and $n = 25$, 48%, respectively) with gastrectomy (Emir et al. 2014). The authors found significantly higher blood loss, transfusion requirement, and length of operation in patients who underwent D2 lymph node dissection compared to those who underwent D1. Other investigators have found no difference in complications from gastrectomy with D2 lymphadenectomy between elderly and younger patients, suggesting that extended lymph node dissection may be safely performed in elderly patients. Jeong et al. prospectively evaluated 383 patients with gastric cancer who underwent a gastrectomy with D2 lymphadenectomy, comparing postoperative complications and hospital courses between patients less than 70 years ($n = 282$) with patients 70 years or grater ($n = 101$) (Jeong et al. 2010). Despite having higher preoperative comorbidity rates and American Society of Anesthesiologist scores, there were no statistically significant differences in surgical complication rates or medical complication rates between elderly and non-elderly patients (18.8% vs. 17.4%, P = 0.746; 5.0% vs. 1.8%, P = 0.137).

In addition to evaluating complication rates based on extent of lymphadenectomy, investigators have also sought to evaluate whether the survival benefit associated with D2 lymphadenectomy is also present in elderly patients. Rausei et al. compared complications and outcomes in 1322 elderly and/or highly co-morbid gastric cancer patients who received D2 to those who received D1 lymphadenectomy (Rausei et al. 2016). They found similar overall postoperative morbidity rates (33.2% in D1 and 29.9% in D2). However, in elderly patients with a high number of co-morbidities, D2 lymphadenectomy resulted in higher postoperative morbidity (39.6%). In regards to survival outcomes, D2-lymph node dissection was associated with significantly increased disease-specific survival at 5 years in elderly patients, while this survival benefit was not found with regards to 5-year overall survival. However, in elderly patients with positive lymph nodes, D2-lymphadenectomy improved both 5-year overall survival and 5-year disease specific survival (29.7% vs. 21.2% in D1, p = 0.008 and 47.5% vs. 30.6% in D1, $p = 0.001$, respectively). When elderly patients with both positive lymph nodes and high co-morbidities were evaluated, the survival advantage was found only with regards to disease-specific survival.

Similarly, when comparing surgical and survival outcomes in 104 patients with gastric cancer aged 80+ years to 1,089 < 80 years, Takeshita et al. found gastrectomy with limited lymph node remove to be more common in the elderly group – however, it did not significantly impact disease-specific survival (Takeshita et al. 2013). Yoshikawa similarly evaluated limited lymphadenectomy in elderly patients with gastric cancer, stratifying patients into those 80 years or older ($n = 44$), those 70–80 ($n = 139$), and those less than 70 ($n = 219$) (Yoshikawa et al. 2016). While there was no significant difference in surgical complications between groups, limited lymphadenectomy was significantly higher in

the oldest group. Despite receiving limited lymphadenectomy at a higher rate, patients in this age group did not experience a significantly different cancer-specific survival than in patients that achieved an R0 resection, suggesting the extended procedure may be unnecessary in elderly patients.

When putting these data together, and despite some conflicting results, the extent of surgery should be geared to providing the results with the best cancer outcomes, in well-selected elderly patients. Having said that, and based on the specific patient's treatment goals and overall risk of surgery, we believe that a more limited surgery (D1 lymphadenectomy) will provide appropriate resection of the tumor with less risk of complications/mortality and a similar oncologic result. A multidisciplinary team discussion including the surgeon, medical and radiation oncologists, and a geriatrician, together with the patient, will serve as the most appropriate and comprehensive way to examine the different treatment options considering patient-, geriatric-, and tumor-related factors.

Perioperative Therapy

The current standard of care for advanced gastric cancer follows one of two courses: either perioperative chemotherapy or upfront gastrectomy followed by adjuvant chemotherapy and concurrent chemoradiation. The treatment carries high morbidity and the efficacy and tolerability in elderly has not been established in a randomized trial.

Saif et al. performed a comprehensive literature review on gastric cancer in the elderly and found similar rates of toxicity and outcome benefits between elderly patients and nonelderly patients who meet the inclusion criteria for clinical trials; however, patients enrolled in clinical trials have a better performance status and may not be applicable to the general population (Saif et al. 2010). Jin et al. found a survival benefit to adjuvant chemotherapy in their retrospective evaluation of 360 elderly gastric cancer patients (aged 65+) who underwent D2 gastrectomy, 34.7% of whom additionally received adjuvant fluoropyrimidine-based chemotherapy (Jin et al. 2013). The authors reported a significant overall survival benefit to adjuvant chemotherapy (HR 0.60, 95%CI 0.42–0.83, P = 0.003). However, stage-stratified analysis showed that this trend was specific to patients with stage III cancer (HR 0.67, 95%CI 0.47–0.97, P = 0.033) only. Additionally, chemotherapy with platinum showed no significant increase in survival compared to chemotherapy without platinum (HR 0.84, 95%CI 0.49–1.45, P = 0.530). In a similar study, Jo et al. examined adjuvant chemotherapy in patients 70 years or older who underwent D2 gastrectomy for stage II or III gastric cancer, and found median relapse-free survival to be significantly higher in patients who received adjuvant chemotherapy compared to those who did not (20.4 vs. 35.5 months, P = 0.030) (Jo et al. 2015). Given that systemic treatment is often withheld from elderly patients due to fear of the associated toxicity and doubt as to its survival benefits, these data suggest that old age should not necessarily prohibit the administration of chemotherapy and that there are clear benefits to a multimodal approach in well-selected patients.

There are a number of retrospective studies evaluating the safety of chemotherapy for resectable gastric cancer, with conflicting results. In general, when considering preoperative chemotherapy for the elderly, one must ensure this will not result in a high degree of toxicity that may preclude the ability to proceed with surgery. On the other hand, planning for an adjuvant approach may also be limited by postoperative complications and delayed surgical recovery. In this context, careful multidimensional evaluation with comprehensive geriatric tools may guide the decision of initiating perioperative chemotherapy, but understanding that based on specific treatment goals, a surgery-alone approach may prove to be appropriate for some patients in whom resection of the primary tumor may provide enough benefits and be aligned with the treatment goals of the individual patient.

Adjuvant Radiation Therapy

The benefit of adjuvant combined chemotherapy and radiation therapy has been shown in

patients who undergo gastrectomy with extended lymphadenectomy for gastric cancer. However, the question as to whether the same benefit persists in an elderly patient population is less clear (Snyder et al. 2012).

Strauss et al. evaluated the impact of combined chemoradiation with 5-Fluororacil following gastrectomy for gastric cancer on survival in patients aged 65 or older (Strauss et al. 2010). They found a lower mortality rate in patients who received adjuvant chemoradiation compared to those who underwent gastrectomy alone (hazard ratio, 0.83; 95% confidence interval, 0.71–0.98) in the 1,476 patients who were between 65 and 85 years old and survived more than 4 months. However, with age stratification, adjuvant therapy resulted in no survival advantage for IB cancer, a trend toward decreased mortality for stage II and significantly decreased mortality for stages III and IV (M0). Eighty to eighty five years was the only age category that the trend toward improved survival did not persist.

Liu et al. examined cancer-specific (CSS) survival in elderly patients aged 75 and older with locally advanced gastric cancer; they compared CSS between four different groups separated by treatment modality (adjuvant radiation, radiation alone, surgical resection alone, and no radiation or surgical resection) (K-t et al. 2017). The highest rates of CSS at 5-years were found in the adjuvant radiation group (43.8%) and the surgical resection alone group (28.5%), while 5-year CSS in the radiation alone group was only 14.9% and 1.4% in the no-radiation or surgery group (univariate log-rank test [$P < 0.001$] and multivariate Cox regression [$P < 0.001$].). Additionally, every age group (75–79 years, 80–84 years, and 85+ years) showed significantly improved survival with adjuvant radiation (all $P < 0.001$).

These results are in contrast to those found by Hoffman et al., who examined the impact of adjuvant chemoradiation on survival in 1023 elderly patients aged 65 years and older who underwent resection for non-metastatic gastric cancer, 30% of whom additionally received adjuvant concurrent chemoradiation (Hoffman et al. 2012). The receipt of adjuvant chemoradiation was significantly associated with nodal involvement ($P < 0.0001$), recent diagnosis ($P = 0.0284$), and young age ($P < 0.0001$). The authors found that there was no significant survival benefit associated with adjuvant therapy ($P = 0.3453$), suggesting that elderly patients may be safely spared the toxicity associated with adjuvant chemoradiation. More data – especially from prospective studies – are required to determine whether adjuvant radiation or chemoradiation confers any survival benefit in elderly patients with gastrectomy.

Metastatic Gastric Cancer in the Elderly

Metastatic gastric cancer also warrants evaluation of treatment options in an elderly patient population, which usually presents with more advanced disease and may not tolerate treatment as well as younger patients. Moreover, elderly patients are under-represented in metastatic gastric cancer trials. There is evidence to suggest that overall survival in patients with metastatic gastric cancer decreases with increasing age. In a study of 13,840 patients with metastatic gastric cancer, patients 44 years old or younger had an overall survival rate double of patients who were 75 years or older (6 vs. 3 months) ($P < 0.001$) (Yang et al. 2011). A number of randomized trials have evaluated the efficacy of different chemotherapeutic regimens in elderly patients with metastatic gastric cancer.

Park et al. compared S-1 with capecitabine as first-line chemotherapy in 107 elderly patients with metastatic gastric cancer in a phase II randomized trial (Park et al. 2013). The authors reported higher rates of tearing (51.9% vs. 28.3%; $P = 0.017$) and vomiting (40.4% vs. 17.0%; $P = 0.010$) in the group that received S-1 ($N = 53$) vs. capecitabine ($N = 54$), while HFS was less frequent in the S-1 group (25.0% vs. 58.5%; $P = 0.001$). There were no significant differences in overall survival between the two groups or median time to progression. The overall response rate though was higher in the group that received S-1 (28.6%; 95% CI, 15.9–41.3%). Both treatments were fairly well tolerated, with a 3.8% incidence of Grade 3/4 neutropenia in each group.

A phase II study was undertaken to assess the efficacy and tolerability of modified FOLFOX

chemotherapy in 43 elderly patients aged 70 and older, who had metastatic gastric cancer (Catalano et al. 2013). The authors found the treatment to be active, resulting in a 34.9% overall response rate with 12 patients exhibiting partial responses and 3 patients complete response. Moreover, treatment was well tolerated, with grade 3 neutropenia occurring in only 9.3% of patients ($n = 4$), vomiting in 4.6% ($n = 2$), fatigue in 7% ($n = 3$), peripheral neuropathy in 2.3% ($n = 1$) and grade 2 peripheral neuropathy in 11.6% ($n = 5$). These data suggest that the modified FOLFOX regimen used in this study is a potentially appropriate treatment modality for elderly patients with metastatic gastric cancer.

Turkeli et al. also retrospectively examined the safety and effectiveness of chemotherapy as a first-line treatment in elderly patients aged 70 years and older ($n = 89$), who had metastatic gastric cancer and received at least two cycles of chemotherapy (Türkeli et al. 2016). The authors reported a 7-month (95% CI: 5.2–8.9) median overall survival and a 5 months (95% CI: 3.7–6.3) median progression free survival in their patient population, in which 43% of the patients had controlled disease and 56.2% of patients experienced progression.

Aldemir similarly studied first-line chemotherapy in 305 elderly metastatic gastric cancer patients between 17 centers, finding it to be both safe and efficacious, reporting partial response in 26.2% and stable disease in 16.7% of the patients (Aldemir et al. 2016). The most common chemotherapy related grade 3–4 hematologic toxicity was neutropenia (22%). The number of drugs in the regimens was positively correlated with both response rates of treatment and with grade 3–4 neutropenia rates ($p = 0.004$, $p < 0.001$; respectively). Engin et al. also found docetaxel, cisplatin, and fluorouracil combination to be both tolerable and effective in patients older than 70 with metastatic gastric cancer with good performance status (Hüseyin Engin 2013).

More prospective studies are necessary to determine which particular regimen is most efficacious and tolerated with the lowest toxicity in elderly patients with metastatic gastric cancer; however, with these data it is clear that there is an oncologic benefit of systemic chemotherapy for elderly patients with metastatic gastric cancer and that overall toxicity appears to be not prohibitive.

Conclusion

As the population continues to age, a substantial increase in the number of elderly patients with primary tumors of the liver, pancreas and stomach, and secondary tumors (metastasis) to the liver is expected. At present, treatment disparities are driven in part by inaccurate perceptions of providers regarding the risks and benefits of standard of care treatment. Elderly patients often receive substandard cancer care, may not be referred to appropriate specialists, and as a result have worse outcomes. However, the available data support the safety and efficacy of aggressive and multimodal treatment of properly selected elderly patients. Whenever possible, referral to high-volume centers has been shown to improve outcomes. Furthermore, assessment of transitional outcomes upon hospital discharge and quality of life will aid clinicians in managing these complex patients. Areas for future improvement should focus on multidisciplinary and multidimensional assessment of the geriatric patient, and a more thorough and robust decision-making process, in which patient treatment goals are heavily considered and guide the different treatment alternatives when also weighing standard measures of health, tumor biology, and geriatric conditions.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Digestive Organ Aging and Cancer
- ▶ Frailty in Cancer Patients
- ▶ Population Trends in Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management

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Head and Neck Tumors in Older Adults: Systemic Treatments and Combination with Local Strategies

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Abstract

As older patients are very rarely included in clinical trials, and without any dedicated clinical trials in curative or palliative setting, there are at now no standards of treatment for elderly head and neck cancer (HNC) patients. Treatments recommended for younger patients are therefore adapted to older in the daily practice. Combinations of systemic treatments (chemotherapy or cetuximab) with radiotherapy are usually only proposed to "fit" elderly patients, without any support of evidence-based medicine.

Systemic treatment is therefore essentially discussed for recurrent and/or metastatic HNC patients. The choice between a monotherapy and a platinum-cetuximab combination is based on the *performance status*, which is not suitable and/or sufficient for elderly patients. The main difficulty is therefore to evaluate their ability to receive a systemic treatment and the evaluation of functional age using geriatric assessment is recommended. However, access to comprehensive geriatric assessment is limited in many centers, and the choice of the type of treatment is often not based on objective and reproducible criteria. As a result, vulnerable elderly HNC patients may be overtreated with a risk of increased toxicity and fit patients proposed for suboptimal treatment with a risk of failure of tumor control. Therefore, it is necessary to develop and evaluate customized treatments, based on a simple and reproducible geriatric assessment to guide practitioners to conduct the most suitable therapy. It is therefore crucial to enroll patients in dedicated therapeutics trials for elderly HNC, such as the ELAN studies, exploring new approaches such as promising immunotherapies.

This review focuses on squamous cell HNC patients.

Keywords

Elderly · Head and neck · Cancer · Systemic treatment · Checkpoint inhibitors

Introduction

In the Western countries, head and neck cancers (HNC) correspond to about 5% of cancers. Approximately, 30% of patients with HNC are aged 70 years and over, and 10% are over 80 years old (Huang et al. 2011). This population has certain specificities compared to the young population: proportion of women increased, less history of alcohol consumption, low proportion of cancers of the larynx/hypopharynx, and predominance of cancers of the oral cavity. The management of HNC in elderly patients is complex due to tumor-related symptoms and the high toxicity of standard treatments. Palliative treatments are difficult to manage in this population because of the highly symptomatic character of the evolution or the tumor recurrence (pain, dysphagia, dyspnea), which leads to a major alteration of the quality of life. It is therefore necessary to propose to elderly patients a treatment sufficiently optimized to control the tumor while avoiding the loss of autonomy. In this population with frequent comorbidities, the main challenges for physicians are therefore to cope with the benefit/risk ratio of treatments and with the tumor-related symptoms (Mountzios 2015; Sarris et al. 2014).

As only few older patients are included in clinical trials (Lewis et al. 2003; Le Saux et al. 2016), and without any results of dedicated clinical trials in curative or palliative setting, there are no standards of treatment for HNC elderly patients to date. As most of the elderly patients enrolled in randomized trials are fit and that the main data are extracted from the subgroup analyses, the results of these studies are applicable to a small proportion of elderly HNC patients (Le Saux et al. 2016).

Treatments recommended for younger HNC patients are therefore adapted to older patients in the daily practice. Radiotherapy (RT) often indicated due to inoperability factors, induces acute toxicities, whose frequency increases with age. Combinations of systemic treatments (chemotherapy (CT) or cetuximab) with RT are usually only proposed to "fit" elderly patients, without any support of evidence-based medicine. Induction therapy delivering standard docetaxel-cisplatin-5FU regimen (TPF), which is mainly used for larynx preservation, is not recommended for older patients due to its toxicity, and alternatives have not yet been validated.

A systemic treatment is therefore essentially discussed for recurrent and/or metastatic (R/M) HNC patients. The choice between a monotherapy and a platinum-cetuximab combination is based on the *performance status* (PS) for HNC patients (Gregoire et al. 2010), which is not suitable and/or sufficient for elderly patients. The main difficulty is therefore to evaluate their ability to receive a systemic treatment (Wedding et al. 2007), and the evaluation of functional age using geriatric assessment is recommended (Wildiers et al. 2014). However, the access to a comprehensive geriatric assessment (CGA) is limited in many centers, and the choice of treatment is often not based on the objective and reproducible criteria. As a result, vulnerable elderly HNC patients may be over-treated with a risk of increased toxicity and fit patients may be proposed for a suboptimal treatment with the risk of failure of tumor control. Therefore, it is necessary to develop and evaluate customized treatments, based on a simple and reproducible geriatric assessment to guide practitioners to conduct the most suitable therapy. It is therefore crucial to enroll patients in dedicated trials for elderly HNC, such as the ELAN studies (Guigay et al. 2014).

This review focuses on head and neck squamous cell cancer (HNSCC) patients.

Systemic Treatment in Curative Intent

In a curative intent, radiotherapy is delivered for patients with inoperable locally advanced HNC or for patients with early-stage cancers not suitable for surgery. In elderly patients, compliance to standard radiotherapy is poor, for two main reasons:

- The acute toxicity with acute functional mucosal reaction is increasing with age: 8% of grade 4 are usually observed in patients under 50 years old, while it is 31% in elderly patients (Pignon et al. 1996). Therefore, in frail patients, these adverse events may become a major concern, conducting to a rapid functional deterioration and a dependence.
- The number of daily transportations in a standard fractionation may imply about 35 daily travels over 7 weeks. Thus, the standard fractionation could be difficult to deliver and the treatment interruption due to fatigue is frequent in elderly patients.

Therefore, physicians have to adapt the radiotherapy schedule for elderly patients, in order to limit potential adverse events, with the risk of under-treating. The Intensity Modulated Radiation Therapy (IMRT) is recommended with adapted schedules of radiotherapy (Grenman et al. 2010).

Retrospective series reported that the radiotherapy schedule delivered to elderly patients with HNC complies with institution's guidelines in less than 50% of cases, emphasizing the need to assess the outcome of personalized/adapted treatment in geriatric patients (Italiano et al. 2008; Lusinchi et al. 1990; Ortholan et al. 2009). The major issue lies in the adaptation that should be done and, then, what could be the individual benefit/risk ratio of this tailored therapeutic decision. To date, there is a need for prospective trials evaluating the efficacy and safety of adapted radiotherapy regimens vs. standard radiotherapy in elderly patients, as the ongoing randomized phase III ELAN-RT trial (NCT01864850) which is comparing hypofractionated split course schedule and standard RT (Guigay et al. 2014). Hypofractionated split course schedules may represent a good compromise between a biologically effective dose and an acceptable tolerance in elderly patients (Hansen et al. 1997).

Systemic Treatments for Locally Advanced (LA) HNC Patients

Concomitant chemoradiotherapy (CCRT) or radiotherapy combined with cetuximab is now a standard for locally advanced HNC, despite an increased toxicity compared to RT alone (Bonner et al. 2006; Pfister et al. 2015; Pignon et al. 2009). However, according to the available data, this intensification seems to benefit only patients less than 65 years old (Bonner et al. 2010; Pignon et al. 2009) (Fig. 1).

A decreasing efficacy of CCRT with an increased incidence of noncancer-related deaths has been reported with increasing age. The acute and late radiation toxicities seem not to be increased with age, and there would be no changes in the radio or chemo-responsiveness with age (Grenman et al. 2010). Among agents combined with RT, cisplatin delivered at a dose of 100 mg/m^2 every 3 weeks is the standard one, which is not suitable for unfit patients.

Anti-epidermal growth factor receptor (anti-EGFR) antibody cetuximab combined with radiotherapy also produced a significant locoregional and survival benefit in moderately advanced HNC (Bonner et al. 2006), but an analysis of 5-year survival data did not show a benefit for elderly patients enrolled in this single randomized study (Bonner et al. 2010).

Therefore, the standard treatment remains adapted RT alone for LA HNSCC elderly patients. Immunotherapy with anti-PD(L)1 is currently tested in combination with RT. As an example, GORTEC trials including elderly patients until 80 years old are ongoing: PembroRad trial is comparing RT-pembrolizumab and RT-cetuximab for locally advanced HNSCC (NCT02707588), and REACH trial (NCT02999087) is comparing RT-avelumab-cetuximab and RT-cetuximab in a cohort of patients not eligible for cisplatin. However, the benefit of immune checkpoint blockers on outcomes of LA HNSCC patients remains unknown.

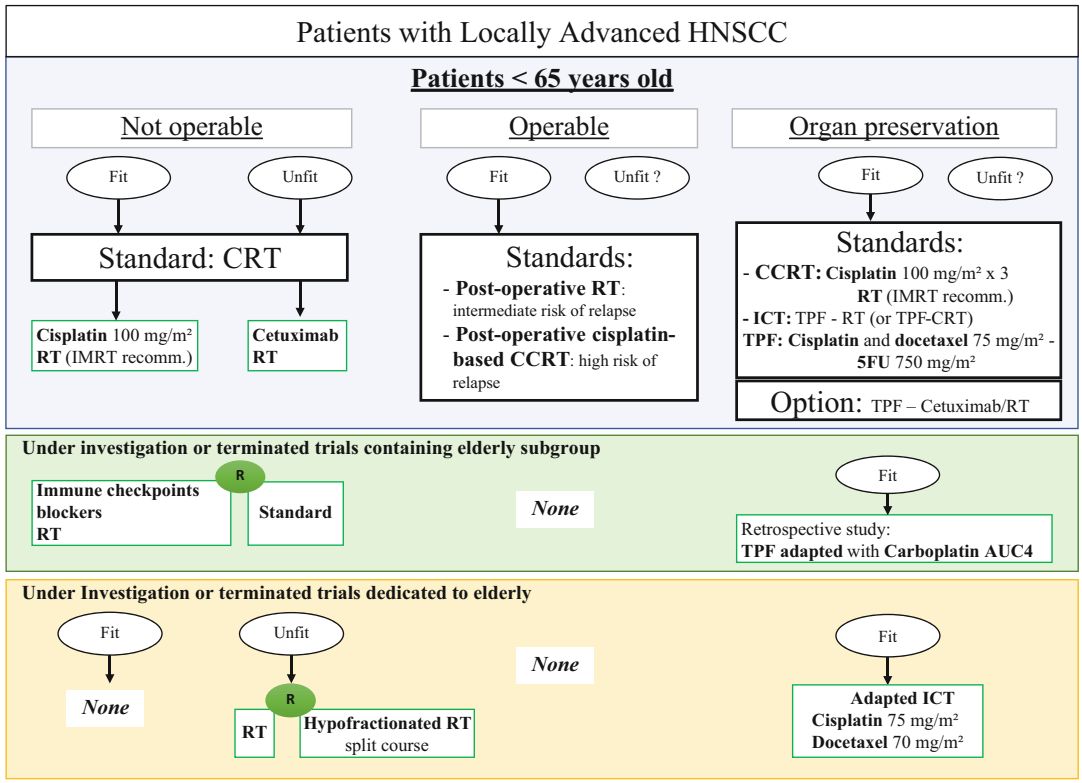

Fig. 1 Treatments of patients with locally advanced HNSCC

Postoperative Radio(Chemo)Therapy

Patients with operable locally advanced HNSCC, for which the surgical piece identifies either microscopically involved surgical margins (R1) or extra-capsular extension (ECE) in positive lymph nodes, are associated with poor prognosis. These "high-risk-for-relapse" patients benefit from the adjunction of cisplatin-based postoperative CCRT (Bernier et al. 2004; Cooper et al. 2004), but this benefit has not been demonstrated for patients at intermediate risk for relapse (Bernier et al. 2005). The role of cetuximab or other targeted therapy has not been validated in postoperative setting.

However, for elderly patients at "high risk for relapse," even evaluated as "fit," cisplatin-based CCRT is not recommended, and the standard treatment for these patients is still postoperative radiotherapy alone. According to the poor outcome of this patients (45% and 55% of 2-year estimates of disease-free survival and overall survival (OS), respectively), there is an urgent need for finding a suitable concomitant treatment to be tested in a dedicated trial (immunotherapy or other).

Induction Chemotherapy

CCRT remains the standard in locally advanced disease (Forastiere et al. 2003), but induction chemotherapy (ICT) is commonly used for larynx preservation. The standard docetaxel-cisplatin-5FU (TPF) regimen with granulocyte colony stimulating factor (GCSF) support (Pointreau et al. 2009) is not recommended for older patients due to renal and hematological toxicities (Ilie et al. 2012). The last GORTEC 2007–02 trial which compared ICT with TPF regimen and CCRT enrolled only fit patients less than 70 years old: 7% of deaths were observed, mainly related to the toxicity of the treatment (Geoffrois et al. 2016).

Alternatives to this combination have not been validated. A phase II study (44 patients) showed that a careful selection of patients over 65 years of age could allow delivering ICT with cisplatin and docetaxel (Choi et al. 2007): the overall response rate was 88%, and hematological toxicity with grade 3–4 neutropenia was 75%. The replacement of cisplatin with carboplatin may be effective, according to a single institution's retrospective analysis (Saada et al. 2012), but no prospective data currently exists to recommend it. Other combinations with cetuximab or new agents such as anti-PD(L)1 need to be explored.

Before administering an ICT, the main point is to discuss in multidisciplinary staff, the real benefit and risk of this treatment compared to CCRT, RT alone, or total laryngectomy.

Supportive Care

The dental and nutritional status of elderly patients should be systematically evaluated before starting any treatment, since rapid deterioration may occur early when delivering CCRT. Dietetic advices and oral nutritional supplements are mandatory, with a regular follow-up of oral intake during treatment. A nutrition by endoscopic gastrostomy or nasogastric feeding tube before treatment should be discussed according to weight loss and swallowing difficulties, especially if mucositis is expected. An ongoing French randomized controlled study (Brugel et al. 2014) is recruiting patients with the main objective to assess the impact of the CGA and the geriatric follow-up on the OS and the functional and nutritional status of elderly patients with HNSCC (NCT02025062). Another randomized Danish study is currently enrolling elderly patients (>70 years old) to assess the impact of an oncogeriatric intervention and follow-up at home (NCT02837679).

The management of skin toxicities related to cetuximab delivered during RT is mandatory (Russi et al. 2015).

Systemic Treatment in Palliative Intent: Recurrent and/or Metastatic (R/M) HNC Patients

There is also no standard palliative treatment for the specific population of elderly patients with R/M SCCHN, and tolerance remains the main

challenge. The main difficulty is therefore to evaluate the ability of elderly HNC patients to receive a systemic treatment (Sacco and Cohen 2015) (Fig. 2).

First-Line Therapy

Fit Elderly HNC Patients

No prospective study on first-line chemotherapy has been conducted in the elderly R/M HNC population. A retrospective analysis has been conducted on 53 fit elderly patients enrolled in two phase III ECOG trials including 399 HNSCC patients (Argiris et al. 2004). ECOG 1393 compared cisplatin-paclitaxel regimen at two dose levels, and ECOG 1395 compared cisplatin-5FU with cisplatin-paclitaxel regimen. Comparing the median OS of older and younger patients, OS did not statistically differ (5.3 vs. 8.0 months, $p = 0.17$), but chemotherapy-related toxicities were increased in elderly HNC patients, namely, nephrotoxicity, diarrhea, thrombocytopenia, and toxic deaths (13% vs. 8%, not significant). The authors recommended not to use cisplatin in elderly HNC patients and emphasized the need to conduct prospective elderly specific studies to better define therapeutic choices.

Cetuximab in combination with platinum-based chemotherapy has been tested in phase III

ECOG 5397 trial including 117 R/M HNSCC patients. Patients were randomized to receive as first-line treatment either cisplatin (100 mg/m^2 every 4 weeks) plus placebo or cisplatin plus cetuximab. For the whole population, the addition of cetuximab to cisplatin improved the overall response rate from 10% to 26% ($p = 0.03$), but did not significantly improve

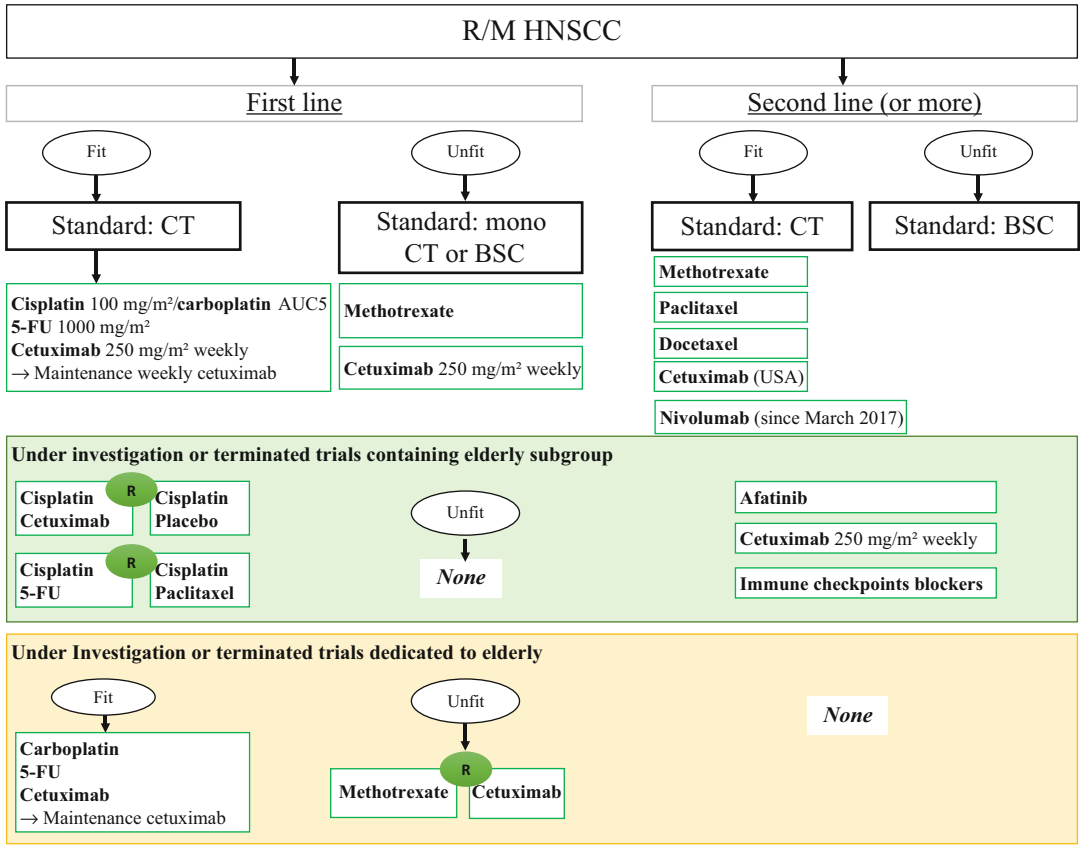

Fig. 2 Treatments of patients with recurrent and/or metastatic HNSCC

either progression-free survival (PFS) or OS. Age group (<55 years, 55–69 years, or ≥ 70 years) was not predictor of PFS or OS ($p > 0.20$). Safety was not analyzed according to age (Burtness et al. 2005).

Cetuximab and platinum-based chemotherapy combination has become a standard of care in first-line treatment of fit patients with R/M HNSCC since the publication in 2008 of the results of the randomized EXTREME study, showing that adding weekly cetuximab to every 3-week regimen combining cisplatin (100 mg/m^2) or carboplatin (AUC 5) and 5FU (1000 mg/m^2 during 96 h in continuous infusion) increased ORR, PFS, and OS (Vermorken et al. 2008). However, the number of elderly patients enrolled in the "EXTREME study" was low (77 patients aged 65 or older), and analysis of results showed a reduced clinical benefit in this subgroup of patients. Objective response rates, median OS, PFS, and time to progression (TTP) are presented in Table 1.

Usually, most of older patients receive carboplatin instead of cisplatin in the first-line R/M setting compared with younger patients (Clement et al. 2016). A prospective phase II trial is currently ongoing to evaluate the efficacy and safety of carboplatin (AUC 5)-5FU (1000 mg/m^2 during 96 h in continuous infusion)-cetuximab (500 mg/m^2 every 2 weeks) combination in fit elderly patients (Guigay et al. 2014).

Delivering chemotherapy combination in elderly HNC patients needs the use of GCSF and erythropoietin to maintain the dose intensity and reduce the hematological toxicity (Wedding et al. 2007; Bokemeyer et al. 2004).

There are, at now, no available data about the efficacy of immune checkpoints blockers in first-line therapy for R/M HNSCC. Trials testing monotherapy or combinations including older patients are ongoing, and results are eagerly awaited.

Unfit Elderly HNC Patients

In frail patients with R/M HNSCC, for which polychemotherapy tolerability is anticipated to be poor, monotherapy is usually recommended. All trials with conventional chemotherapy have failed to demonstrate any advantage over methotrexate (MTX) alone in terms of OS or PFS. Weekly methotrexate may be considered as the accepted standard treatment (proof level I, A). Cetuximab alone has a favorable toxicity profile with activity that is comparable to methotrexate alone, and is thus considered as an option (Gregoire et al. 2010).

Since there is no comparison between taxanes and methotrexate as monotherapy, it is difficult to state whether taxanes are useful in this context, as toxicity of docetaxel is increased in elderly patients (Minami et al. 2004).

However, the objective response rate (ORR) demonstrated with MTX remains usually low: less than 5% (Specenier and Vermorken 2009). Data about the tolerance of MTX in elderly HNSCC patients are missing. In previous published trials, analysis of tolerance of MTX at doses used in HNSCC did not separate the elderly

Table 1 Results of trials including recurrent and/or metastatic HNSCC elderly patients

Author, Year	Regimen	N		ORR, %		Median OS, months		Median PFS, months		Median TTP, months	
		< 65	≥ 65	< 65	≥ 65	< 65	≥ 65	< 65	≥ 65	< 65	≥ 65
First-line											
Argiris, 2004*	PF	79	23					-	-		
	PT	267	30	32.8	28.3	8.05	5.26	-	-	4.8	5.25
Vermorken, 2008	C-PF-> C	183	69	-	-	10.5	9.1	5.7	4.2	-	-
	PF	182	38	-	-	7.3	7.8	3.3	3.2	-	-
Second-line											
Vermorken, 2007	C	79	24	13	13	5.7	6.3	-	-	2.3	2.7
Clément, 2016	Afatinib	239	83	10	10.8	6.8	7.3	2.6	2.8	-	-
	MTX	116	45	5.2	6.7	6.2	6.4	1.6	2.3	-	-

ORR: Objective response rate; OS: Overall Survival; PFS: Progression -Free Survival; TTP: Time-To-Progression; PF: cisplatin-5FU; C: cetuximab; PT: cisplatin-paclitaxel; MTX: methotrexate

*Argiris et al. patient subgroups were < 70 and ≥ 70

from the rest of the population enrolled. However, some data are provided by the experience based on the treatment of other diseases. As an example, MTX is used in elderly patients with CNS lymphoma. Despite higher doses (either 1.5 g/m^2 to 3.5 g/m^2 every 3 weeks based on renal function) than those used in HNSCC (40 mg/m^2 weekly), toxicity is considered as manageable in elderly patients (Welch et al. 2012; Zhu et al. 2009). Despite their advanced age, most patients in these studies tolerated therapy well. No one developed nephrotoxicity higher than a grade 2, and there were only two MTX dosage reductions for a transient rise in creatinine. In contrast, myelotoxicity was more common in this elderly population, a finding consistent with previous work in geriatric oncology that demonstrated an inverse association between aging and bone marrow reserve (Hurria et al. 2011). In a second study in CNS lymphoma, grade 3 or 4 toxicities in patients 70 or more years of age were uncommon (9.7% of patients). Only 4 of 31 patients (12.9%) discontinued MTX because of toxicity (Zhu et al. 2009).

Among molecular targeted therapies developed in HNC, cetuximab as monotherapy was approved in the USA in the second-line treatment after failure of a platinum-based chemotherapy, showing a 13% ORR and a median time to progression of 80 days (Vermorken et al. 2007). A recent study conducted by Maubec E. showed that, as first-line monotherapy in elderly patients with unresectable skin squamous cell carcinoma, weekly cetuximab alone was manageable and effective with prolonged responses (Maubec et al. 2011). This phase II multicenter study enrolled 36 patients with a median age of 79 years (23 pts. > 70y). Disease control rate was 69% (32% ORR). Tolerance was considered good by the authors with no cetuximab-related deaths. Grade 1 to 2 rash acneiform occurred in 78% of patients and was associated with prolonged PFS. There were three treatment-related serious adverse events: two grade 4 infusion reactions and one grade 3 cetuximab-related grade 3 interstitial pneumopathy.

As part of a combination regimen with maintenance treatment, cetuximab is usually delivered every week. Tabernero et al. conducted pharmacokinetic studies of cetuximab in patients with metastatic colorectal cancer. Cetuximab doses from 400 to 700 mg/m^2 q2w were well tolerated, and the maximum tolerated dose was not reached. Pharmacokinetic analysis demonstrated that trough plasma concentration levels for the 500 mg/m^2 q2w, 600 mg/m^2 q2W and weekly 250 mg/m^2 regimens were comparable (Tabernero et al. 2010). Based on this work and similar studies (Martin-Martorell et al. 2008; Pfeiffer et al. 2008), cetuximab 500 mg/m^2 q2w was identified as the most convenient and feasible dose in the colorectal cancer patient population. Recent trials conducted in HNSCC (Fury et al. 2011; Guigay et al. 2015, 2016) have shown that cetuximab as monotherapy every 2 weeks (500 mg/m^2) was manageable without the increase of toxicity. The central finding of these studies is that cetuximab 500 mg/m^2 q2W was well tolerated as palliative monotherapy for patients with R/M HNSCC and demonstrated comparable efficacy (11% confirmed partial response rate) as conventional dosing of cetuximab in this population. The most common cetuximab-related AEs (all grades) among treated subjects were rash, fatigue, and hypomagnesemia. Although there are no randomized trials, it seems that there are no differences in terms of efficacy (Fury et al. 2011; Guigay et al. 2015, 2016). This schedule is now widely used to decrease the frequency of infusions, especially for frail patients and long-term maintenance. For elderly patients with R/M HNSCC, cetuximab 500 mg/m^2 q2w monotherapy is an acceptable alternative regimen to conventional weekly cetuximab dosing.

In summary, the only effective drugs recommended in monotherapy in HNC are methotrexate and cetuximab. A randomized phase III study comparing these two drugs (weekly MTX and cetuximab q2w) in first-line treatment in unfit elderly patient with R/M HNSCC is currently ongoing (Guigay et al. 2014). To date, the other anti-EGFR drugs gefitinib and zalutumumab have failed to demonstrate any advantage over methotrexate (Stewart et al. 2009).

To resume, it seems reasonable, after a careful evaluation of the frailty of the elderly HNSCC patient, to propose a platinum-based combination to fit elderly patients and a monotherapy or only best supportive care (BSC) to unfit elderly patients (Peyrade et al. 2013; Sacco and Cohen 2015).

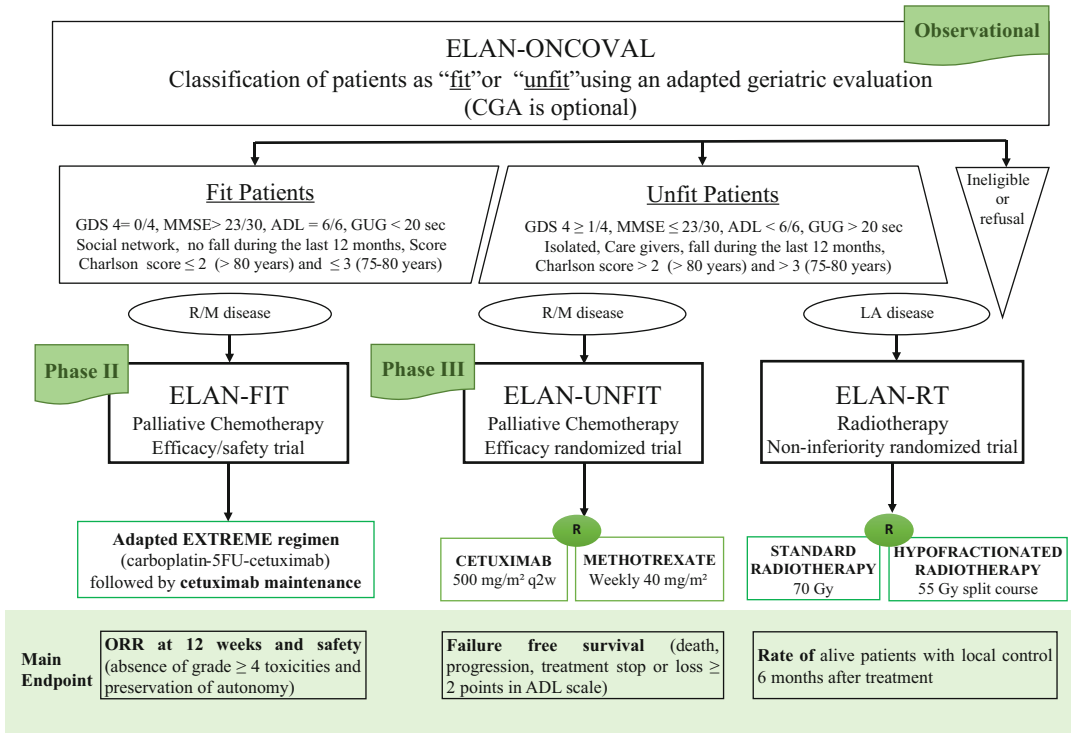

Fig. 3 ELAN studies

ELAN studies are ongoing (Fig. 3), in which elderly R/M HNSCC patients are firstly classified as fit or unfit based on an adapted geriatric evaluation (ELAN-ONCOVAL), before proposing a first-line therapy. Elderly fit patients are then proposed to be enrolled in the phase II ELAN-FIT trial evaluating the clinical benefit of cetuximab/carboplatin/5FU (NCT01884623) and elderly unfit patients in a randomized phase III trial comparing cetuximab with methotrexate monotherapy (NCT01864772) (Guigay et al. 2014). Relationships between HPV status and results of treatment have not been studied in elderly HNSCC patients. ELAN is also investigating this.

Second-Line and More Systemic Treatment

R/M HNSCC patients progressing on/after first-line platinum therapy have a dismal prognosis and treatment options are limited. Second-line treatment for R/M HNSCC based on chemotherapy (methotrexate or taxanes) has a limited efficacy, with only a low ORR and short survival (Gregoire et al. 2010; Pfister et al. 2015). Elderly HNSCC patients often do not receive these therapies due to the high risk of toxicities, and the treatment is usually resumed to BSC.

New agents should provide changes in the management of platinum-refractory HNSCC patients. Cetuximab is only approved in the United States for second-line R/M HNSCC. There are no published dedicated studies evaluating cetuximab in older R/M HNSCC patients. However, the subgroup analyses in a phase II study on cetuximab administered in patients after failure of a platinum-based therapy, reported similar efficacy outcomes in patients aged <65 or ≥ 65 years, but safety was not analyzed according to age (Vermorken et al. 2007). Please refer to Table 1.

Afatinib is an oral, irreversible, anti-EGFR agent which binds to human EGFR 1, 2, and 4 and inhibits signaling from all ErbB family

members. In the phase III LUX-Head and Neck 1 (LHN1) trial, comparing afatinib and MTX, afatinib significantly improved PFS and patient-reported outcomes in platinum-refractory R/M HNSCC patients (Machiels et al. 2015). Among 483 patients enrolled, 128 were aged ≥65 years (83 afatinib; 45 methotrexate), and 25% were aged ≥75 years categorizing the majority as "young old." Similar PFS benefit with afatinib versus methotrexate was observed in older (median 2.8 vs. 2.3 months, HR = 0.68 [95% CI 0.45–1.03], P = 0.061) and younger patients (2.6 vs. 1.6 months, HR = 0.79 [0.62–1.01], P = 0.052) (Table 1). It was associated with a trend toward improvement in OS, ORR, and some disease-related symptoms (Clement et al. 2016). The subgroup of patients aged ≥70 years were too small for meaningful analyses. Toxicities, mainly rash/acne and diarrhea, were similar between age group, and no unexpected safety findings or afatinib-related deaths occurred in older patients. However, as patients with PS ≥2 and/or significant comorbidities were excluded, older patients enrolled in this trial are considered to be fit (Clement et al. 2016).

Recently, immune checkpoint blockers (e.g., anti-CTLA4, anti-PD-1, anti-PD-L1) demonstrated promises in various cancer types including HNSCC. Recent prospective nonrandomized KEYNOTE trials showed promising efficacy of pembrolizumab in heavily pretreated R/M HNSCC patients, with prolonged survival (36% patients living at 1 year) (Seiwert et al. 2016). Notably, the administration of nivolumab (anti-PD-1) to R/M HNSCC patients refractory to platinum-based chemotherapy led to better overall survival and patient-reported outcomes compared to investigator choice (IC) treatment (methotrexate, docetaxel, or cetuximab) in the randomized CHECKMATE 141 trial (Ferris et al. 2016). That is the first randomized trial showing an improvement in OS of platinum-refractory R/M HNSCC patients, and nivolumab has obtained a FDA and European Medicines Agency (EMA) approval in this setting. At baseline, 68 pts. (28.3%) in the nivolumab arm and 45 pts. (37.2%) in the IC arm were ≥ 65 years old. Only a few patients aged >75 years were enrolled in this trial. Baseline characteristics and relative nivolumab dose intensity were generally similar across age groups. OS and tumor response benefits with nivolumab vs. IC were maintained regardless of age. The 30-month OS rates of 11.2% (<65 years) and 13.0% (≥65 years) with nivolumab were more than tripled vs. corresponding IC rates of 1.4% and 3.3%, respectively. As in the overall population, the nivolumab arm had a lower rate of treatment-related adverse events (TRAEs) vs. ICo (Saba et al. 2018). Ongoing trials with other immune checkpoint blockers will provide more information, and these first encouraging data need to be confirmed, keeping in mind that hyper-progressions during immunotherapy may occur in R/M HNSCC (Saada-Bouzid et al. 2017) and that events have been described more frequently in elderly patients (Champiat et al. 2017).

Conclusion

The optimal treatment paradigm in curative or palliative setting for elderly patients with HNSCC has not been well defined, presumably mainly because of the exclusion of these patients (based on age) from clinical trials. Confounding variables such as medical comorbidities, poor performance status, limited social support, functional status, and frailty are also involved in this fact. As a result, without any dedicated clinical trials, there are at now no standards of treatment for HNC elderly patients.

Therefore, the inclusion of elderly HNSCC patients in clinical trials including an adapted geriatric assessment should be routinely offered and encouraged. More dedicated trials for this population are also needed, in addition to the ongoing ELAN program, exploring new systemic treatments such as immunotherapy.

Cross-References

- ▶ Comorbidity in Aging and Cancer
- ▶ Decision Making and Safety Issues in Older Cancer Patients

- ▶ Immunosenescence and Cancer Immunotherapy at Old Age: Basics
- ▶ Principles of Chemotherapy in Older Adults
- ▶ Principles of Radiation Therapy in Older Adults

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Ovarian Cancer in the Older Woman

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Mohammad Hissourou III and William P. Tew

Contents

Abstract

Ovarian cancer is the seventh most common cancer in women worldwide and accounts for nearly 4% of all new cases of cancer in women. Almost half of all ovarian cancer patients are over the age of 65 at diagnosis, and over 70% of deaths from ovarian cancer are occurring in this same age group. As the population ages, the number of older women with ovarian cancer is increasing. Compared to younger women, older women with ovarian cancer receive less surgery and chemotherapy, develop worse toxicity, and have poorer outcomes. They are also significantly underrepresented in clinical trials, and thus application of standard treatment regimens can be challenging. Performance status alone has been shown to be an inadequate tool to predict toxicity of older patients from chemotherapy. The use of formal geriatric assessment tools is a

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promising direction for stratifying older patients on trials. Elderly- specific trials and adjustments to the eligibility criteria of current frontline trials may allow greater participation of older women. Modified treatment regimens and interventions to decrease morbidities in the vulnerable older population should be useful.

Keywords
Ovarian cancer · Geriatric oncology · Geriatric assessment · Neoadjuvant chemotherapy

Introduction

Cancer is recognized as a disease of older adults, with over 50% of new cases being diagnosed after age 65 and over 70% of deaths from cancer occurring in this same age group (Oberaigner et al. 2012; Edwards et al. 2002). Ovarian cancer is the seventh most common cancer in women worldwide and accounts for nearly 4% of all new cases of cancer in women (Yancik and Ries 2004). It is also the eighth most common cause of cancer death in the world.

Almost 50% of ovarian cancer is diagnosed in women over the age of 65 (Oberaigner et al. 2012). This ratio is expected to increase in the coming decades as our population ages and life expectancy improves. Outcomes steadily worsen as the age of the patient rises. One European report showed age-standardized relative survival rates at 1 year of 57% for women aged 65–69 years, 45% for those aged 70–74 years, and 33% for those aged 80–84 years (Vercelli et al. 2000).

There have been various theories put forward to account for the decreased survival in older women, including (1) more aggressive cancer with advanced age, including higher grade and more advanced stage; (2) inherent resistance to chemotherapy of cancers occurring in older women; (3) individual patient factors such as multiple concurrent medical problems, polypharmacy, functional dependence, cognitive impairment, depression, frailty, poor nutrition, and limited social support leading to greater toxicity with therapy; and (4) physician and healthcare biases toward the elderly which lead to inadequate surgery, suboptimal chemotherapy, and poor enrollment in clinical trials (Tew et al. 2014).

To improve the outcomes of our older women with ovarian cancer, we will need to better understand biologic differences between tumors of younger and older patients and develop better decision aids to discriminate those patients who will and will not tolerate standard cytoreductive surgery and chemotherapy. Our trials and reports cannot focus exclusively on the healthiest subsection of older women. We may need to modify chemotherapy dosing, scheduling, and timing (neoadjuvant or postoperative) to reduce toxicity in the more vulnerable patients. Finally, there is a need to develop interventions to improve the ability of vulnerable older women to undergo surgery and receive chemotherapy.

Geriatric Assessment

Background

Geriatric assessment (GA) provides clinicians with information about a patient's functional status (i.e., ability to live independently at home and in the community), comorbid medical conditions, cognition, psychological status, social functioning support, and nutritional status. In the cancer setting, several studies have demonstrated the predictive value of GA for estimating the risk of severe toxicity from chemotherapy and surgery (Hurria et al. 2011a, b; Kanesvaran et al. 2011).

Presurgery Assessment

A validated instrument for assessment of the older adult patient with cancer does not yet exist. However, there are several assessments under study for breast and other solid tumors, which may be applicable to women with ovarian cancer. For example, the preoperative assessment of cancer in the elderly (PACE) tool was developed to combine elements of the comprehensive geriatric assessment with surgical risk assessment tools. The authors found no significant association of age

with postoperative complications. IADL, moderate to severely elevated scores on the Brief Fatigue Inventory (BFI), and abnormal performance status (PS) were most predictive of 30-day morbidity. Lower scores for activities of daily living (ADL; basic activities such as eating, bathing, dressing), instrumental activities of daily living (IADL; more complex activities such as managing finances and shopping), and worse performance status (PS) were associated with extended hospital stay (Participants et al. 2008; Pope et al. 2006).

The NRG Oncology Cooperative Group recently completed a GA study in older women undergoing cytoreductive laparotomy surgery for newly diagnosed ovarian cancer (NRG-CC002), both as primary and interval surgery after neoadjuvant chemotherapy. The study uses a modification of the PACE tool to determine the benefit of a GA in predicting postsurgical complications. Preliminary results were presented at the SIOG meeting in 2016. Due to a study population with almost 20% patients with benign disease at the time of surgery, the tool was not predictive of postoperative complication.

Prechemotherapy Assessment

A short screening test to assess toxicity risk for older vulnerable women with ovarian cancer undergoing chemotherapy is needed. The Cancer and Aging Research Group (CARG) Geriatric Assessment (GA) and Toxicity Score is an example. CARG-GA predicted grade 3–5 chemotherapy toxicity far better than performance status (Hurria et al. 2011b). The CARG study did include a small proportion of women with ovarian cancer (50 patients, 10%), and a retrospective subgroup analysis showed that grades 3–5 toxicity occurred in 19 patients (37%). Abnormal CA125 was associated with assistance with IADL, low PS, chemotherapy toxicity, and dose reductions (Won et al. 2013).

The French Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) has developed a "Geriatric Vulnerability Score (GVS)" from a series of up-front trials in older women with ovarian cancer. This includes low albumin (<35 g/L), low ADL score (<6), low IADL score (<25), lymphopenia (<1 G/L), and a high Hospital Anxiety and Depression Score (HADS) (>14) (Falandry et al. 2013). With a cutoff score of 3, two groups of patients were identified. Compared with patients with a GVS score of 3 or higher, a lower score was associated with significantly worse overall survival (11.5 versus 21.7 months; hazard ratio [HR] 2.94), lower rate of completion of chemotherapy (65 versus 82%; odds ratio [OR] 0.41; $p = 0.04$), and higher incidence of severe adverse events (53 versus 29%; OR 2.8; $p = 0.009$), including unplanned hospitalization (53 versus 30%; OR 2.6, $p = 0.002$).

While the use of GVS score appeared helpful in selecting those at greatest risk, prospective validation studies are needed before it can be routinely utilized in clinic. The GINECO and NRG groups have developed multiple studies incorporating a GA, and these studies are currently being performed and/or results are pending.

Chemotherapy

Background

Older women are less likely to be offered standard or, for that matter, any chemotherapy. A SEER-Medicare analysis showed that among women aged 65 years or older diagnosed with ovarian cancer between the years of 2001 and 2005, 29% received no chemotherapy, 25% received only a partial course of chemotherapy, and just 47% completed their planned chemotherapy course. Those aged older than 80 years were twice as likely to not complete chemotherapy, and those with two or more comorbidities were 83% more likely to not complete chemotherapy. The authors suggested that these results show that chemotherapy may be underused in elderly women, but high-level retrospective analyses cannot determine if the "underuse" of chemotherapy might, in fact, have been medically appropriate. That first-line chemotherapy improves survival in older women with ovarian cancer and has been

shown in observational studies. Unfortunately, only half of this population received platinum-based chemotherapy. A Surveillance, Epidemiology, and End Results (SEER) review, including almost 8000 women older than 65 years with stage III or IV epithelial ovarian cancer, suggested that while patients who underwent surgery only had similar survival compared with patients who received no treatment (22 versus 17 months), patients receiving chemotherapy as the sole treatment for their disease had a better overall survival (14.4 months) (Fairfield et al. 2011). Those who received debulking surgery and optimal chemotherapy (six cycles within an appropriate timeframe) had the best overall survival (39 months), an association that was maintained after multivariate analysis controlling for demographics, cancer type, and comorbidities.

Older patients are more vulnerable to certain chemotherapy toxicities. The most common toxicities of platinum-taxane regimens, the usual first-line therapy for ovarian cancer, are cytopenias and neuropathy. This was highlighted in a large retrospective analysis of outcomes and toxicities seen in the 620 patients aged 70 years and older enrolled on GOG182, a phase III trial studying triplet-chemotherapy regimens for patients with newly diagnosed ovarian cancer (Tew et al. 2010). Older women enrolled on such a trial are likely to be healthier than the average older woman with ovarian cancer, but older patients still had poorer performance status, lower completion rates of all eight chemotherapy cycles, and increased toxicities, particularly grade 3+ neutropenia and grade 2+ neuropathy (36% vs 20% for younger women on the standard carboplatin/paclitaxel arm). Although the difference in median time to disease progression was only 1 month, older women had significantly shorter median overall survival (OS) (37 vs. 45 months, $p < 0.001$).

A number of prospective ovarian cancer trials have enrolled exclusively older women or have analyzed their older subjects separately. Modified regimens studied or being studied in vulnerable populations include increased use of growth factor, single-agent carboplatin chemotherapy, and weekly low-dose chemotherapy.

Chemotherapy: First Line

European Studies: The GINECO has performed a series of frontline chemotherapy trials for patients aged $\geq$70 years with advanced ovarian cancer and used them to develop a decision aid for identifying which patients will not tolerate aggressive chemotherapy (GVS, described above) (Falandry et al. 2013; Tredan et al. 2007; Freyer et al. 2005). The trials used carboplatin/cyclophosphamide, paclitaxel/cyclophosphamide, and single-agent carboplatin. Rates of completion of six cycles of chemotherapy were 75.6%, 68.1%, and 74%, for the three trials, respectively. Overall survival for each of the trials was 21.6 months/25.9 months/17.4 months. The GVS score is being used in the ongoing EWOC (Elderly Women in Ovarian Cancer) trial that randomizes newly diagnosed ovarian cancer patients with a GVS of three or higher to treatment with single-agent carboplatin AUC 5–6, every 3-week carboplatin AUC 5–6 plus every 3-week paclitaxel 175 mg/m^2, and carboplatin AUC 2 plus paclitaxel 60 mg/m^2 both administered weekly for 3 weeks on an every 4-week schedule.

Weekly dosing of chemotherapy is particularly of interest. Carboplatin and paclitaxel were explored in the phase II Multicentre Italian Trial in Ovarian cancer (MITO-5) study, which included 26 vulnerable patients aged $\geq$70 years old with stage IC to IV. In this study, the response rate was 38.5%, and median overall survival was 32.0 months. Toxicity was low, with 23 patients (89%) treated without experiencing serious adverse events. While not specific to older adult women, these data were confirmed in a phase III Multicentre Italian Trial in Ovarian cancer (MITO-7) study subsequently compared carboplatin (AUC 6) with paclitaxel (175 mg/m^2) every 3 weeks to a weekly carboplatin (AUC 2) and weekly paclitaxel (60 mg/m^2) regimen given over 18 weeks in over 800 women with newly diagnosed ovarian cancer at any age (median 59 and 60 years, respectively) and any stage (over 80% with stage III to IV disease). Compared with the women in the every-3-week arm, there was no difference in progression-free survival (PFS) with weekly dosing (median, 17.3

versus 18.3 months, HR 0.96, $p = 0.066$). However, weekly dosing was associated with better quality of life scores (evaluated standardized questionnaires) and lower toxicities, including grade 2 or worse neuropathy and serious (grade 3–4) hematologic toxicity. These data suggest that weekly doing of carboplatin and paclitaxel may be a more reasonable option for older patients, especially those deemed to be at higher risk for treatment-related toxicities, for whatever reason (Pignata et al. 2014).

The GINECO also collected peripheral blood lymphocytes from the patients treated on trial with single-agent carboplatin. Telomere length was estimated using standard terminal restriction fragment analysis. Patients who had a shorter than median telomere length had shorter survival and a higher risk of severe adverse events with chemotherapy (Falandry et al. 2012). There is considerable interest in whether "aging biomarkers" such as leucocyte telomere length, p16INK4a expression in T lymphocytes, or inflammatory cytokine expression might predict toxicities of therapy and supplement clinical measures of function. The European Organization for Research and Treatment of Cancer (EORTC) Elderly Task Force has initiated an aging biomarkers program to test this hypothesis (Pallis et al. 2014).

US Studies: Von Gruenigen and her colleagues conducted an elderly-specific trial of women 70 years and older with newly diagnosed ovarian cancer receiving first-line platinum-based chemotherapy (GOG273) (Von Gruenigen et al. 2017). Patients and their physicians selected from two different regimens: (Arm 1) every 3-week carboplatin AUC 5, paclitaxel 135 mg/m^2, and pegfilgrastim support or (Arm 2) every 3 week single-agent carboplatin AUC 5. Patients could be enrolled either after cytoreductive surgery or prior to any surgical intervention. One hundred fifty-two women enrolled into Arm 1 and 60 into Arm 2. Women on Arm 2 (single-agent carboplatin) were older, had lower performance status, had lower IADL scores, and were more likely to receive chemotherapy prior to surgery and less likely to complete all four cycles without dose reduction or a more than 7-day delay. However, in general, overall completion of four cycles of chemotherapy was high (Arm 1: 92% and Arm 2: 75%). After adjusting for age and PS, baseline IADL was independently associated with the choice of regimen ($p = 0.035$). The baseline IADL score was not found to be associated with completion of four cycles of chemotherapy without dose reduction or delays ($p = 0.21$) but was associated with completion of four cycles of chemotherapy regardless of dose reduction and delay ($p = 0.008$) and toxicity, with the odds ratio (OR) of grade 3+ toxicity decreasing 17% (OR: 0.83; 95% CI: 0.72–0.96; $p = 0.013$) for each additional activity in which the patient was independent. After adjustment for chemotherapy regimen, IADL was also associated with overall survival ($p = 0.019$) for patients receiving CP. This study highlights the importance of IADL scores in pretreatment assessment.

After Arm 1 and 2 completed enrollment, Tew and colleagues explored the widely used dose-dense paclitaxel regimen. Patients were treated with carboplatin (AUC5) every 3 weeks and dose-reduced weekly paclitaxel (60 mg/m^2) on an every 3-week cycle; this arm was designed to test the hypothesis that the geriatric assessment score can predict toxicity to chemotherapy. Enrollment is complete; final results are being prepared for manuscript.

Neoadjuvant Chemotherapy (NACT)

NACT is the delivery of chemotherapy prior to cytoreduction surgery (CRS). NACT use is gaining popularity in both the USA and Europe, particularly for older and frail patients, because it is associated with less surgical toxicity. In an analysis of Medicare patients with stage II–IV ovarian cancer who survived at least 6 months from diagnosis, the use of NACT had increased from 19.7% in 1991 to 31.8% in 2007 and is likely higher now (Wright et al. 2014). Randomized trial data suggest that outcomes with NACT and primary surgery are similar overall, though different subgroups may benefit from different approaches. A prospective randomized study of NACT from the EORTC (Vergote et al. 2010) randomly assigned 632 patients with newly diagnosed

stage IIIC or IV epithelial ovarian cancer to either primary CRS followed by six cycles of platinum-based chemotherapy or three cycles of platinum-based NACT followed by an interval CRS followed by an additional three cycles of platinum-based chemotherapy. The median age was 62 years (25–86) in the primary surgery group and 63 years (33–81) in the NACT group. Survival outcomes in the two arms were similar with a median overall survival of 29 months in the primary surgery group and 30 months in those assigned to NACT. Surgical complications were higher in the primary surgery group, with postoperative death in 2.5% vs 0.7% and infection in 8.1% and 1.7% of participants. Similar results were seen in a preliminary report from the MRC CHORUS trial, which involved an identical randomization and showed 12-month survival rates of 70% for primary surgery and 76% for NACT (Kehoe et al. 2013). Exploratory subgroup analyses of the EORTC trial did not show differences in benefit by age: 5-year survival rates of patients over the age of 69 ($n = 166$) were 20% with primary surgery and 18% with NACT (van Meurs et al. 2013). Interestingly, patients with stage IV tumors and large tumor volume appeared to do better with NACT, while patients with low-tumor burden appeared to do better with primary surgery.

Intraperitoneal Chemotherapy

Intraperitoneal (IP) chemotherapy has shown a survival benefit in multiple randomized trials of patients with optimally cytoreduced ovarian cancer (Markman et al. 2001; Armstrong et al. 2006; Alberts et al. 1996). Only a small fraction of the women enrolled on these trials were over the age of 70 years. All of the randomized trials used cisplatin, which has more nephrotoxicity and ototoxicity than carboplatin. Although some reports have suggested that healthy older patients can tolerate IP chemotherapy (Tew et al. 2009), one small report on women over age 75 treated with aggressive surgery followed by hyperthermic intraperitoneal chemotherapy found a 78% morbidity rate (Cascales-Campos et al. 2014). A SEER-Medicare analysis reported that only 3.5% of ovarian cancer patients in the Medicare population received IP chemotherapy between 2005 and 2009; they did not have an increase in use of acute care services (Fairfield et al. 2014).

Chemotherapy for Recurrent Disease

Older patients with platinum-sensitive disease would seem to be a relatively favorable group; they must have both responded to and survived primary chemotherapy. However the SOCRATES retrospective review of women with platinum-sensitive disease treated in Italy from 2000 to 2002 found that greater age at recurrence was independently associated with worse survival. Despite similar recurrence-free interval, performance status, and number of disease sites, women over 70 years had a median overall survival of only 23.6 months from recurrence versus 30.7 months for younger women. Older women also had less secondary surgery, more frequent single-agent chemotherapy, and lower response rates to chemotherapy (67.2% vs 46.5%) (Pignata et al. 2009).

For patients with platinum-sensitive disease in general, randomized trials show a PFS advantage to a doublet combination with carboplatin and either paclitaxel, gemcitabine (Pfisterer et al. 2006), or liposomal doxorubicin (Pujade-Lauraine et al. 2010) versus treatment with carboplatin alone, and platinum-based doublet therapy is therefore standard. However, an overall survival benefit has been seen only on the ICON-4 trial with the addition of paclitaxel, and a substantial number of patients on that trial had not received paclitaxel in frontline therapy, so single-agent carboplatin remains a viable option for frailer patients (Parmar et al. 2003). Choice of regimen is often based on the toxicity profile, and in older patients, gemcitabine can produce higher rates of cytopenias and paclitaxel higher rates of neuropathy. A subset analysis of patients aged 70 years and older treated on the CALYPSO trial (carboplatin/paclitaxel (CP) versus carboplatin/liposomal doxorubicin (CD)) showed that elderly patients completed the planned six cycles at the

same rate as younger patients (79% for CP and 82% for CD) and had similar rates of hematologic toxicity. Grade 2 or greater peripheral neuropathy was greater among older patients treated with paclitaxel (36% vs 24% for younger patients), and interestingly, carboplatin hypersensitivity reactions were significantly less common in older women (Kurtz et al. 2011).

For platinum-resistant disease, chemotherapy is typically given as single agent, and responses range from 10% to 25% with a median duration from 4 to 8 months. Common options include liposomal doxorubicin, topotecan, gemcitabine, weekly paclitaxel, and vinorelbine (Tew and Lichtman 2008). Gronlund and colleagues described their experience with topotecan (1 mg/m^2 over 5 days) in 57 elderly patients and found no significant differences in toxicity profile or response between an older (>65 years) or younger (<65 years) cohort (Gronlund et al. 2002). Liposomal doxorubicin and gemcitabine are reasonable choices for older patients with platinum-resistant disease, given their relatively good toxicity profiles. However, since these chemotherapy options only offer a low chance of disease palliation, it may be reasonable to focus on better supportive measures, rather than more chemotherapy, in the setting of platinum-resistant disease. Disease progression on two consecutive lines of therapy has been recommended as a guide to stop therapy (Griffiths et al. 2011). In one study, there was a significant cost difference with no appreciable improvement in survival between ovarian cancer patients treated aggressively with chemotherapy versus those enrolled in hospice at the final months of their life. The authors suggest that earlier hospice enrollment is beneficial, particularly in older frail patients (Lewin et al. 2005).

Targeted Agents

The targeted agents currently of most relevance to the treatment of ovarian cancer are the Poly (ADP-ribose) polymerase (PARP) inhibitors and antiangiogenic agents, particularly bevacizumab and the antiangiogenic tyrosine kinase inhibitors.

PARP inhibitors are oral agents and have been approved for women with recurrent ovarian cancer with a BRCA somatic or germline mutation, as well as in the second remission setting as maintenance therapy for all women regardless of BRCA status. There are no elderly-specific data on PARP inhibitors, but they appear generally to be well tolerated. Toxicities of olaparib, for example, have generally included low grade fatigue, cytopenias, GI symptoms, and rash (Kaye et al. 2012). While BRCA-linked hereditary ovarian cancers, particularly BRCA1-associated cancers, tend to occur at a younger age than non-hereditary/sporadic ovarian cancer, the mean age at time of ovarian cancer diagnosis for mutation carriers ranges significantly (BRCA 1: 54 years (31–79), BRCA2: 62 years (44–77), and sporadic 63 years (25–87)) (Boyd et al. 2000). Genetic counseling and consideration of PARP inhibitor therapy are appropriate regardless of age.

Antiangiogenic agents require more caution in the older population. While the effect of bevacizumab on survival outcomes appears to be similar in older and younger patients with ovarian cancer (Burger et al. 2011), a variety of toxicities are increased in the older population. Of particular concern are vascular events. The package insert for bevacizumab as of September 2014 notes that in an exploratory pooled analysis of 1745 patients treated in five randomized controlled studies, the rate of arterial thromboembolic events in bevacizumab-treated patients was 8.5% for those aged 65 years and older versus 2.9% for those younger than 65 years of age (Insert AP 2014). Patients with a history of prior stroke or TIA should not receive bevacizumab, and close attention must be paid to blood pressure control. Mohile et al. conducted a prospective analysis of toxicity older patients receiving bevacizumab in combination with chemotherapy for colon cancer or NSCLC. The addition of bevacizumab increased toxicity, particularly grade 3 hypertension, but no geriatric assessment variables were found to be associated with increased toxicity (Mohile et al. 2013).

Anti-VEGF tyrosine kinase inhibitors are of increasing interest in ovarian cancer with recent preliminary reports of increased progression-free survival in the AGO-OVAR16 randomized trial of pazopanib (Du Bois et al. 2013) and increased

progression-free survival in two trials using cediranib (Ledermann et al. 2013; Liu et al. 2014). While the toxicities of cediranib on these trials appeared manageable, they were substantial, including fatigue, diarrhea, and hypertension.

Class toxic effects of the anti-VEGF oral tyrosine kinase inhibitors (TKIs) appear worse in older patients. Data on older patients with other tumor types treated with sorafenib and sunitinib variably suggest higher incidences of dose reductions, neutropenia, fatigue, and gastrointestinal symptoms (Wong et al. 2011; Gonsalves and Ganti 2011). Age over 65 years predicted increased toxicity on one trial of carboplatin/paclitaxel/cediranib in lung cancer patients (Goss et al. 2010). Cediranib appears to have even greater effects on blood pressure than some of the older anti-VEGF TKIs. A phase II study of cediranib in ovarian cancer reported that women aged 65 or older had a higher average increase in systolic blood pressure by day 3 than younger women (15.9 vs 7.0 mmHg). Caution and close attention to blood pressure management will be needed in older women as this agent is more widely tested/used in ovarian cancer.

Surgery

In an analysis of over 12,000 patients, ovarian cancer patients over the age of 80 years were found to be less likely to receive surgery and less likely to have an optimal cytoreduction. They were also less likely to be treated by oncologists (Hightower et al. 1994). A report by Fairfield et al. showed that there is regional variation in ovarian cancer mortality in the Medicare population and that access to cancer-directed surgery explains some of this variation. Hospital referral region (HRR), assigned by zip code, was a significant predictor of cancer-directed surgery in a SEER-Medicare data analysis of patients with ovarian cancer, with surgery rates ranging from 53% to 88%. HRR was also a significant predictor of all-cause mortality but was no longer significant when cancer-directed surgery was added to the model (Fairfield et al. 2010). This lends support to the idea that surgery may be "underused" in older women and that this contributes to some of the poor outcomes seen in this population.

However, there is clearly substantial toxicity associated with aggressive primary surgical cytoreduction in older patients. A SEER-Medicare analysis showed that of women aged 65 and older with stage III or IV ovarian cancer who had primary cytoreductive surgery, those admitted electively ($n = 4517$) had a 30-day mortality of 5.6%, while those admitted emergently had a 30-day mortality of 20.1%. Those aged 75 and older with either stage IV disease or stage III disease and a comorbidity core of one or more had a 30-day mortality of 12.7% even when admitted electively (Thrall et al. 2011). There is also concern that toxicities of surgery may prevent older women from receiving chemotherapy. One retrospective report on 85 patients over the age of 80 undergoing cytoreductive surgery (mostly primary) showed that 13% died prior to discharge and 20% died within 60 days of surgery. Thirteen percent never received adjuvant therapy, and of those treated, 43% completed less than three cycles of therapy (Moore et al. 2008).

These and other data on the increased toxicity of primary cytoreductive surgery in the elderly have led to the increased use of NACT and interval cytoreductive surgery in older patients (see above). Although randomized trial data discussed above have suggested that survival with NACT and primary chemotherapy is similar, there are likely patients in whom primary surgery produces better outcomes. While older patients present with more poor prognostic disease, a subset can be cytoreduced to no residual disease. AGO found that rates of no residual disease after primary surgery of patients on a clinical trial were 45.1% in patients less than 50 years of age, 25.7% in patients 50–65 years, and 24.5% in patients over the age of 65 (Wimberger et al. 2006). Among patients over the age of 65, surgical outcomes generally continue to appear progressively worse with increasing age. In a series of 280 consecutive patients $\geq$65 years of age treated with primary surgery at the Mayo clinic, rates of residual disease over 1 cm were 43% in women aged 80 years or older versus 25% in women aged 65–69. Three-month mortality was 25% in women 80 years old

or older versus 4% in women aged 65–69 years (Langstraat et al. 2011).

The ability to assess who is fit enough to undergo aggressive CRS followed by chemotherapy and who should be offered an alternative pathway such as neoadjuvant chemotherapy (NACT) and interval cytoreductive surgery or primary chemotherapy alone is an unmet need. Aletti identified a high-risk group of women who do not appear to benefit from primary surgery. Risk features included stage IV disease, high initial tumor distribution, poor performance status (ASA score >= 3), poor nutritional status (albumin <3.0 g/dL), and older age (>= 75 years) (Aletti et al. 2011). Although each patient plan must be individualized, at this time, these criteria are reasonable to use as guidelines for a NACT approach. There are ongoing efforts, as described above, to develop more formalized tools to assess preoperative risk for older patients; most of them are not tested in the setting of aggressive primary cytoreduction surgery for ovarian cancer. The Gynecologic Oncology Group (GOG) will shortly begin accrual to a Preoperative GA Study (ELD1301) to determine whether a score calculated from a modified GA can predict postsurgical complications in women with ovarian cancer undergoing primary cytoreductive surgery. This score is also being tested for its value in predicting chemotherapy complications, and it would be ideal if a simple tool could be used in both presurgical and prechemotherapy settings.

Conclusion/Future Directions

In order to improve the benefit and tolerability of cancer treatment, we must develop new geriatric-specific trials and better geriatric assessment tools and encourage enrollment of older patients onto clinical trials. Age is a strong predictor of survival in ovarian cancer and often influences the treatment plan. Elderly patients, broadly defined as older than age 65 year of age, may be inappropriately not offered participation in clinical research or provided with substandard chemotherapy or surgical options. Since first-line platinum-based chemotherapy with cytoreductive surgery is a potentially curative treatment plan, all standard treatment options should be explored (intravenous, neoadjuvant, and/or intraperitoneal chemotherapy). In the future, a better understanding of the biology of aging and of tumors in older women and interventions designed to decrease the toxicity of treatment in older women will be needed. At this time, we must balance the specific needs of the older patient and be aware of the increased risk of side effects. The oncologist should clearly define the goals (palliative versus curative) and specific risks of treatment to patients and their families. As the field of geriatric oncology evolves and prospective trials tailored to older woman with ovarian cancer are developed, specific guidelines will ultimately assist in these difficult decisions.

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Lung Cancer in Older Adults: Local Treatment

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Contents

Abstract

Lung cancer is a malignancy that primarily affects the elderly. It is commonly diagnosed in patients with comorbidities who may have concerns about complications from aggressive therapies. This chapter is written for the non-oncologist to provide guidance on how best to approach elderly patients with lung cancer. An emphasis is made regarding the value of a multi-disciplinary team-based approach, given the evidence continues to evolve for an optimal approach in many clinical situations. It describes the advantages of minimally invasive thoracic surgery that have been reported in randomized clinical trials. It also summarizes the serendipitous outcomes following stereotactic radiotherapy for early stage disease that currently calls into question the time-honored belief that surgery provides the only hope for cure. A section is dedicated to the evaluation of treatment paradigms for patients with locally advanced lung cancer which has led to lower

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doses and smaller fields of radiotherapy than ever before. Finally, an update is provided regarding management options for localized small-cell lung cancer.

Introduction

Lung cancer predominantly affects the elderly and is responsible for more deaths than the next five most common cancers combined. The median age at diagnosis is 70 years, and therefore many patients present with comorbidities that introduce management challenges. Elderly patients and their providers are frequently concerned about the risks of treatment and at times may prefer observation even when a tumor is localized (Wang et al. 2012). Such an approach is not widely endorsed in the oncologic community as it often leads to rapid declines in quality of life since most elderly patients live long enough to die from uncontrolled lung cancer (Haque et al. 2018; McGarry et al. 2002).

Fortunately, significant developments in lung cancer therapies now offer treatments that are well-tolerated, even in an elderly population. There have been significant advances in thoracic surgery that have improved its safety for patients who have historically been at a high risk of perioperative complications (Armstrong et al. 2016). There have also been milestone developments in radiotherapy that call into question the time-honored belief that surgery offers the only hope for cure (Chang et al. 2015; Moghanaki and Chang 2016). Each of these life-prolonging therapies has become safer, is more available, and often offers a more favorable option than observation.

This chapter is therefore written to guide non-oncologists who are considering the referral of an elderly lung cancer patient with localized disease for surgery or radiotherapy. It emphasizes the value and importance of tissue diagnosis, of accurate staging, and of a multidisciplinary approach to management. It also provides a contemporary update of outcomes with surgery or radiotherapy, as well as the ongoing controversies.

Surgery for Early Stage Lung Cancer

The importance of an accurate diagnosis and staging workup: It is well-accepted that the suitability of any lung cancer therapy depends upon accurate diagnosis and staging. While CT and PET scans offer useful information to identify the extent of disease, they are insufficient to confirm that a given lung mass is actually a lung cancer. For this reason, lung cancer specialists uniformly endorse obtaining a tissue diagnosis whenever feasible. This offers an opportunity for histologic review to confirm malignancy, to assess the possibility of a malignancy that is not of bronchial or lung origin (e.g., metastasis, sarcoma, or lymphoma), and, when it is in fact lung cancer, to distinguish whether it is a non-small cell or small cell histology.

The least invasive strategies to confirm a pathological diagnosis include sputum cytology, bronchoscopy, and lavage. When unsuccessful, efforts should progress to moderately invasive techniques such as CT-guided needle biopsy, endobronchial ultrasound-guided needle biopsy (EBUS), esophageal ultrasound-guided needle biopsy (EUS), and navigational bronchoscopy. At times, more invasive techniques are needed and may include either a thoracoscopic-guided needle biopsy or excisional biopsy.

Once a cancer diagnosis has been confirmed, accurate staging is required to guide discussions of therapy. “Early stage disease” refers to smaller tumors that have not yet spread to regional lymph nodes that are commonly treated with surgical resection or locally ablative therapies. “Locally advanced” disease refers to scenarios where the disease has spread to the regional lymph nodes in the hilum or mediastinum that are more difficult to cure, even with combinations of chemotherapy, radiotherapy, and surgery. Finally, “metastatic” (stage IV) disease has spread to other organs and is no longer curable with currently available systemic therapies. Clearly then, therapies designed for localized disease will not be successful in the setting of locally advanced or metastatic disease, and every effort should be made to accurately stage the disease in each patient. For elderly patients confirmed to have only localized disease,

there are now several safe and effective options that can produce long-term disease-free survival with minimal risk.

The importance of surgeon expertise. Surgical resection of early stage lung cancer has been historically considered the most effective treatment for patients with early stage disease. It is frequently available, although in the USA only 25% of these procedures are performed by board-certified cardiothoracic surgeons who focus their practice on thoracic surgery (Farjah et al. 2009; Howington et al. 2013). Approximately 30% are performed by general surgeons and 45% by board-certified cardiothoracic surgeons who instead focus their practice on cardiac surgery. A surgeon's limited expertise in thoracic surgery is not trivial, is associated with less understanding of oncologic principles, and is associated with higher rates of postoperative mortality (Howington et al. 2013). Studies have shown that complications, and length of hospitalization, are reduced when thoracic or cardiothoracic surgeons vs general surgeons perform the operation (Schipper et al. 2009; Goodney et al. 2005). A recent meta-analysis reported perioperative mortality, comparing cardiothoracic or general surgeons to thoracic surgeons with specialization in lung cancer management. Respectively, the odds ratios were 0.78 (95% CI, 0.7–0.88; $P \leq 0.0001$) and 0.82 (95% CI, 0.69–0.96; $P < 0.016$) (von Meyenfeldt et al. 2012). It was notable that the improved outcomes with increased surgical expertise persist when considering that more specialized thoracic surgeons often manage sicker patients with more comorbidities (Ferraris et al. 2012). While this information should naturally give pause to any referring clinician, it should also serve as a reminder to consider the surgeon's judgment in selecting patients for resection. Both prospective and retrospective trials have demonstrated that surgical mortality rates can be as low as 0–1% with carefully selected patients (National Lung Screening Trial Research T et al. 2011; Cerfolio et al. 2016). However, when improperly selected, 30-day mortality rates can reach as high as 29%, as reported in a 2016 European study that evaluated the outcomes of over 47,000 patients (Brunelli et al. 2017).

The importance of institutional expertise. There is overwhelming evidence that lung cancer surgery outcomes are superior at high-volume centers of excellence. While historically available only at leading academic institutions, high-quality care may now be found in select community medical centers that have sufficient resources dedicated to a thoracic oncology program, in which thoracic surgeons work collaboratively via excellent lines of communication with pulmonologists, radiation oncologists, and medical oncologists each specializing in lung cancer. They are typically engaged in continuous peer-review and are well-staffed to address the continuum of care that includes patient navigation to reduce a delay to complete an evaluation for treatment, social work, and nutritional services when needed. Although the assessment of patients for thoracic surgery is conceptually straightforward, it frequently requires multiple tests and appointments for which timely coordination and efficient navigation through laboratory, pulmonary, and cardiac evaluations are beneficial. High-quality programs also typically have advanced perioperative services in anesthesia, intensive care, and respiratory therapy which can be equally important to surgical skill. This is particularly important given that large studies ($n > 70{,}000$) have demonstrated the 30-day mortality rate in patients $\geq$75 years with comorbidities can be more than four times that of patients <75 years without comorbidities (5.3% v 1.3%, $p < 0.01$) (Husain et al. 2015).

The advantages of minimally invasive surgery. Over the past several decades, technological advances such as video-assisted thoracic surgery (VATS) have been introduced as a minimally invasive approach for lung cancer. Prospective randomized trials have now measured a variety of meaningful clinical advantages with VATS when compared to a conventional open thoracotomy. This includes reduced operative time and perioperative blood loss (Bendixen et al. 2016), reduced frequency of postoperative air leaks (Kirby et al. 1995), shorter duration of epidural anesthesia and hospital stay (Bendixen et al. 2016), less postoperative pain (Bendixen et al. 2016; Long et al. 2007a, b), lower acute-phase cytokine concentrations associated with surgical

stress (Craig et al. 2001), and improvements in quality of life (Bendixen et al. 2016; Long et al. 2007a, b). Additionally, retrospective case-matched studies have found that VATS is associated with a reduced chest tube duration, reduced length of stay, reduced postoperative complications, lower rates of grade 3 complications and of pain at 3 weeks, earlier return to full preoperative activities, and a lower rate of perioperative mortality (Cattaneo et al. 2008; Demmy and Curtis 1999). These improvements have not yet been aligned with improvements in long-term survival, even considering a randomized trial specifically designed to evaluate this endpoint (Sugi et al. 2000). However, such data offer meaningful insights into the clinical gains that can be afforded by VATS for patients who present with a high risk of perioperative complications.

Concerns about surgery in any elderly patient. Despite advances in surgical care, elderly patients often harbor comorbidities that can complicate the postoperative recovery period given a limited physiological capacity to heal. This can occur even among those who are found by evidence-based risk stratification tools to be a more ideal candidate for a lung resection (Samson et al. 2016). Many of these tools underestimate the importance of impaired vision and hearing, urinary incontinence, falls, depression, poor baseline nutrition, and cognitive disorders such as dementia and delirium (Rao et al. 2016). As such, the recovery period is occasionally prolonged, can take up to months, and may even require transfer to a skilled nursing facility. In an analysis of 1007 surgically treated lung cancer patients in the CanCORS database (Cancer Care Outcomes Research and Surveillance Consortium), it was found that the risk of nursing home placement 1 year after surgery precipitously increased from 2% for patients younger than 74 years of age to 11% for patients over the age of 80 years (Billmeier et al. 2013). In addition to the continued care of patients even after they return home, protracted convalescence is often associated with financial burden and affects both patients and family. Fortunately, meaningful advances in lung cancer research have introduced nonsurgical options that offer alternative treatment strategies that may be equally effective. As described below, one of these is stereotactic radiotherapy, which should at least be presented for discussion as a treatment option to all elderly patients with localized non-small cell lung cancer.

Stereotactic Radiotherapy for Early Stage Lung Cancer

Technological advances in radiotherapy (RT). For much of the past century, lung cancer radiotherapy has been reserved for those who are medically inoperable. Its purported futility was originally declared by Graham and Singer in 1933 in their initial report of the first successful surgical resection of a lung tumor (Graham and Singer 1933). This idea became engrained in 1963 when a small randomized trial of 58 patients at the Hammersmith Hospital demonstrated the superiority of surgery versus conventional radiotherapy (Morrison et al. 1963). While this study predated computed tomography and utilized lower, palliative doses of RT that targeted "the opaque area of the lung" seen on X-rays, its results were highly influential and engrained the belief that surgical resection offered the only hope for cure. It supported lectures and publications in the literature that declared RT was "worse than useless" (Shorvon 1947). Furthermore, it impeded efforts to evaluate radiotherapy's role as an alternative to surgery for the next half-century (Timmermann 2007). As a consequence, the majority of reports in the literature that have evaluated the outcomes of radiation therapy for early stage lung cancer remained widely unfavorable, given its use was largely limited for the treatment of "surgical rejects" (Timmermann 2007).

Technological milestones in the 1990s facilitated the safe delivery of high doses of radiotherapy to moving lung tumors with a new form of treatment known as stereotactic body radiation therapy (SBRT) – also known as stereotactic ablative radiotherapy (SABR) (Blomgren et al. 1995). Improved accuracy facilitated the escalation of radiation doses to levels previously considered unsafe. With dose escalation and more accurate targeting, with only three outpatient treatments,

tumor control rates exceeding 90% were soon reported in several series (McGarry et al. 2005; Timmerman et al. 2003, 2010, 2014; Baumann et al. 2009; Fakiris et al. 2009; Hof et al. 2007; Onishi et al. 2007; Senthi et al. 2012; Guckenberger et al. 2013). Of equal interest, prospective trials have documented a 0% risk of treatment-related mortality at 5 years (Timmerman et al. 2014). In a milestone prospective single-arm trial, toxicities such as dyspnea requiring steroids, or self-limited hemoptysis, were identified after SBRT, actuarially, in 16% at 5 years. However, each case occurred within 3 years (Timmerman et al. 2010, 2014). Over time, more careful selection of patients receiving SBRT helped avoid the occurrence of any severe esophagitis. Promising outcomes were eventually reproduced in multiple centers around the world via both prospective and retrospective analyses (Baumann et al. 2009; Timmerman et al. 2010, 2014; Fakiris et al. 2009; Hof et al. 2007; Onishi et al. 2007; Senthi et al. 2012). The published results eventually contributed to the widespread acceptance of SBRT as the preferred form of radiotherapy for patients with early stage lung cancer (Howington et al. 2013), and the utilization of SBRT subsequently increased around the world (Corso et al. 2017).

The importance of technological expertise. Similar to high-quality thoracic surgery programs, centers of excellence for SBRT are not yet available everywhere. They are identified not only by the skill and knowledge of the radiation oncologist but also when appropriate technology is available with an advanced medical physics team whose expertise is essential to the safe delivery of SBRT. That is because the treatment of moving targets in the lung with high doses of SBRT is not straightforward and requires appropriate software, as well as standardized operating procedures with detailed quality assurance programs (Solberg et al. 2012). This is particularly important for tumors close to critical structures such as the spinal cord, trachea, or proximal bronchi. As discovered in the early days of lung SBRT, severe complications such as fatal hemoptysis can occur with tumors close to critical structures near the mediastinum. Thus, radiation therapy teams must be cognizant of patient selection criteria and updated recommendations that presently facilitate the safe delivery of SBRT to patients who have early, potentially curable lung cancer (Chang et al. 2014; Senan 2012).

The occasional conundrum of post-SBRT surveillance imaging. The evaluation of tumor control after SBRT is often straightforward, but not always. Serial chest CT scans every 6 months following treatment are advised, reserving positron emission tomography (PET) only for a strong suspicion of relapse or metastasis. The CT scan images commonly demonstrate diffuse radiographic changes near the initial tumor location. At times, they can be difficult to interpret, particularly for radiologists unfamiliar with the effects of high-dose radiotherapy. When uncertainties emerge, providers may develop "scanxiety" and order more frequent posttreatment imaging studies (Paul et al. 2016). A failure to appreciate post-SBRT patterns of fibrosis can lead to unnecessary invasive procedures that have included biopsies or even salvage lobectomies for benign fibrotic changes (Neri et al. 2010; Taira et al. 2014).

Proper radiographic evaluations should therefore investigate whether radiographic densities resemble a "disc-like" pattern that mimics the beam arrangement of most lung SBRT prescriptions. As illustrated in Fig. 1, these changes often appear much larger on axial slices and are better visualized on coronal and sagittal reconstructed images. Evaluations that merely consider enlarging opacities at the primary site have a specificity for recurrence of only 67% (Huang and Palma 2015). Characteristics more specific for relapse include sequential enlargement (100%), linear margin disappearance (100%), loss of air bronchogram (96%), cranio-caudal growth of $\geq$5mm and $\geq$20% (83%), enlargement after 12 months (83%), or a bulging margin (83%) (Huang and Palma 2015).

Salvage surgery for relapse. There is evidence to support the idea that long-term survival may not be compromised in patients who develop a local relapse after upfront SBRT for early stage lung cancer. Building upon the results of multiple randomized clinical trials of organ preservation for malignancies of the larynx, breast, anus,

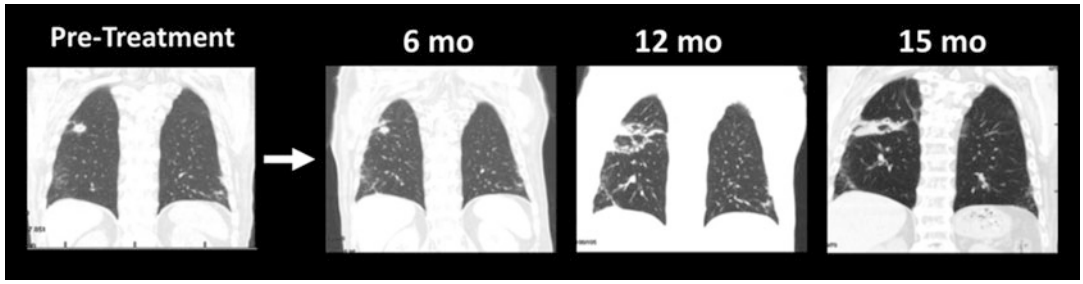

Fig. 1 The delivery of SBRT occasionally leads to substantial fibrotic changes that evolve in a disc-like pattern, mimicking the pattern of treatment beams. These changes are less concerning when viewed on sagittal, as pictured here, or coronal projections, to facilitate more accurate evaluation of cranial-caudal growth, which is highly specific for tumor progression (Huang and Palma 2015). They are best followed with shorter interval scans, with FDG-PET/CT imaging reserved for only when there is a strong suspicion for tumor progression

bladder, and extremities, there are many tumors that today are managed with upfront radiotherapy or chemoradiotherapy, with reservation of a salvage oncologic resection only for the minority who develop local-only progression (Timmerman et al. 2014). This approach has now been found to be safe in early stage lung cancer, as thoracic surgeons have found minimal to no adhesions in the thorax following SBRT to small tumors during salvage resections, even with a minimally invasive technique (Verstegen et al. 2016). This has now permitted the emergence of a new clinical scenario in the management of early stage lung cancer (Bradley 2010). Appreciating that SBRT has historically been used to treat medically inoperable patients and that the long-term survival equivalence of upfront SBRT as compared to pulmonary resection has yet to be validated, increasing numbers of operable patients are now opting for upfront SBRT while reserving salvage lung cancer surgery if relapse occurs (Timmerman et al. 2013; Senthi 2014). Such a paradigm can help many patients avoid the need for general anesthesia.

Deciding Between Surgery and Radiotherapy

Shifting referral patterns. The favorable outcomes with SBRT have created a conundrum following widespread enthusiasm for its use as an alternative to lung cancer surgery (Corso et al. 2017). This is even though its long-term efficacy compared to surgery remains a vital question. Although it has yet to be endorsed by evidence-based guidelines for patients who are operable, SBRT for lung cancer is an FDA-approved treatment that has been increasingly prescribed in healthier populations (Haque et al. 2018). This shift has facilitated the evaluation of SBRT for patients harboring less comorbidities. While it's unclear if any operable patient has compromised their survival by preferring upfront SBRT, the growing body of experience has provided a more accurate evaluation of its long-term comparative effectiveness as an alternative to surgery. As summarized in Table 1, a growing body of literature with over 1000 patients now suggests that SBRT survival rates are equivalent, or superior, to resection. While these data are encouraging, it's critical to appreciate that they do not derive from level 1 evidence, at times include patients without biopsy-confirmation of malignancy, and include limited survival data beyond median follow-up periods of about 3 years.

The equipoise to open randomized trials. In order to better understand the value of SBRT as a primary treatment option in operable patients, a total of eight prospective randomized trials have been launched since 2008, directly comparing SBRT and surgery with a primary endpoint predominantly being overall survival. Unfortunately, enrollment has been difficult given the challenges of equipoise. The first group of studies all closed prematurely due to poor accrual

Table 1 Summary of overall survival rates in operable patients with stage I NSCLC who refused surgery and were treated with SBRT instead

Survival after SBRT in operable patients with stage I NSCLC					
Author	N	Median F/U (months)	2-year OS	3-year OS	5-year OS
Timmerman et al. (2013)	26	25	84.4%		
Uematsu et al. (2001)	29	36		86%	
Lagerwaard et al. (2012)	177	32		85%	
Chang et al. (2015)	31	40		95%	
Nagata et al. (2015)	64	67		77%	
Komiyama et al. (2015)	661	35		79%	
Onishi et al. (2011)	87	55			72% (IA)
					63% (IB)
Shibamoto et al. (2015)	60	53			74%

(NCT00687986, NCT00840749, NCT01336894, and NCT01622621). A new generation of trials has since opened with innovative recruitment strategies that shed light on provider biases, a factor widely believed to have limited accrual in the first set of trials (NCT02629458, NCT01753414, NCT02468024, and NCT02984761) (Berman et al. 2016). This includes the VALOR trial which is sponsored by the Veterans Affairs Cooperative Studies Program and is the largest phase III trial ever attempted for this study population (Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy (VALOR) n.d.). With a primary endpoint of overall survival beyond 5 years, it aims to randomize 670 low-risk operable patients between an anatomic pulmonary resection (lobectomy or anatomic segmentectomy) and SBRT. The final results of each of these studies are greatly anticipated by many individuals in the lung cancer community.

The conundrum of retrospective studies. In lieu of randomized evidence, multiple comparative effectiveness research studies have compared outcomes following SBRT or surgery. The results have been mixed, revealing either an association of higher survival with surgery (Zhang et al. 2014), no difference between either treatment (Shirvani et al. 2014), or improved survival with SBRT (Chang et al. 2015). While insightful, each of these studies is best viewed as hypothesis generating with each facing the limitations of selection bias that is inherent whenever comparing overall survival between operable and inoperable cohorts. The imbalance in baseline life expectancy has been difficult to adjust for, not only because of incomplete data that often omits pulmonary function test values (e.g., in analyses using the National Cancer Database) but also because of the ongoing preference of surgeons and many radiation oncologists for reserving SBRT for patients with short life expectancy using factors that simply cannot be measured by health service researchers and data scientists. Furthermore, some of the comparative studies have included patients who received SBRT without tissue confirmation of lung cancer, and only a few have compared survival beyond 3 years.

It is incorrect to compare overall survival outcomes in carefully selected surgical patients to SBRT results in surgically unfit patients. In fact, when one compares surgically fit patients treated with SBRT with surgically fit patients treated with surgery, there are comparable results (Crabtree et al. 2014). For example, a propensity-matched comparison based on age, tumor size, comorbidity score, pulmonary function test, and location of tumor produced 56 matched pairs in an analysis by the thoracic surgeons at Washington University in St Louis. The 3-year overall survival was 52% for SBRT and 68% for surgery ($P = 0.05$). Yet, at 3 years the local recurrence-free survival was 90% versus 92% for SBRT and surgery.

The importance of shared decision-making. The lung cancer community typically benchmarks the success of its therapies to overall survival. As a result, many intellectual debates about the merits of surgery and SBRT focus on this endpoint. However, it is known that elderly patients are commonly less interested in treatments that offer

"survival at any cost." Instead, they frequently prefer clinical management strategies that prioritize quality, over quantity of life. This was best demonstrated in a 1978 landmark study of lung cancer patients that was published in the *New England Journal of Medicine* and titled "Fallacy of the Five-Year Survival in Lung Cancer" (McNeil et al. 1978). It revealed that when patients were offered either lung cancer surgery or radiotherapy, they often preferred the less invasive approach even when it was made clear that there would be an increased probability of long-term survival with surgical resection. It's important to note that if repeated today, this study might yield different findings. This is not only because the outcomes with surgery or radiotherapy have significantly improved since the 1970s but, as mentioned above, because the practice of reserving surgery for salvage was not commonly accepted at that time.

The dilemma of incomplete nodal staging. The omission of surgery in the upfront setting has raised concern that it might miss a critical opportunity for more accurate and earlier nodal upstaging in approximately 10–15% of patients who have a negative preoperative workup of the hilar and mediastinal lymph nodes (Pignon et al. 2008; Douillard et al. 2006). It's argued that patients who harbor occult nodal disease, detected only upon surgical staging, might therefore miss out on the 5% survival benefit at 5 years with postoperative chemotherapy that's been demonstrated in randomized clinical trials for patients with node-positive lung cancer (Pignon et al. 2008; Douillard et al. 2006). However, as many elderly patients are unable to tolerate postoperative chemotherapy, clinical models estimate that only 1 in 200 patients might benefit from a paradigm of operating on all patients to achieve more accurate nodal staging (Louie et al. 2015). That is because out of every 200 thoracotomies for stage I NSCLC, approximately 30 (15%) will be upstaged, of which only 20 (10%) will likely receive a course of adjuvant chemotherapy. These estimates are based on the NATCH randomized phase III trial where only two-third of node-positive patients received adjuvant chemotherapy after their thoracotomy (Felip et al. 2010). Among the 20 patients from this cohort who may eventually receive postoperative chemotherapy, a 5% survival benefit would translate into a single additional patient being alive at 5 years in this cohort of 200 patients. This benefit of a 0.5% survival gain at 5 years would naturally disappear if the perioperative mortality rate exceeded 0.5%. Meanwhile, by avoiding upfront surgery, more normal lung tissue can be preserved which may be important in the event that additional treatment(s) are needed when there is relapse or a secondary new lung cancer, which occurs in about 15–20% of patients after primary treatment (Pasini et al. 2003).

Treatment of Locally Advanced Disease

The diagnosis of locally advanced lung cancer is established when tumors have spread to the regional hilar and/or mediastinal lymph nodes. The 5-year survival rates in these patients are heavily dependent on the degree of lymph node burden and can range from 45% to 5% when patients present with stage II–III disease. For this reason, decisions to pursue definitive treatment can be more difficult in an elderly population given the less certain trade-offs of quality vs quantity of life. However, there are key clinical principles that can help optimize and individualize treatment selection for a given patient.

Locally advanced lung cancers are commonly treated with a combination of radiotherapy and chemotherapy. The sequence of these treatments matters, with randomized trials establishing superior local control and overall survival when the treatments are delivered concurrently (Curran et al. 2011). While this intensified approach has been shown to prolong survival, it frequently comes at an increased risk of complications in the lung, esophagus, and heart, which can be permanently debilitating at times. Disclosure of these potential risks, when shared with elderly patients, often leads to decisions for de-intensified therapies such as sequential chemotherapy before radiotherapy, radiotherapy without chemotherapy, and even best supportive care with palliative intent in up to 20% of patients with locally advanced disease (Dickhoff et al. 2016). Fortunately, strategies to reduce toxicity are

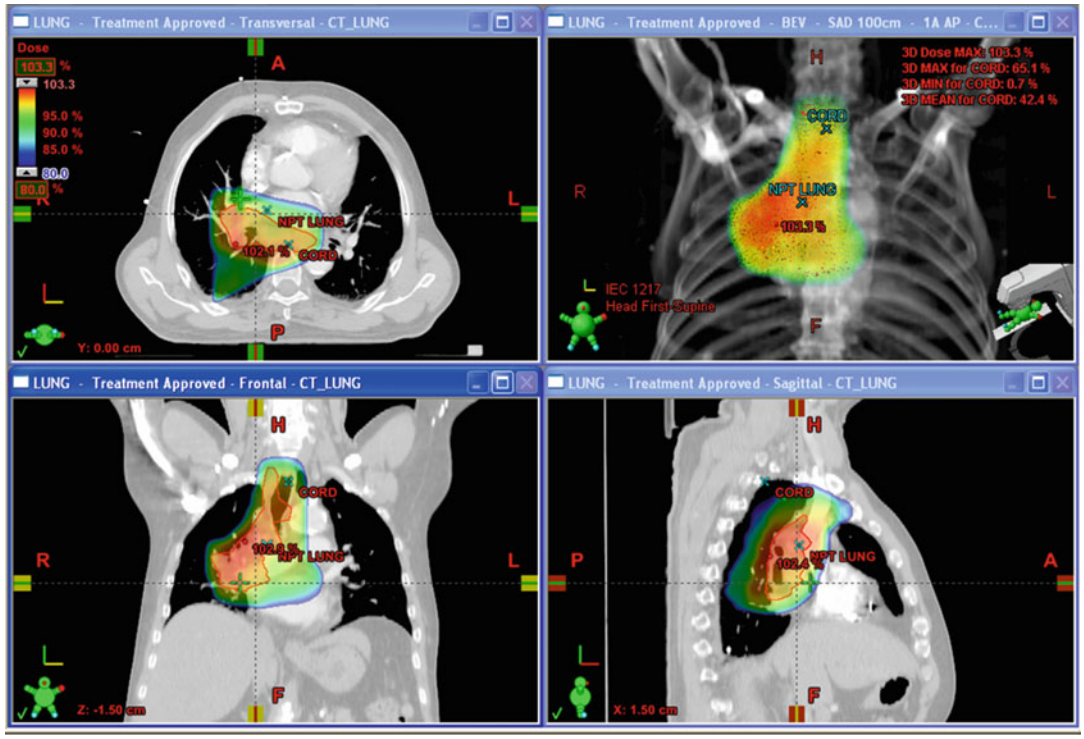

Fig. 2 This screen capture illustrates a radiotherapy treatment plan designed for a patient with locally advanced non-small cell lung cancer that has spread to multiple lymph nodes in the mediastinum. The treatment fields target the primary right perihilar mass and entire ipsilateral hilum and mediastinum. As a consequence, there is an extensive amount of esophagus in the field, and the development of treatment-related esophagitis is inevitable. The degree of esophagitis can be reduced by limiting the total dose of radiotherapy and avoiding concurrent administration of chemotherapy during radiotherapy

frequently possible depending on the tumor's size and location. These include (1) targeting only the involved site of disease (e.g., omitting elective radiation of uninvolved lymph nodes) (Rosenzweig et al. 2007), (2) limiting the total dose of radiotherapy to 60 Gy (Bradley et al. 2015), and (3) using intensity-modulated radiation therapy (IMRT) techniques to reduce the volume of normal lung, esophagus, and heart tissue exposed to therapeutic doses of radiotherapy (see Figs. 2 and 3).

Small-Cell Lung Cancer

Small-cell lung cancer (SCLC) is a more aggressive form of lung cancer and unfortunately presents more commonly at an incurable metastatic stage. However, when locally confined, it is also often controllable with concurrent chemoradiotherapy and prophylactic cranial irradiation (Miller et al. 1969). In fact, the long-term survival rates are more favorable in patients with SCLC versus NSCLC (Turrisi et al. 1999), 5-year survival exceeding 30% (Faivre-Finn et al. 2016).

Patients who are treatable with concurrent chemoradiotherapy must first be classified as having "limited stage" SCLC. This determination is made by radiation oncologists who assess whether the entire extent of disease can be safely encompassed within a tolerable radiotherapy field. As in NSCLC, radiotherapy treatment plans are commonly designed to target only the involved sites of disease (without elective coverage of uninvolved lymph nodes). The radiotherapy treatment schedule can be either twice-daily over 3 weeks or daily over 6–7 weeks, in either setting with chemotherapy. This treatment is typically followed by a short course of consolidation chemotherapy. As the blood-brain barrier can

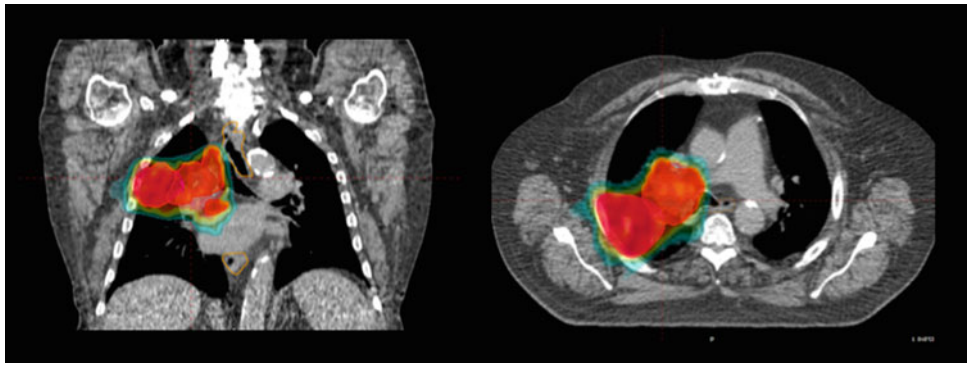

Fig. 3 This screen capture illustrates a highly conformal intensity-modulated radiation therapy (IMRT) treatment plan that avoids elective coverage of uninvolved lymph nodes. As compared to the prior figure, a shorter length of esophagus is in the field which helps minimize the degree of treatment-related esophagitis. In such a case, the concurrent administration of chemotherapy may be reasonably well-tolerated, offering a treatment that improves the probability of local tumor control and long-term survival

limit the bioavailability of chemotherapy to the brain, which is a common site of metastasis for SCLC, a course of low-dose prophylactic cranial irradiation is also routinely delivered, given its association of improved survival by an additional 5% in patients with a complete response after chemoradiotherapy (Auperin et al. 1999). When chemotherapy cannot be delivered, expectations are tempered, and radiotherapy treatment plans may often be designed with only palliative intent.

A role for surgery or SBRT in early stage SCLC. Given the aforementioned potential toxicities with concurrent chemoradiotherapy to the thorax, patients with node-negative SCLC are frequently offered a surgical resection as the definitive treatment in order to avoid the risks of radiotherapy or chemotherapy. SBRT has also been offered as an alternative to concurrent chemoradiotherapy (Stahl et al. 2017), though there are almost no direct comparisons of surgery vs SBRT for early stage SCLC to know whether there are advantages with either. Given the higher probability of occult lymph node involvement vs NSCLC, there are theoretical advantages with surgery over SBRT for early stage SCLC, if it includes a more comprehensive evaluation of the hilar and mediastinal lymph nodes. That is because SCLC has a rapid cell growth rate, and earlier detection of occult higher stage disease would expedite the appropriate adjustment of care to address a previously unrecognized locally advanced disease.

Conclusions

Elderly patients with localized lung cancer are frequently concerned about the risks of treatment and its impact on quality of life. As a consequence, many prefer observation with best supportive care. This is an approach that can lead to rapid deterioration of quality of life and premature death in patients who could have been cured with either minimally invasive surgery or radiotherapy. Each of these treatments is better tolerated than ever before and now appears to offer similar benefits. As such, a recommendation for either might be best made through an individualized approach in a multidisciplinary setting that respects patient values in a shared decision-making process (Berman et al. 2016). This is particularly important for elderly patients who are nearing the final chapters of their lives and may be no longer interested in survival at any cost.

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Lung Cancer in Older Adults: Systemic Treatment

49

Elisabeth Quoix

Contents

Abstract

Lung cancer is the first cause of death by cancer throughout the entire world. Its incidence increases with age, and thus median age at diagnosis is 70 years in the USA.

As in younger counterparts, non-small-cell lung cancer represents 85% of the cases, but squamous cell carcinoma is more frequent than in younger patients. Diagnosis is often performed at an advanced stage, and thus systemic treatment is frequently to be discussed. It is only last two decades that clinical trials devoted to elderly patients have been conducted, and until recently, treatment was often suboptimal, with poor results which contributed to nihilistic attitudes among patients, relatives, and doctors.

Regarding small cell lung cancer, the doublet carboplatin-etoposide is the most frequently used in elderly patients. For non-small-cell lung cancer, targeted therapies should be used in those patients with *EGFR* or V600E *BRAF* mutations and *ALK* or *ROS1* translocations whatever the performance status (PS). For patients without targetable mutations, carboplatin-based doublet can be used as

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frontline therapy in patients with PS 0–2. Regarding second-line therapy, the most frequently studied in elderly patients has been erlotinib. The role of checkpoint inhibitors in elderly patients is still not well established as the only data we have are subgroup analyses of phase III randomized trials with no age upper limit and with no specific clinical trials.

Keywords
Lung cancer · Elderly · Chemotherapy · Targeted therapy · Immunotherapy

Introduction

Lung cancer remains the first cause of death by cancer throughout the world. Due to the conjunction of two factors: increased life expectancy and increased incidence of cancers with age, older patients represent now half of the patients with a median age of 70 years at diagnosis in the USA (Siegel et al. 2012). The probability of developing a lung cancer beyond 70 years of age is 1 in 15 men and 1 in 20 women compared to 1 in 44 males and 1 in 58 females between 60 and 69 years (Siegel et al. 2012). Seventy years is also the cutoff most frequently used to define older adults in clinical trials (Gridelli 2001; Gridelli et al. 2003; Pallis et al. 2010a; Quoix et al. 2011). Whereas adenocarcinoma is the main histological subtype nowadays, squamous cell carcinoma remains more frequent in older patients than in their younger counterparts probably because older patients did not use filters and smoked preferentially dark tobacco. The use of filters and Virginia (blond) tobacco results in deeper inhalations favoring the development of peripherally arising lung cancers which are adenocarcinomas, whereas cigarettes with dark tobacco and no filters yield to small inhalations favoring centrally arising lung cancers (squamous cell carcinomas) (Alberg et al. 2013). However, the role of tobacco is less important in the development of lung cancers in elderly patients, and never smokers are more frequent among them than in younger counterparts. Unfortunately at diagnosis almost half of the patients with lung cancer have already a stage IV disease (Chawla et al. 2014). Also, chemotherapy, which is the cornerstone treatment in small cell lung cancer (SCLC), plays an increasing role in the treatment of non-small cell lung cancer (NSCLC). As a matter of fact, (neo)adjuvant chemotherapy is recommended for early stage (stage IIA to IIIA) disease, chemotherapy combined to radiation therapy for inoperable NSCLC (stage IIIA or IIIB) and of course in metastatic stage (stage IV) or locally advanced stage not eligible for radiation therapy (Masters et al. 2015).

Besides chemotherapy, targeted therapies represent a considerable improvement in treatment outcomes in around 15% of Caucasians (far more in Asian people) with NSCLC who exhibit driver mutations ((*EGFR* or *BRAF V600E*) or rearrangements (*ALK* or *ROS1*)). Recently checkpoint inhibitors have been shown to be of considerable interest in second-line therapy and probably as first line (Hanna et al. 2017). Regarding immunotherapy, no specific studies have been performed in older adults.

Specific Factors Helping Therapeutic Medical Decision in Elderly Patients with Lung Cancer?

The therapeutic choice is highly dependent on histological subtype, stage of the disease, and performance status (PS) and comorbidities in patients with lung cancer. For example, chemotherapy with cisplatin + etoposide is the recommended one for SCLC combined with radiation therapy for patients with limited disease stage (LD) (Jett et al. 2013). However this treatment may not be possible in patients with cardiac or renal insufficiency which preclude the use of cisplatin. In patients with stage IV NSCLC with no oncogenic driver, a cisplatin-based doublet is recommended which is not possible in patients with PS2. Thus PS is a very important decisional factor. However, in older adults, PS is not sufficient to predict the outcome of the patients, and this has been shown in several studies (Repetto et al. 2002; Maione et al. 2005). Also physiologic changes in organ function with age

do not allow, for example, the use of cisplatin in older adults. The decline of hematopoiesis may be responsible for greater hematological toxicity of chemotherapy and supports the use of hematopoietic factors which are equally efficacious in older patients (Balducci and Carreca 2002). Comorbidities (assessed usually with Charlson index) are generally speaking more frequent in elderly patients especially those linked with tobacco use and have important consequences on medical decision (Mellemgaard et al. 2015). Polymedication is also frequent in older adults because of comorbidities and addition of self-prescribed over-the-counter drugs which are not reported to the doctors (Lees and Chan 2011). This polymedication may result in interactions with systemic treatment of lung cancer inducing more toxicity and/or less efficacy.

A comprehensive geriatric assessment (CGA) is time-consuming and may not be easily feasible in a nongeriatric environment. Simplified geriatric scores have been developed such as VES-13 and G8 (Soubeyran et al. 2014) and can be used in nongeriatric departments although their sensitivity and moreover their specificity are not optimal (Hamaker et al. 2012). After geriatric assessment, older patients may be classified into three groups (Balducci and Extermann 2000). The first group is made up of patients with no serious comorbidity, who may be treated in the same way as younger patients. Group 2 is made up of patients with dependent instrumental activity daily living (IADL) and a few comorbidities. If the patients' problems are reversible, they may be treated in the same way as Group 1 patients. If they are irreversible, patients must be treated with special precautions, and dose and/or number of drugs reductions should be considered. Group 3 includes patients who are dependent, with severe comorbidities and geriatric syndromes. These patients should receive supportive care only.

However, at least two clinical trials have shown that geriatric indexes may be of prognostic value but that they have no predictive value (Quoix et al. 2011; Corre et al. 2016). Thus, the systematic use of geriatric indexes besides PS is still subject of debate.

Representativity of Elderly Patients in Clinical Trials

Older patients are underrepresented in clinical trials, and their proportion does not reflect at all the frequency of elderly patients with a given cancer (Talarico et al. 2004) This was still the case in a later review (Sacher et al. 2013). As a matter of fact, elderly patients have not been the subject of much research until the end of the 1980s. At the best, they were not excluded from clinical trials (those with no upper limit of age) or partially excluded (when an upper limit was defined, generally speaking 75 years). Even when there was no upper limit defined, most of the elderly patients included were between 70 and 75 years old (Sacher et al. 2013). Moreover, stringent inclusion criteria in those trials designed for a majority of younger patients lead to a selection of the elderly patients included and prevent of any generalizability of the results.

The first phase III study devoted to elderly patients with advanced NSCLC was published in 1999 and compared a single agent therapy vinorelbine to best supportive care in patients aged 70 years and more (Gridelli 2001). Since this study, to the best of our knowledge, only seven phase III studies performed in elderly patients with metastatic stage NSCLC were published (Frasci et al. 2000; Gridelli et al. 2003; Kudoh et al. 2006; Quoix et al. 2011; Abe et al. 2015; Tsukada et al. 2015; Corre et al. 2016), and one is ongoing in SCLC (Eba et al. 2015).

Systemic Treatment in Small Cell Lung Cancer

There have been very few studies conducted in elderly patients with small cell lung cancer, and most of them combined elderly patients and patients with poor performance status. Too many elderly patients either receive no chemotherapy but radiation therapy alone or best supportive care. In the SEER database analysis from 1992 to 2001 (Caprario et al. 2013), more than 20% of the patients aged 65 years or more did not receive chemotherapy.

The chemotherapy recommended in patients with SCLC was not modified since the 1980s and consists in four to six cycles of the combination of a platin salt with etoposide (Jett et al. 2013). The platin salt can be either cisplatin (for fit patients) or carboplatin for PS2 and/or elderly patients. Among the phase II studies devoted to elderly patients, one analyzed the PAVE combination (four cycles of intravenous cisplatin 30 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1 mg/m^2, and etoposide 100 mg/m^2 on day 1 and oral etoposide 100 mg/m^2 on day 3 and 5) in patients aged more than 65 years (median age was 72 in LS, 69 in extensive disease stage (ED) meaning that in fact there were no very old patients). Radiation therapy was delivered concomitantly for LD patients (suppression for one cycle of doxorubicin and vincristine). Median survival was 70 weeks for LD patients and 46 weeks for ED patients (Westeel et al. 1998).

Some randomized phase II or III studies have been performed comparing a lower intensity regimen (either reduced doses of combination chemotherapy schemes (Ardizzoni et al. 2005) or single agent with standard doses (Souhami et al. 1997) regimen). Again these randomized trials were not specifically devoted to elderly patients, although they represented the majority, but also to younger patients with poor PS. In the trial comparing full dose of cisplatin + etoposide (EP) to low dose of the same combination (Ardizzoni et al. 2005), median age was 73 with a range between 70 and 80 years, meaning that the use of cisplatin prevented inclusion of very old patients with standard doses regimen. In the second trial, oral etoposide was compared to standard EP alternating with cyclophosphamide, adriamycin, and vincristine. In both studies, the outcomes were poorer in the attenuated regimens with only small reduction of toxicity.

These trials are quite old reflecting that studies regarding SCLC and moreover SCLC in elderly, are very sparse.

A phase III study comparing EP to carboplatin etoposide was performed in 220 patients with ED (Okamoto et al. 2007). Ninety-two percent of the patients were ≥70 years old with a PS of 0–2, whereas 8% of the patients were less than 70 years old with a PS of 3. In this study, median age was 74 years (range 55–86, indicating that there were quite a number of very old patients included); there was no difference regarding the response rate, progression-free survival (PFS), or overall survival (OS). Toxicity was also similar except for thrombocytopenia grade 3 or 4, which was more frequent in the carboplatin arm. Despite this study, finally the combination of carboplatin + etoposide is the best studied through a number of phase I–II studies (Quoix et al. 2001; Larive et al. 2002; Fukuda et al. 2006) and is the one recommended for the treatment of SCLC in elderly patients.

Systemic Treatment in NSCLC

Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended for stage II and III disease after complete resection and nodal dissection.

In a systematic review (Cochrane database), 35 trials were identified which evaluated surgery plus adjuvant chemotherapy versus surgery alone (Burdett et al. 2015) There was a clear benefit of adding chemotherapy after surgery with a hazard ratio (HR) of 0.86 (95% CI 0.81–0.92) with an absolute increase of survival of 4% at 5 years. There was no significant effect of age in this review, and patients older than 70 years derived a similar benefit. However, again, there is no specific trial for older patients, and thus there was a selection bias of those patients included in the clinical trials.

The recommendations are to perform adjuvant chemotherapy in patients with stage II and IIIA disease (seventh classification) (Pisters et al. 2007), and the most frequently used chemotherapy scheme in the various clinical trials was cisplatin + vinorelbine. In the lung adjuvant cisplatin evaluation (LACE) meta-analysis, a specific analysis of the effect of cisplatin-based chemotherapy was performed according to various categories of age (Fruh et al. 2008). Only 9% of the patients were aged 70 or more (414 among 4584 patients included in five clinical trials comparing

surgery + cisplatin-based doublet to surgery alone). The HR was 0.86 (95% CI 0.78–0.94) for patients aged below 65 years, 1.01 (95% CI 0.85–1.21) for the category of patients aged 65–69, and 0.90 for elderly patients (95% CI O.70–1.16). The elderly patients received significantly less cycles of adjuvant chemotherapy and significantly less cisplatin dose. Although the HR is proximal to that observed in younger counterparts, the upper limit of the CI is above 1. Thus, there is an uncertain benefit for this category of patients. Moreover, almost no patients were aged more than 75 years.

Locally Advanced NSCLC

The standard treatment of locally advanced NSCLC is chemoradiation therapy as shown by meta-analysis of various clinical trials comparing radiation therapy to chemoradiation therapy (Non-small Cell Lung Cancer Collaborative Group 1995). It has also been shown that concurrent chemoradiation therapy is of benefit compared to sequential chemoradiation therapy (Auperin et al. 2010).

Whether this applies to elderly patients remains controversial as there are very limited data regarding chemoradiation therapy for locally advanced NSCLC in patients aged 70 or more. Moreover in two retrospective analyses of the SEER database and the veterans affairs cancer registry (Wang et al. 2012), around 35% of patients aged 65 or more did not receive any treatment. To the best of our knowledge, there is no specific randomized trial addressing elderly patients.

Based on the results of retrospective subgroup analyses of randomized trials including patients with no upper limit of age, the advantage of the combination of chemotherapy and radiotherapy over radiotherapy alone in elderly patients is debatable. A subgroup analysis of the Radiation Therapy Oncology Group (RTOG), ECOG, and Southwest Oncology Group (SWOG) randomized trial comparing sequential chemoradiotherapy with radiotherapy alone showed that the best median survival was observed with radiotherapy alone in patients >70 years (Yuen et al. 2000) In this study, only 50 among 381 patients (13%) were 70 years and more. In the randomized phase III trial of the Hoosier Oncology Group LUN 01-24 (Jalal et al. 2012), chemotherapy (cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 on days 1–5 and 29–33) and chest radiation consisting in 1.8 Gy daily, 5 days a week for a total of 25 fractions (45 Gy) to the primary tumor and mediastinum from day 1, followed by a boost to the primary tumor and to enlarged regional lymph nodes (1.8 Gy/day in eight fractions) were delivered to all patients. Those without evidence of progression and a PS 0–2 were then randomized to observation or consolidation docetaxel (75 mg/m^2 IV every 3 weeks for three cycles). A total of 243 patients were included between 2002 and 2006, and 166 were randomized. Elderly patients were defined as patients aged 70 years or more. Of the 242 patients included in the survival analysis, 64 were ≥70 years of age (26%). Elderly patients included 42 patients between 70 and 74 years, 17 patients between 75 and 80 years, 4 between 80 and 85 years, and 1 patient >85 years. There was no benefit of consolidation docetaxel, on the whole population and in the different age subgroups. Median and 3-year overall survival from baseline was 17.1 months (95% CI: 10.9–28 months) and 21.8% (95% CI: 11.1–34.8) in patients ≥70 years and 22.8 months (95% CI: 18.6–28.3 months) and 34% (95% CI: 26–42%) in patients <70 years, respectively ($p = 0.1461$). There was no difference in PFS according to age. During induction chemoradiation, there was a significantly higher rate of grade 3 and 4 toxicities in elderly patients (87% vs. 73%, $p = 0.02$). Among grade 3 and 4 non hematological toxicities, there was a non-significant excess of esophagitis (22% vs. 15%), infections (13% vs. 6%), and asthenia (17% vs. 6%) but a significant increase of dehydration (17% vs. 6%, $p = 0.008$) and anorexia (8% vs. 2%, $p = 0.03$). Among grade 3 and 4 hematological toxicities, elderly patients experienced significantly more neutropenia (56% vs. 39%, $p = 0.02$). Hospitalization was significantly more frequent in elderly patients (45% vs. 32%; $p = 0.03$). There was no increase in toxic deaths according to age.

Table 1 Subgroup analyses of patients aged 70 or more in non-specific clinical trials

Author (year)	Total no of patients/no patients > = 70 years	Treatment arms	Response rate <70 years/> = 70 years	Median survival time (months) <70/> = 70 years	1-year survival rate <70 years/> = 70 years
Langer et al. (2002)	574/86	CDDP + VP16 vs. CDDP + Pacli	21.5%/23.3%[a]	9.1[a]/8.5	38%[a]/29%
Lilenbaum et al. (2005)	561/155	Carbo + Pacli vs. Pacli	28%/36%	9/8	38%/33%
			15%/21%	6.8/5.8	35%/31%
Belani (2005a)	1218/401[b]	CDDP + Doc vs. Carbo + Doc vs. CDDP + VNR		11.0/12.6 9.7/9 10.1/9.9	44%/52% 37%/39% 41%/41%
Ansari et al. (2011)	1135/338	Carbo + Gem Pacli + Gem Carbo + Pacli	30.1%/28.2%/ 24.8%/24.4%[c]	8.6/8.8/6.5/7.9 §	36.5%/36.0%/ 27.2%/27.5%[d]
Blanchard et al. (2011)	616/122	CDDP + VNR and Carbo + Pacli	27%/30%	9 vs. 7 ($p = 0.04$)	40%/27%
Zukin et al. (2013)	205/74	Carbo + Pem vs. Pem	?	9.9 vs. 5.3 ($p = 0.006$)	?

Abbreviations: *CDDP* cisplatin, *VP16* etoposide, *Carbo* carboplatin, *Pacli* paclitaxel, *Doc* docetaxel, *VNR* vinorelbine, *Gem* gemcitabine, *Pem* Pemetrexed

[a]Global percent or median survival time for the two arms together

[b]401 patients aged > = 65 years

[c]Response rate by categories of age, the three arms being combined: <70 years, 70–74 years, 75–79 years, 80, and more

[d]Median survival and 1-year survival rate by same age categories, the three arms being combined: significant difference between 70 and 74 years and over

In this trial, elderly patients included were highly selected, and in the absence of studies devoted to elderly patients with locally advanced disease, combination of chemotherapy with radiation therapy should be carefully monitored in these patients. Possibly sequential chemoradiation therapy would be an acceptable alternative.

Systemic Treatment in Stage IV Disease

Chemotherapy

We have some data from randomized trials with no upper limit of age (Langer et al. 2002; Lilenbaum et al. 2005; Belani and Fossella 2005b; Blanchard et al. 2011; Ansari et al. 2011). These randomized trials are displayed on Table 1.

In those trials, either several platin-based doublets were compared between them (with mostly similar outcomes in elderly and younger counterparts, except for one study (Blanchard et al. 2011), or platin-based doublet was compared to single agent therapy in two studies dedicated to PS2 patients, the first one comparing paclitaxel alone versus carboplatin + paclitaxel (Lilenbaum et al. 2005) in 205 patients, among which 74 patients were more than 70 years old, and the second one comparing pemetrexed to carboplatin + pemetrexed in PS 2 patients with 74 among 205 being 70 years old or more (Zukin et al. 2013). In the first study, there was no benefit of survival with the doublet compared to single agent therapy, and there was no difference regarding OS between elderly patients and younger counterparts. In the second study, there was a benefit of survival in favor of the doublet in the whole population of patients and also in the elderly patient subgroup (Table 2).

However, as said above, elderly patients included in clinical trials designed for adults aged over 18 years are highly selected, and thus the results cannot be transposed to the general population of patients.

Dedicated studies for elderly patients are not so numerous. The first one was conducted by Gridelli and included 154 patients aged 70 years and more with stage IV NSCLC (Gridelli 2001). These patients were randomized between

Table 2 Phase III trials of chemotherapy dedicated to older patients with advanced NSCLC

Author (year)	Drugs	N° patients	Response rate (%)	Median survival (months)	1-year survival rate (%)	P
Gridelli (2001)	VNR	76	19.7	6.5	32	0.03
	BSC	75	–	4.9	14	
Frasci et al. (2000)	VNR	60	15	4.5	13	<0.01
	VNR+Gem	60	22	7	30	
Gridelli et al. (2003)	VNR	700	21	8.5	42	Ns
	Gem		16	6.5	28	
	VNR+Gem		18.1	7.4	34	
Kudoh et al. (2006)	VNR	92	9.9	9.9	NR	Ns
	Doc	90	22.7	14	NR	
Quoix et al. (2011)	VNR or Gem	226	10	6.2	25.4	0.0004
	Carbo + weekly Pacli	225	27	10.3	44.5	
Tsukada et al. (2015)	Doc	63	26.2	10.7	45.2	0.0384
	CDDP + Doc	63	55	17	66.6	
Abe et al. (2015)	Doc	134	24.6	14.8	58.2	Ns
	CDDP + Doc	138	34.4	13.3	54.5	
Corre et al. (2016)	CGA or standard allocation	243 251		6.1 6.4	NR NR	

Abbreviations: *VNR* vinorelbine, *BSC* best supportive care, *Gem* gemcitabine, *Carbo* carboplatin, *Doc* docetaxel, *CDDP* cisplatin, *CGA* comprehensive geriatric assessment, *ns* not significant, *NR* not reported

vinorelbine and best supportive care (BSC). There was a very significant benefit of survival in the vinorelbine arm (median OS of 28 weeks vs. 21 weeks; 1-year survival rate of 32% vs. 14%). Following this trial, a randomized study performed by the Italian group SICOG in 120 patients compared vinorelbine to the combination of vinorelbine and gemcitabine (Frasci et al. 2000). Median OS was 29 weeks in the combined arm versus 18 weeks in the vinorelbine alone arm. Surprisingly the median survival time with the doublet was that obtained in the Gridelli's study with vinorelbine alone, and the result with vinorelbine alone was about the same as observed in the best supportive care of Gridelli's study (Gridelli 2001). A larger randomized study was performed by the Multicenter Italian Lung Cancer in the Elderly Study (MILES) group in Italy comparing vinorelbine alone to gemcitabine alone and to the combination of the two drugs (Gridelli et al. 2003). A total of 700 patients were included, and there was no benefit of the doublet compared to either drug alone. In a Japanese study, vinorelbine was compared to docetaxel (Kudoh et al. 2006). Although the differences in response rate and survival were not significant (median OS of 9.9 months in the vinorelbine arm and 14 months in the docetaxel arm, response rate 9.9% vs. 22.7%), there was a numerical advantage in favor of docetaxel.

Following these trials, the recommendations published in 2010 (Pallis et al. 2010b) were to treat elderly patients with a single agent.

Two Japanese trials compared platin-based chemotherapy to docetaxel. In the first one, weekly docetaxel was compared to cisplatin plus docetaxel in 126 patients with a median age of 76 years (range 70–88) (Tsukada et al. 2015). This trial was prematurely closed on ethical grounds because in the age category, 70–74 docetaxel was found not to be an appropriate control arm. The second Japanese study (Abe et al. 2015) compared weekly docetaxel plus cisplatin to docetaxel every 3 weeks and was also prematurely closed after inclusion of 276 patients with a median age of 76 (range 70–87). After the first interim analysis, the probability that the doublet would be of benefit compared to the single agent was less than 1%, and thus the study was closed. Median OS was 14.8 months for the single agent arm and

13.3 months for the doublet with a HR of 1.18 (95% CI 0.83–1.69).

The French Intergroup of Thoracic Oncology (IFCT) conducted a randomized trial comparing monthly carboplatin + weekly paclitaxel to either gemcitabine or vinorelbine alone in 451 patients (Quoix et al. 2011) with a median age of 77 (range 70–89). There was a significant increase of PFS duration in the doublet arm compared to the monotherapy arm (6.1 months vs. 2.8 months) and of median OS (10.3 months vs. 6.2 months) with a 1-year probability of survival of 44.5% versus 24.5%. This benefit was obtained at the expense of increased toxicity grade 3–4 toxicity, especially hematologic, in the doublet arm illustrating the fact that careful monitoring of elderly patients is needed. Although there were also more toxic deaths in the doublet arm (4.4% compared to 1.4% in the monotherapy arm), the difference was not significant, and despite this, the rate of early death (within 3 months) was by far inferior in the doublet arm (16.4%) compared with the single agent arm (26.5%). Moreover, the survival benefit was observed in all subgroups (PS 0–1 and PS2, patients aged 70–80 and those >80 years, those with a body mass index <20 or >20, those with a stage III not amenable to irradiation and stage IV, those patients with a normal activity daily living index (ADL), and those in which the ADL was <6). The only factor for which there was no significant benefit of the doublet was the mini-mental score (MMS). When lower than 24, there was no benefit observed with the doublet. However, very few patients had a MMS <24.

Following this study, the recommendations regarding treatment of elderly patients with advanced stage were modified (Ganti et al. 2012) in favor of the use of carboplatin + weekly paclitaxel doublet whenever possible.

Should the treatment be decided upon a comprehensive geriatric assessment or according to standard factors (PS)? This question was the subject of a French randomized trial (Corre et al. 2016) in which the treatment allocated was decided either according to the PS and age (carboplatin-based doublet if PS 0–1 or age >75) or according to CGA (carboplatin-based doublet for fit patients, docetaxel for vulnerable patients, and BSC for frail patients. There was less toxicity in the CGA arm (but also more patients receiving only BSC) but no improvement of survival.

Maintenance therapy (continuation with pemetrexed or switch maintenance with pemetrexed) after four cycles of induction is now recommended in patients with stage IV NSCLC (Azzoli et al. 2011), but this has not been specifically studied in elderly patients. A post hoc subgroup analysis of 92 patients older than 70 years in the PARAMOUNT study (Gridelli et al. 2014) of continuation maintenance by pemetrexed (median age 73 compared to 60 years in the 447 patients less than 70 years old) showed similar benefit in PFS but no benefit in survival and higher rates of grade 3–4 hematologic toxicities with more hospitalizations and transfusions. A randomized trial comparing in patients older than 70 years maintenance therapy versus no maintenance after four cycles of monthly carboplatin and weekly paclitaxel conducted by the IFCT has just been completed with the inclusion of 522 patients, and results are pending.

Targeted Therapies

The frequency of driver mutations differs between Asian and Caucasians people but also with age. For example, ALK rearrangement in NSCLC is observed in patients with younger age than *BRAF* mutations. Driver mutations are observed in still a minority of Caucasian patients with NSCLC, but they are important to detect because of the development of targeted therapies. *EGFR* mutations are observed in about 11% of patients, *ALK* rearrangements in 4.8%, and V600E *BRAF* mutations in 1.8% as reported by the IFCT in a 1-year recruitment of near 18,000 patients (Barlesi et al. 2016). Median age of the whole population of patients analyzed was 64.5 years, range 18–98. Median ages of patients with *EGFR* mutation, *ALK* rearrangement, and V600E *BRAF* mutation were, respectively, 68.4, 61.2, and 65.9 meaning that, globally, targetable mutations or rearrangements are probably found in the same proportion of elderly and young patients.

Age should not preclude the use of targeted therapies as, although again, there are no dedicated phase III studies for elderly; subgroup analyses of the trials comparing tyrosine kinase inhibitors (TKI) to chemotherapy show that similar outcomes are obtained in elderly and younger patients (Minuti et al. 2015). In a phase II study (Inoue et al. 2015) performed in 32 patients aged >75 years with a median age of 80 years, whose tumor harbored *EGFR* mutations, response rate with erlotinib was 56.3% (95% CI 39.4–72.0%), and the disease control rate was 90.6% (95% CI 75.2–97.6%). Median progression-free survival was 15.5 months (95% CI 11.2 not reached). These results are quite similar to those obtained in younger counterparts with the same mutation.

Regarding patients without driver mutation, it has been shown that erlotinib was of interest as second-line therapy compared to BSC in the Canadian BR21 trial (Shepherd et al. 2005). Again there was no specific study devoted to elderly patients. However in the trial comparing carboplatin + weekly paclitaxel to weekly paclitaxel, second-line therapy was to be erlotinib in those patients whenever possible (Quoix et al. 2014). Erlotinib could be given to nearly 65% of the patients included in this trial, and the outcomes regarding PFS and overall survival were quite similar to those obtained in the BR 21 study (Shepherd et al. 2005). As a matter of fact, a subgroup analysis in this study of patients aged 70 or more showed similar outcomes than their younger counterparts (Wheatley-Price et al. 2008). Thus, erlotinib as second-line therapy could be considered in elderly patients with no driver mutations, although immunotherapy with checkpoint blockers might modify the paradigm (see below).

Bevacizumab has been shown to provide survival benefit in patients with stage IV disease of non-squamous cell carcinoma (Sandler et al. 2006) or only PFS benefit in the AVAIL study (Reck et al. 2010). A subgroup analysis of patients aged 65 or more in the AVAIL study showed similar benefit for these patients compared to younger counterparts (Leighl et al. 2010), but median age of this subgroup of patients was only 68 years. In a preplanned subgroup analysis of patients aged 65 and more in the single arm study assessing the safety and efficacy of first-line bevacizumab in combination with standard chemotherapy in 2212 patients, it was also shown that these patients with a mean age of 70.6 years had similar outcomes as their younger counterparts (Laskin et al. 2012). Another study using the cutoff of 70 years analyzed the outcomes of the patients aged 70 years and more in the Sandler study (Ramalingam et al. 2008) and found increased response rate, a trend toward longer PFS but no OS benefit and more severe toxicities. Thus, one should be very cautious regarding the use of bevacizumab in patients aged 70 years or more.

Immunotherapy

This point is of utmost importance as the increased incidence of cancers in elderly may be at least partly due to immune dysfunction (Ferrara et al. 2017). There is a reduced proliferative activity, reduced effector function, and reduced cytotoxic activity of T cells but also decreased numbers or impaired function of dendritic cells (DCs) and also decreased expression of the co-signaling molecules (CD80 and CD86) on aged DCs, which may contribute to the reduced capacity for T cell stimulation by DCs during aging (Tomihara et al. 2013). All these facts may lead to less efficacy of immune checkpoint blockers in elderly patients. Unfortunately, at this time, there have been no specific studies for elderly patients. Most of our knowledge regarding the potential benefit of immune checkpoint blockers in elderly patients with stage IV NSCLC comes from subgroup analyses from the majority of randomized clinical trials without upper limit of age. These trials (Borghaei et al. 2015; Brahmer et al. 2015) are those comparing nivolumab to docetaxel as second-line therapy and pembrolizumab to docetaxel (Herbst et al. 2016) as second-line therapy. Table 3 shows the age characteristics of the patients included in various randomized second-line trials with immune checkpoint blockers.

The updated recommendations of ASCO are now to use nivolumab or pembrolizumab or atezolizumab (according to the level of expression

Table 3 Phase III trials of checkpoint blockers in second line or first line

Trial	1st/2nd line	Median age range	Nb (%) of pts aged >75	HR for OS 65–74 >75
Non-squamous (Checkmate 057) docetaxel vs. nivolumab	2nd	62	43	0.63 (0.45–0.89)
		21–85	(7%)	0.90 (0.43–1.87)
Squamous (Checkmate 017)	2nd	63	29	0.56 (0.34–0.91)
Docetaxel vs. nivolumab		39–85	(11%)	1.85 (0.76–4.51)
Keynote-010 docetaxel vs. pembrolizumab	2nd	63	?	?
		?		?
Docetaxel vs. atezolizumab	2nd	64	(>65) 397	(>65)
		34–85	(46,7%)	0.66 (0.52–0.83)
Keynote-024 pembrolizumab vs. chemotherapy	1st	64.5	?	(HR for PFS <65/> = 65)
		33–90		0.61 (0.40–0.92)
				0.45 (0.29–0.70)

of PD-L1) as second-line therapy after the use of a platin-based doublet (Hanna et al. 2017). There is no specific recommendation for elderly patients, but at least until 75 years old, the same positive results were observed, and thus they should not be denied to receive this therapy.

Conclusion

Systemic treatment of elderly patients with small-cell lung cancer consists in carboplatine + etoposide 4 to 6 cycles. Whenever mediastinal radiation therapy, is indicated, it will be performed rather sequentially (after induction chemotherapy) than concomitantly.

Regarding non-small cell lung cancer, like in small-cell lung cancer, carboplatine should be used instead of cisplatin whenever a platin-based doublet is to be given. We should be very cautious with adjuvant therapy because of the absence of dedicated studies (only subgroup analyses). After 75 years, adjuvant chemotherapy should not be routinely given. For locally advanced disease, again, chemoradiation therapy should be given rather sequentially than concomitantly with careful monitoring.

For metastatic stage, if there is no driver mutation and PS is 0-2, the doublet monthly carboplatine + weekly paclityaxel is the reference with 4 cycles to be delivered. At this time, there is no published results regarding maintenance therapy in the elderly but results of the trial by IFCT studying this aspect will be presented at ESMO 2018. In case of driver mutation or rearrangement, targeted therapies can be used whatever the PS.

Regarding checkpoint inhibitors, there is no dedicated study for elderly patients although they could be included in all trials as well regarding first line or second line therapy. Taking into account the possible impact of what is called immunosenescence, dedicated studies for elderly patients are urgently needed.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Comorbidity in Aging and Cancer
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Drug Interactions in Aging and Cancer
- ▶ Frailty in Cancer Patients
- ▶ Hematopoiesis and Aging
- ▶ Immunosenescence and Cancer Immunotherapy at Old Age: Basics
- ▶ Lung Cancer in Older Adults: Local Treatment
- ▶ Population Trends in Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management
- ▶ Principles of Cancer Targeted Therapy in Older Adults
- ▶ Principles of Chemotherapy in Older Adults
- ▶ Respiratory Organ Aging and Cancer

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CNS Tumors in Older Adults

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Abstract

Primary tumors of the central nervous system (CNS) comprise a broad variety of neoplasms with specific patterns of age distribution, pathological and molecular genetic features, and outcome. Major recent advances in understanding the molecular pathogenesis of many primary CNS tumors have resulted in a revision of the World Health Organization (WHO) classification of brain tumors in 2016. Secondary CNS tumors are represented by brain and leptomeningeal metastases and are more common than primary CNS tumors. The most common primary CNS tumors, glioblastomas and

meningiomas, are particularly common in the elderly. Notably glioblastomas in the elderly carry a very poor prognosis. Similarly, secondary CNS tumors are common in the elderly since they reflect the increasing risk of systemic cancer with advanced age. Multimodality treatment with its increasing complexity regarding drug interactions and comorbidity-associated risk of toxicity poses specific challenges in the elderly.

Keywords
Elderly · Age · Comorbidity · CNS · Brain · Leptomeningeal metastases · Glioma · Glioblastoma

Introduction

Tumors of the central nervous system (CNS) can be primary CNS tumors originating from cells of the CNS or secondary tumors originating from primary cancers of extra-CNS origin. Secondary CNS tumors, that is, brain and leptomeningeal metastases, are probably five to ten times more common than primary CNS tumors.

Primary CNS tumors are very diverse in terms of morphology, molecular genetic landscape, and outcome. They are classified primarily by morphological criteria based on presumed cell of origin and are assigned a grade of malignancy from I to IV according to assumed natural course of disease. The new World Health Organization (WHO) classification of brain tumors has introduced also molecular markers to aid in defining more homogeneous disease entities, specifically changing the approach to gliomas of adulthood (Louis et al. 2016). Moreover, primary CNS tumors show very distinct profiles of age-dependent incidences: some tumors like medulloblastomas or pineal parenchymal tumors are typical tumors of childhood where primary CNS tumors are common and a major cause of morbidity and mortality. In contrast, some of the most frequent primary brain tumors, glioblastoma and meningioma, have their highest incidence in the elderly (Table 1) (Ostrom et al. 2015). Thus, the annual incidence rate for glioblastoma is 15.24 in the age group of 75–84 years as opposed to 1.21 in the age group of 35–44 years. Similarly, meningiomas are very common with a 39.11 annual incidence rate in the age group of 75–84 as opposed to 5.16 in the age group of 35–44.

Moreover, age is a strong negative prognostic factor for most primary CNS tumors (Table 2). Age-dependent differences in survival are particularly prominent in diffuse astrocytomas: 2 years survival is 85.2% versus 10.8% in patients aged 20–44 as opposed to older than 75, and 10 years survival is 80.3% versus 2.0% in the same age groups. Similarly, 2 years survival is 37.6% from 20 to 44 years as supposed to 3.3% in glioblastoma patients aged more than 75 years. Outcome differences by age are less prominent but still remarkable for meningioma with 2 and 10 years survival rates of 95.4% versus 55.3% and 82.2% versus 36.3% in the age groups of 20–44 years versus more than 75 years.

The reasons for inferior outcome in elderly patients with CNS tumors are probably manifold: there may be reduced tolerance of therapeutic interventions, physicians' bias toward undertreatment, differential response to therapy, potentially related to immunosenescence, and distinct molecular genetic differences which cause a more aggressive clinical behavior of some tumors in the elderly. Clinical trial data on elderly patient populations with primary brain tumors are sparse since advanced age was often an exclusion criterion in clinical trials, or, if this was not the case, exclusion of various comorbidities reduced the proportion of elderly patients.

History, Clinical Presentation, and Clinical Findings

Brain tumors may become clinically apparent either by symptomatic epileptic seizures, by headaches, by progressive focal neurological deficits, or by chronic organic mental changes. The type of clinical presentation largely depends on tumor location and on whether tumors grow as a circumscribed mass or primarily as an infiltrative, locally destructive lesion. Non-infiltrative lesions

Table 1 Average annual incidence adjusted on age (CBTRUS data, adapted from Ostrom et al. 2015)

	Age at diagnosis									
	35–44		45–54		55–64		65–74		75–84	
Histology	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Tumors of neuroepithelial tissue	4.45	4.36–4.54	6.86	6.75–6.97	11.66	11.51–11.82	17.13	18.89–17.38	19.60	19.26–19.94
Pilocytic astrocytoma	0.12	0.11–0.14	0.09	0.08–0.10	0.09	0.07–0.10	0.06	0.04–0.07	0.07	0.05–0.09
Anaplastic astrocytoma	0.40	0.37–0.43	0.46	0.43–0.49	0.65	0.61–0.68	0.92	0.86–0.98	0.91	0.84–0.98
Glioblastoma	1.21	1.16–1.25	3.54	3.47–3.62	8.08	7.35–8.21	13.05	12.84–13.27	15.24	14.94–15.54
Oligodendroglioma	0.45	0.42–0.48	0.40	0.37–0.42	0.31	0.28–0.33	0.21	0.19–0.24	0.20	0.16–0.23
Anaplastic oligodendroglioma	0.17	0.15–0.19	0.18	0.16–0.20	0.21	0.19–0.23	0.16	0.14–0.19	0.11	0.09–0.14
Ependymal tumors	0.48	0.45–0.51	0.62	0.58–0.65	0.56	0.53–0.60	0.58	0.54–0.63	0.43	0.38–0.48
Choroid plexus tumors	0.03	0.02–0.04	0.04	0.03–0.05	0.04	0.03–0.05	0.04	0.03–0.05	0.05	0.03–0.07
Neuronal and mixed neuronal-glial tumors	0.24	0.22–0.26	0.23	0.21–0.25	0.21	0.19–0.24	0.20	0.17–0.23	0.17	0.14–0.20
Tumors of the pineal region	0.05	0.04–0.06	0.04	0.03–0.05	0.04	0.003–0.05	0.03	0.02–0.05	0.03	0.02–0.04
Embryonal tumors	0.11	0.10–0.13	0.08	0.07–0.09	0.05	0.04–0.06	0.04	0.03–0.06	0.03	0.02–0.05
Tumors of cranial and spinal nerves	1.81	1.75–1.87	2.86	2.79–2.93	4.01	3.92–4.10	4.55	4.43–4.68	3.51	3.36–3.65
Nerve sheath tumors	1.81	1.75–1.87	2.85	2.78–2.92	4.01	3.92–4.10	4.55	4.43–4.68	3.51	3.36–3.65
Tumors of meninges	5.16	5.06–5.26	9.39	9.17–9.52	15.24	15.06–15.42	26.45	26.14–26.76	39.11	38.64–39.5
Meningioma	4.82	4.72–4.91	9.02	8.89–9.14	14.77	14.59–14.95	25.96	25.66–26.27	38.70	38.22–39.18
Lymphoma and hematopoietic neoplasms	0.27	0.25–0.29	0.43	0.40–0.46	0.89	0.85–0.93	1.82	1.74–1.90	2.40	2.28–2.52
Lymphoma	0.26	0.24–0.28	0.41	0.39–0.44	0.87	0.82–0.91	1.79	1.71–1.87	2.38	2.26–2.50
Germ cell tumors and cysts	0.05	0.04–0.06	0.03	0.02–0.04	0.02	0.01–0.03	0.03	0.02–0.04	0.03	0.02–0.05
Germ cell tumors, cysts, and heterotopias	0.05	0.04–0.06	0.03	0.02–0.04	0.02	0.01–0.03	0.03	0.02–0.04	0.03	0.02–0.05
Tumors of sellar region	4.52	4.43–4.61	4.85	4.76–4.95	5.61	5.50–5.72	7.55	7.39–7.72	7.54	7.32–7.75
Tumors of the pituitary	4.36	4.27–4.45	4.64	4.55–4.73	5.37	5.27–5.48	7.30	7.14–7.46	7.32	7.11–7.53
Craniopharyngioma	0.16	0.14–0.18	0.21	0.19–0.23	0.24	0.22–0.26	0.25	0.22–0.28	0.22	0.18–0.26

Table 2 Survival rates at 2 and 10 years for selected primary CNS tumors by age (CBTRUS data, Ostrom et al. 2015)

Histology	Age group (year)	Total number of cases within the SEER registries between 1995 and 2012	2 years		10 years	
			%	95% CI	%	95% CI
Diffuse astrocytoma	20–44	2349	85.2	83.6–86.6	47.2	44.5–49.8
	45–54	1046	60.2	57.0–63.2	31.2	27.5–35.1
	55–64	933	34.4	31.2–37.6	12.8	9.8–16.2
	65–74	712	24.3	21.0–27.7	9.3	6.3–5.2
	75+	603	10.8	8.3–13.8	2.0	0.6–5.2
Anaplastic astrocytoma	20–44	1346	73.5	70.9–75.9	37.4	33.9–40.9
	45–54	729	48.6	44.7–52.3	18.5	14.7–22.6
	55–64	711	27.5	24.0–31.1	6.4	3.7–10.1
	65–74	579	15.2	12.2–18.6	3.9	2.0–6.6
	75+	419	7.2	4.8–10.3	–	–
Glioblastoma	20–44	3166	37.6	35.8–39.4	10.4	9.0–11.9
	45–54	5851	22.7	21.5–23.8	3.3	2.6–4.1
	55–64	8780	15.7	14.9–16.6	1.5	1.1–2.1
	65–74	8143	8.9	8.2–9.6	0.8	0.5–1.4
	75+	6831	3.3	2.8–3.8	–	–
Oligodendroglioma	20–44	1832	95.4	94.3–96.3	68.6	65.7–71.3
	45–54	792	89.1	86.6–91.2	61.8	56.7–66.4
	55–64	431	78.2	73.6–82.1	48.3	41.1–55.2
	65–74	176	68.4	60.1–75.2	34.4	23.3–45.8
	75+	98	50.6	38.7–61.4	18.4	7.3–33.4
Anaplastic oligodendroglioma	20–44	579	84.2	80.8–87.1	51.4	45.9–56.6
	45–54	338	73.6	68.2–78.2	42.3	35.4–49.2
	55–64	290	59.9	53.6–65.6	28.8	21.2–36.7
	65–74	141	33.9	25.7–42.2	7.7	2.6–16.5
	75+	57	–	–	–	–
Ependymal tumors	20–44	934	94.7	92.9–96.0	89.2	86.3–91.5
	45–54	524	91.6	88.6–93.9	85.5	82.2–88.8
	55–64	364	88.8	84.6–91.9	85.5	77.7–90.8
	65–74	179	80.1	72.3–86.0	72.6	59.4–82.1
	75+	96	69.6	56.7–79.4	25.7	9.3–46.0
Neuronal and mixed neuronal-glial tumors	20–44	147	92.3	86.3–95.8	61.4	49.0–71.7
	45–54	135	89.8	82.7–94.1	74.9	62.4–83.8
	55–64	101	72.5	61.5–80.8	47.4	32.0–61.4
	65–74	57	77.3	61.3–87.3	39.9	13.9–65.2
	75+	–	–	–	–	–
Meningioma	20–44	165	95.4	90.5–97.8	82.2	74.1–88.0
	45–54	200	87.0	81.1–91.2	70.1	61.4–77.2
	55–64	286	79.6	74.0–84.1	54.5	46.0–62.2
	65–74	264	72.9	66.4–78.4	51.7	43.3–59.5
	75+	309	55.3	48.4–61.6	36.3	24.2–48.1
Lymphoma	20–44	1150	36.0	33.2–38.9	24.7	21.7–27.7
	45–54	814	48.2	44.6–51.7	28.1	24.1–32.1
	55–64	1033	50.1	46.8–53.3	27.6	23.8–31.5
	65–74	1127	39.7	36.7–42.8	14.7	11.4–18.4
	75+	975	23.1	20.2–26.2	10.8	7.0–15.4

like most meningiomas can grow to large lesions and typically cause symptoms and signs of raised intracranial pressure, whereas destructive lesions such as glioblastomas cause focal deficits resulting from impaired function of the affected brain region. Some benign tumors such as meningiomas may be diagnosed as incidental findings when neuroimaging is conducted for other reasons.

There are few considerations that specifically apply for elderly patients. Because of less brain volume and less tendency for lesion-associated edema formation, tumors may grow to larger volumes before being detected. Moreover, subtle mental changes are more likely to be interpreted as symptoms of aging or age-associated neurodegenerative or vascular disease. Delayed diagnoses are particularly common in patients with preexisting diagnoses of multiple strokes or Alzheimer's or other dementive disease.

Diagnostic Strategies

There are no specific diagnostic strategies for elderly patients suspected of having a brain tumor except that repeat neuroimaging must be considered in patients with diagnoses of other neurological diagnoses who exhibit decline or novel symptoms, as outlined above. Cerebral magnetic resonance imaging (MRI), without and with contrast enhancement, is the gold standard of diagnosis of brain or spinal tumors (Wen et al. 2010; Weller et al. 2017). Computed tomography (CT) scans are only indicated if there are contraindications for MRI or in an emergency setting when MRI may not be feasible. There is only a limited role for cerebrospinal fluid (CSF) studies in elderly patients with suspected primary brain tumors because tumors which seed via the CSF are largely restricted to the pediatric and young adult population, e.g., medulloblastomas, pineal parenchymal tumors, and ependymomas. In contrast, CSF studies to rule out leptomeningeal metastasis are often indicated in patients with documented solid brain metastasis or patients with metastatic cancer who develop unexplained neurological symptoms and signs.

Primary Brain Tumors

Gliomas

Gliomas are the most common malignant primary brain tumors in adults. Their diagnostic assessment has been improved in the 2016 WHO classification; while there are still increasing grades of malignancy from WHO grade I to IV, two molecular markers, isocitrate dehydrogenase mutation and 1p/19q codeletion, have now been integrated and redefine three major classes of non-ependymoma gliomas in adulthood: (i) isocitrate dehydrogenase mutant and 1p/19q-codeleted gliomas which are typically oligodendroglial in morphology and carry a favorable prognosis, (ii) isocitrate hydrogenase mutant and 1p/19q-non-codeleted gliomas with dominantly astrocytic morphology and intermediate prognosis, and (iii) isocitrate dehydrogenase nonmutant tumors which are mostly glioblastomas, typically associated with chromosome 7 gains and losses on chromosome 10, advanced age, and poor outcome (Louis et al. 2016; Weller et al. 2015).

Higher age alone is a major negative prognostic factor in patients with diffuse gliomas of WHO grades II–IV (Table 2). In fact, even grading loses its prognostic significance somewhat in the elderly since also WHO grade II and III gliomas are typically associated with poor outcome in the elderly (Hartmann et al. 2010; Wick et al. 2012). The reasons for the profound association of age with outcome have not been fully elucidated. Isocitrate dehydrogenase mutations which define a less aggressive group of gliomas are virtually absent in elderly patients with anaplastic gliomas and glioblastomas (Hartmann et al. 2010). Efforts at defining further molecular signatures that are characteristic of gliomas in the elderly and indicative of poor outcome have not met with great success: there is an increase of classical (receptor tyrosine kinase II, RTK II) and mesenchymal glioblastoma subtypes (Sturm et al. 2012), and transcriptomic analyses based on The Cancer Genome Atlas (TCGA) have revealed age-associated hypermethylation of polycomb group protein target genes as well as

increased expression of angiogenesis-related genes in the elderly (Bozdag et al. 2013).

Age is commonly considered a relevant factor when selecting the most appropriate treatment for patient with gliomas. Wait-and-see strategies are felt to be appropriate for selected younger patients with WHO grade II gliomas notably after macroscopically complete resection, but almost never considered in elderly patients with diffuse glioma of any grade (Weller et al. 2017).

Concomitant and maintenance TMZ chemotherapy plus RT (TMZ/RT→TMZ) became the standard of care in the management of adult patients newly diagnosed with glioblastoma and good general and neurological condition in 2005, with enrolment in the pivotal study limited to patients aged up to 70 years (Weller et al. 2017; Stupp et al. 2005, 2009). An ensuing trial was conducted by NCIC and EORTC focused on patients aged 65 years or more and explored whether the combination of TMZ with hypofractionated RT of 40 Gy delivered in 15 fractions was superior with regard to overall survival, too. Since this was the case (Table 3) (Perry et al. 2016), unlike previous assumptions based on subgroup analysis of the registration trial of 2005 (Stupp et al. 2005), age seems not to modulate the benefit of TMZ when added to RT in the treatment of newly diagnosed glioblastoma.

Methylation of the promoter region of the O6-methylguanine DNA methyltransferase (MGMT) gene has long been identified as a predictor of benefit from alkylating agent chemotherapy in glioblastoma (Hegi et al. 2005; Weller et al. 2010). This observation, combined with the notion that combined modality treatment may not be appropriate for many elderly or frail patients, led to the design of two clinical trials performing a head-to-head comparison of RT alone versus TMZ alone in the elderly, NOA-08 and Nordic (Wick et al. 2012; Malmström et al. 2012). Both trials indicated that patients with tumors without MGMT promoter methylation should not be treated with TMZ alone but that TMZ alone is superior to RT alone if tumors exhibit MGMT promoter methylation. Accordingly, the guideline of the European Association for Neuro-Oncology (EANO) defined testing for MGMT promoter methylation as standard of care in the elderly and advocated clinical decision-making based on MGMT status in the elderly (Weller et al. 2014). In the absence of information on MGMT status, RT should be preferred since MGMT promoter methylation is less frequent with approximately a third of tumors and since the efficacy of RT is clearly superior to TMZ in patients with tumors lacking *MGMT* promoter methylation. The recent NCIC EORTC trial reported benefit from TMZ also in patients with tumors without MGMT promoter, yet MGMT status data were available only in a subgroup of selected patients which explains the observation that survival was longer in MGMT promoter unmethylated patients than in the overall study population (Table 3). Accordingly, the upcoming update of the EANO guideline proposes to use TMZ/RT→TMZ in patients with MGMT promoter methylated tumors if feasible but to

Table 3 Outcome with RT versus TMZ/RT→TMZ in elderly glioblastoma patients (Perry et al. 2016)

		PFS	HR/p	OS	HR/p
All patients					
RT	$n = 281$	3.9 (3.5–4.3)	0.5	7.6 (7–8.4)	0.67
TMZ/RT→TMZ	$n = 281$	5.3 (4.6–6.2)	<0.0001	9.3 (8.3–10.3)	<0.0001
MGMT promoter not methylated					
RT	$n = 96$	4.4 (3.9–4.9)	0.79	7.9 (6.9–10)	0.75
TMZ/RT→TMZ	$n = 93$	4.8 (4.3–5.6)	0.12	10 (8.3–10.7)	0.055
MGMT promoter methylated					
RT	$n = 77$	3.9 (3–4.6)	0.33	7.7 (5.8–10.7)	0.53
TMZ/RT→TMZ	$n = 88$	7.9 (6.4–9.9)	<0.0001	13.5 (10.2–15.3)	0.0001

continue to view RT alone standard of care in elderly (≥70 years) or frail patients with tumors without MGMT promoter methylation (Weller et al. 2017).

Meningiomas

Meningiomas are overall the most common intracranial tumors, and the risk of developing a meningioma is strongly age-associated, with a major female preponderance across age groups (Ostrom et al. 2015). More frequent use of cranial MRI or CT in the elderly may have resulted in the impression of increased prevalence rates of meningiomas. Most meningiomas are biologically benign, are assigned WHO grade I, and can be cured by surgical resection alone if feasible by location. A smaller proportion of meningiomas is considered atypical (WHO grade II) or ANAPLASTIC (AND NOT atypical) (WHO grade III) (1), (Louis et al. 2016), associated with correspondingly decreased overall survival. In contrast to gliomas, watch-and-wait strategies are often appropriate notably in the elderly patient population where meningiomas may have been diagnosed incidentally during work-up for stroke or dementia (Goldbrunner et al. 2016). In contrast, large symptomatic meningiomas with very typical radiological appearance may occasionally be managed by primary radiotherapy alone if the risk of surgery appears to outweigh the benefit of establishing a precise diagnosis associated with cytoreduction. The recently identified mutations suggested to play a major role in meningioma biology appear to be age-associated.

Primary CNS Lymphoma (PCNSL)

PCNSL is another malignant primary brain tumor where age is highly relevant for outcome. PCNSL is potentially curable with high-dose methotrexate-based chemotherapy without or with stem cell transplantation but only in younger patients. Elderly patients tolerate such aggressive treatments less well, but there seem to be additional biological features that render prolonged disease control challenging in this disease: a secondary analysis of the largest PCNSL trial ever performed, G-PCNSL-SG-1 (Thiel et al. 2010), revealed that elderly patients are as likely as younger patients to achieve a radiologically complete or partial response but that responses are rarely sustained in the elderly (Roth et al. 2012). Irrespective of age, whole brain radiotherapy has largely been abandoned in the treatment of PCNSL, both because of moderate and only transient therapeutic activity and because of poor tolerability, notably in the elderly.

Brain and Leptomeningeal Metastases

Up to 30% of patients with systemic cancer develop CNS metastases which are the most common brain tumors if considered collectively. The risk of CNS metastases is highest in melanoma, lung cancer, breast cancer, and renal cell cancer, and this risk appears not to be age-associated. CNS metastases commonly signify a poor prognosis but do in general not respond less well to RT or chemotherapy than organ metastases elsewhere. An increasingly used prognostic index, the graded prognostic assessment (GPA), identified patient age above 60 years as one of the four prognosis-defining factors associated with decreased survival (Sperduto et al. 2008, 2010, 2012). This GPA was subsequently expanded to specific histologies of primary tumor, resulting in the identification of age as relevant particularly in lung cancer, both non-small cell lung cancer and small-cell lung cancer, which are also collectively responsible for 50% of all CNS metastases. Yet, age alone is not a limitation for tumor-specific treatment approaches in patients with CNS metastases, and frailty as opposed to merely age is increasingly used to identify patients who may overall not derive benefit from aggressive tumor treatment.

Symptomatic and Supportive Therapy and Palliative Care

There are few considerations specific to elderly patients with CNS tumors. Such patients often

require corticosteroids for the control of steroid-associated edema, and elderly patients may be prone, because of comorbidities, to steroid-induced hyperglycemia and osteoporosis. Because of increased risks of falls and fractures, symptomatic epilepsy associated with CNS tumors should be treated vigorously in the elderly. There is increased risk of drug interactions, again because of comorbidities, e.g., requiring the use of anticoagulants and antiplatelet agents which modulate the safety profile of systemic chemotherapy.

Outlook

Incidence and prevalence of primary and secondary CNS tumors increases probably steadily with advancing age. Since European societies are aging, this results in an increasing burden not only for affected patients and families but also health-care providers and health systems. As more specific and effective treatments become available, careful assessment of their safety and tolerability by dedicated clinical trials is an important task to improve outcome and quality of life of the growing population of elderly cancer patients.

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Part VII

Patient Care Issues

Martine Extermann

Principles of Cancer Surgery in Older Adults

51

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Abstract

The elderly population has recorded an unprecedented growth over the last 20 years. Despite the evidence that cancer is a disease of the elderly, very little level 1 evidence on its treatment comes from current scientific literature, since patients older than 70 are often excluded from clinical randomized trials.

In addition, information obtained from the methodologically well-designed studies does not always apply to elderly patients. Unfortunately, this may also translate in substandard cancer care delivered to this group as recently flagged by EUROCARE-5, the widest collaborative research project on cancer survival in Europe. The same scenario has been reported by the National Cancer Intelligence Network showing how in the UK elderly patients affected by solid tumor receive less surgery as compared to the younger counterpart. The difficulty in applying the "standard of care" more broadly needs to be searched in a combination of patients' comorbidities, psychosocial issues, and physicians' attitude. All these factors contribute to the challenge in the perioperative decision-making, eventually affecting the treatment outcomes.

Keywords

Surgery · Elderly · Cancer · Communication · Complications · Mortality · Minimally Invasive Surgery · Prehabilitation · Overtreatment · Undertreatment · Multidisciplinary · Functional recovery · Quality of life · Patients' perspectives

Introduction

The elderly population has recorded an unprecedented growth over the last 20 years, and the United States (US) censor bureau projects that by 2050, there will be approximately 90 million elderly people living in the USA. Despite the evidence that cancer is a disease of the elderly, very little level 1 evidence on its treatment comes from current scientific literature, since patients older than 70 are often excluded from clinical randomized trials (Zulman et al. 2011).

In addition, information obtained from the methodologically well-designed studies does not always apply to elderly patients, who experience different benefits, side effects, and life expectancy than younger cohorts (Rutten et al. 2008). Unfortunately, this may also translate in substandard cancer care delivered to this group. EUROCARE-5 (De Angelis et al. 2014), the widest collaborative research project on cancer survival in Europe, including 21 million cancer diagnoses provided by 116 cancer registries in 30 European countries, has recently flagged an unfavorable cancer-related survival rate among the oldest patients. The same scenario has been reported by the National Cancer Intelligence Network showing how in the UK elderly patients affected by solid tumor receive less surgery as compared to the younger counterpart (National Cancer Intelligence Network). The difficulty in applying the "standard of care" more broadly needs to be searched in a combination of patients' comorbidities, psychosocial issues, and physicians' attitude. All these factors contribute to the challenge in the perioperative decision-making, eventually affecting the treatment outcomes.

What Do Elderly People with Cancer Want? The Challenge of Communicating, Patients' Perspectives, and Quality of Life

Becoming old means being less and less independent from a number of perspectives. Among the various causes leading to a decrease in functional

capacity, declining health plays a pivotal role. Elderly patients have multiple comorbidities and unpredictable social/family situations; when cancer is diagnosed, this adds frequently to in an already complicated situation. Among the elderly, those who are vulnerable or even frail are the ones who really deviate from the standard curves. The purpose of surgical care in elderly is to obtain a cost-effective, tailored treatment while focusing attention on the patients' quality of life rather than the mean 5-year disease-free survival.

The vast majority of surgeons recognize now the peculiar characteristics of performing surgery in the elderly as compared to the younger population (Deiner et al. 2014). In particular, the uncharacteristic intensity and duration of postoperative treatments, the specific medicolegal issues of obtaining an informed consent, and the ethical questions related to the end-of-life care (Soreide and Wijnhoven 2016).

Communication in these cases is essential, not only with the family, but with the patients themselves, whenever possible, since in many cases, it's surprising how well-aware and practical outcome-oriented senior adults may be, despite facing a challenging situation. Elderly patients should be assumed to have the mental capacity to make decisions about their treatment, until proven otherwise. This being said, patients' healthcare proxy and family must be involved during the treatment pathway not just once but at several steps during the key decision-making moments and with constant follow-ups. The goal of the communication is not ordinary medicolegal compliance, but it needs to help going through the insidious process of facing challenging circumstances for both the family and the clinician (Desserud et al. 2016) (Table 1). King et al. showed that main reason to withdraw surgical care in this group is mainly due to "contraindication despite lack of comorbidities and patient refusal" (King et al. 2016). As Audisio et al. pointed out on their recent editorial in the *Annals of Surgical Oncology*, this choice is usually "justified" during multidisciplinary discussion as "this patient doesn't want surgery" (Audisio and Balch 2016). But patients are sincerely prone to take under serious consideration physicians' recommendations above all if they're receiving truthful answers about their common fears: postoperative pain, functional recovery, and alternatives in case of nontreatment.

Table 1 Potential pitfalls in communication

Clinical setting	Key element	Challenge
Patient's consent/ advanced directive and living will	Oral or written Consult healthcare proxy/guardian	Patient's mental awareness Non-documented living will Proxy's decision
Do-not-resuscitate order	Patient's documented will Define prognosis Available treatments likely to fail Physician experience/ awareness Expectations	Poor available scientific data Experience versus scientific data Patients/ caregiver unwillingness Caregiver's/ patient's expectations versus physician's expectations False hopes/ expectations The value of "keeping the hope alive" Communication
Withholding and withdrawing life support	Provided limitation in care Poor functional/ organs reserve Define prognosis Define risk of permanent dependence from invasive systems (respiratory-cardiovascular, etc.) Define palliation/ comfort measures	Patient's and proxy's understanding/ awareness of clinical situation Expectations Feeling of "giving up"

Patients' perspectives are essential in establishing a proper understanding of the QoL goals. Despite the prevalence of cancer in the elderly population and the increasing requirement

for QoL measurement, not many studies have been published focusing on patient experience (Dunn et al. 2006). In recent years, some qualitative information has been gained from studies designed for younger patients where "uncertainty," "fears for cancer recurrence," "pain," "fatigue," "managing on a day-to-day basis," and "feeling alone" were described as the highest concerns of patients (O'Connor et al. 1990; Taylor 2001; Persson and Hellstrom 2002). Mental and physical health seemed to be interrelated in both young and senior adults with cancer as reported by Weaver et al. (2012), affecting their perspective regarding their disease and the expectations.

Banks et al. (2010) were able to analyze self-reported questionnaire-based data from 89,574 Australian men and women with cancer sampled from the Medicare database. In their study, they were able to conclude that "the risk of psychological distress in individuals with cancer relates much more strongly to their level of disability than it does to the cancer diagnosis itself." Disability and lack of independence in the activities of daily living seem to impact cancer patients more than the cancer prognosis per se.

Some cancer-specific situations have been historically blamed for being responsible for patients' reduced self-esteem and QoL. Among the possible stressors, having a stoma has been traditionally considered as a factor that increases psychological distress in patients with CRC. This assumption has been reconsidered in the past few years. A large meta-analysis on the impact of a stoma-forming procedure [abdominal perineal resection (APR) vs. low anterior resection (LAR)] on 1443 patients with CRC failed to show a reduction in the QoL of patients with fecal diversion (Cornish et al. 2007). The mean age in the two groups was 66.3 $\pm$ 6 and 65.6 $\pm$ 6 years for APR and LAR, respectively. This was again confirmed by Bossema et al. showing no difference in terms of health-related QoL (HRQoL), emotional function, and understanding of the illness among elderly rectal cancer patients with or without a stoma (Bossema et al. 2011).

Patient-centered outcome studies should be implemented in the oncogeriatric field in order to face modern healthcare system challenges (Gabriel and Normand 2012). Data seem to suggest that disability and lack of independence are considered more important than the cancer diagnosis per se. The risk of postoperative disability needs to be fully discussed with patients and family with the goal of promoting faster functional recovery and regaining independence.

Discussing with patients and family about goals, expectations, and health status seems obvious, but self-reported QoL tools have been for a long while ignored by surgeons. In particular, QoL and functional outcome questionnaire (sexual dysfunction, fecal, and urinary incontinence, etc.) evaluations have been considered too "demanding" and "time-consuming" to be systematically incorporated into busy clinical practices.

Only recently, Fernando and colleagues described the use of two self-administered quality-of-life tools (questionnaires) as part of a prospective, randomized control trial of sublobar lung resection for cancer versus sublobar lung resection with locally applied brachytherapy (Fernando et al. 2015). Regardless of the specific outcomes, authors were able to demonstrate that, firstly, self-assessment questionnaires are feasible in the surgical office and in the postoperative ward. Secondly, self-assessment questionnaires have been useful in predicting adverse outcomes after chemotherapy and surgery (Feng et al. 2015; Jaklitsch 2015).

An interesting prospective multicenter study by Scarpa et al. (2013) analyzed the QoL of elderly versus younger patients undergoing colorectal surgery. A total of 116 patients were enrolled in this study: 33 patients >70 year had a laparoscopic colectomy whereas 24 underwent open resection; 44 patients <70 year had a laparoscopic procedure and 15 of them required an open approach. Authors used three questionnaires regarding generic/specific QoL (EORTC QLQ-C30 / CR29) and treatment satisfaction (EORTC INPATSAT32). As expected, they showed that elderly patients undergoing laparoscopic colectomy experienced fewer postoperative complications than patients undergoing an open procedure.

Nevertheless, elderly patients experienced a poorer QoL compared to younger patients. The main fields that were found to be affected were the presence of fatigue, sleep disturbance, appetite loss, and shortness of breath. Data were confirmed by Amemiya et al. (2007) reporting data about elderly with gastric and colon cancer. After an immediate reduction of functional capacity, they showed that QoL measured at 1 week and 6 months progressively and significantly improved ($p < 0.005$). Functional recovery and activities of daily living status improved after surgery in the majority of patients; however, a temporary or prolonged decline in recovery was found in those who developed postoperative complications.

In conclusion, QoL and patients' perspectives can no longer be considered "secondary outcomes" in terms of their relevance for oncogeriatric patients. Restoration of independence seems to be the highest priority and it directly affects QoL perception. HRQoL data at diagnosis also seem to identify vulnerable subpopulations in elderly patients (Fiteni et al. 2015; Fournier et al. 2016); thus, it could be valuable in selecting fit elderly candidates before the treatment. Regardless of the system of choice, data about QoL need to be incorporated in every surgical practice, putting the patient at the center of the care process.

Preoperative Evaluation and Multidisciplinary Decision-Making

Several systems to evaluate patients in order to stratify operative risk and highlight possible areas amenable for prehabilitation have been proposed and validated. The overall message is that, regardless for the system of choice, it is essential to systematically assess elderly cancer patients in order to determine if the patient is fit for surgery, which is the most appropriate surgical plan and which adjustments might be needed before the procedure. As a rule of thumb, it is mandatory, regardless for the preferred system, to obtain information about three main domains: cognitive status (including history of delirium), independence/living situation, and sarcopenia/gait ability/nutrition (Audisio et al. 2008; Fong et al. 2009; Mohri et al. 2013; Huisman et al. 2014; Hempenious et al. 2015).

Screening for frailty and any possible areas of intervention is only a part of the preoperative assessment and decision-making process. Secondly, but with same significance, is that every possible patient is discussed within a multidisciplinary group. The multidisciplinary approach is, as always, of great value when treating elderly, challenging patients in order to not overlook any aspect of patients' complexity. This is particularly valuable within the field of geriatric oncology where a combination of disease- and patient-oriented approach needs to be pursued. Clinical data have confirmed that this approach can improve measurable outcomes and quality of life in the geriatric population undergoing surgery (Terret et al. 2007). The multidisciplinary team should be ideally built around not only cancer-specific professionals (surgical, medical, and radiation oncologists), but geriatricians, anesthesiologists, physical-therapists, nutritionists, case managers, and geriatric nurse practitioners should also play a role in the discussion and decision-making process.

An algorithm reporting the preoperative sequence of events in order to determine patients' access to treatments has been offered in Fig. 1.

Surgical Planning (Not Only Picking a Calendar Date)

It has been established that surgical care should not be withdrawn from elderly patients only because of age, while comorbidities should be regarded as the main cause or an increased risk of failure. Because of this, several perioperative strategies have been implemented and promoted.

Every clinician and surgeon, above all, should bear in mind that the key element for a successful delivery of high-level care starts with a standardized, individual patient's risk evaluation. Preoperative evaluation has been extensively described in previous chapters but it's worth repeating that in a practical world, where the surgical practice is squeezed into a tight schedule, the need for

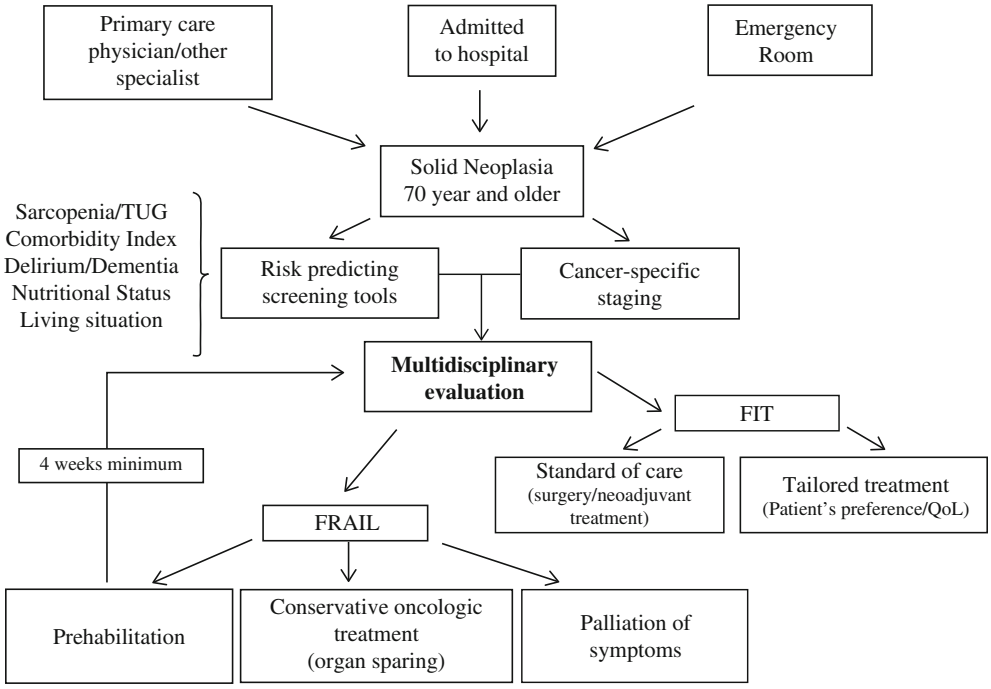

Fig. 1 Multidisciplinary decision-making process flow chart for oncogeriatric surgical patients

simple, easy-to-use risk-predicting systems is a top priority.

Exploring this pathway, the role of the Timed Up and Go (TUG) test, the handgrip strength test, nutritional risk screening, ADL/IADL, and others have been assessed (Audisio et al. 2008; Huisman et al. 2014). Organ-specific diseases, setting, and environmental factors make the pursuit of the "one-size-fits-all" risk-predicting instrument hard to be fulfilled.

The lack of a standardized preoperative assessment is, indeed, one of the main reasons why so few meaningful conclusions can be drawn from too many papers currently published by the "scientific community." In addition, no homogeneity in the study population can be verified or is objectively reported. This is particularly true for elderly patients' literature where intergroup variability is so highly represented and usually so poorly assessed, nullifying the value of possible final conclusions.

The role of a systematic preoperative assessment is focused not only on screening good, fit candidates for surgery but also on identifying situations or conditions that may benefit from a preoperative intervention. After a careful preoperative evaluation, a tailored procedure can be planned with the intent of obtaining the desired result and minimizing stressors. The role of minimally invasive surgery (MIS) has been debated and quite definitive results have been published on the topic highlighting the crucial role of MIS in the elderly. While the role of laparoscopy was extensively addressed (Lacy et al. 2002; Veldkamp et al. 2005; Bonjer et al. 2015), the same could not be reported for the use of other technologies as robotic surgical systems, that while gaining consensus among patients and care providers are failing to show a significant clinical benefit (Patel et al. 2015; Montroni and Wexner 2016). The application of the enhanced recovery protocols in elderly patients will be also briefly described.

Prehabilitation

Despite modern and sophisticated efforts to decrease postoperative morbidity and mortality, there is evidence that, 6–9 weeks after major

abdominal surgery, many patients are not back to their active lives (Wilson et al. 2010). Prehabilitation is a modern strategy, gathering together all the initiatives carried out from the time of diagnosis to the time treatment starts in order to improve functional capacity and functional recovery. Prehabilitation before oncologic surgery is a novel topic compared with the amount of knowledge of posttreatment rehabilitation programs and outcomes for both cancer and non-cancer patients (Silver and Baima 2013). Interestingly, the first study on prehabilitation was published in 1946, describing nutritional and physical training and even recreational intervention in order to turn the unfit military into robust soldiers ready for the battlefield (1946). In recent years, prehabilitation for elderly patients affected by cancer has become more and more intriguing for surgical oncologists as a result of the great benefits shown in the fields of orthopedic and cardiac surgery (Swank et al. 2011; Furze et al. 2009) Medical prehabilitation includes the management and optimization of preoperative conditions, such as diabetes and cardiovascular function and the promotion of smoking cessation. Moreover, the goal of this strategy is to focus not only on muscle strength reinforcement but also on the nutritional and emotional/psychological management of patients undergoing major surgery. The work that Carli et al. (2010) have accomplished in recent years has been of great value from this prospective. They were able to show that functional capacity was improved by prehabilitation, whether by adherence to a strenuous preoperative activity schedule (bike and muscle strengthening exercises) or by a 30-min walking and breathing exercise regimen three times a week. On the other hand, many questions are still open as to how older adults undergoing surgery may or may not benefit from perioperative regimens (Jack et al. 2011).

One of the main issues is the low adherence of patients to the prehabilitation regimen and the need for a prolonged time period from diagnosis to surgery (at least 4–6 weeks) in order to observe tangible improvement in postoperative outcomes. Patients undergoing neoadjuvant treatments seem to be the group with the highest potential (Loughney et al. 2016). What is clear is that prehabilitation is not a substitute for good surgical and tailored postoperative treatment, above all in the elderly. As a consequence, it should not reduce the morbidity and mortality rates. Prehabilitation improves functional recovery and, perhaps, patient independence and active life expectancy (Santa Mina et al. 2014). Li et al. (2013) showed how a trimodal prehabilitation program dramatically changed postoperative functional walking capacity, self-reported physical activity, and health-related quality of life (QoL). This randomized trial was designed for CRC patients awaiting surgical treatment and included 30 min of walking and breathing exercises three times a week, a nutritional supplement of up to 1.2 g/kg body weight, and anxiety reduction techniques. The mean age of the 42 patients enrolled and the 45 patients in the control group was 67.4 $\pm$ 11 years; a prehabilitation protocol was carried out for a mean time of 33 days (range, 21–46 days). Interestingly, the patients in the intervention group increased the distance covered at the 6-min walking test during prehabilitation, surpassing the preoperative results of the control group. Four and 8 weeks after surgery while control patients' physical ability declined and did not reach their pretreatment level, prehabilitated patients regained the ability to walk farther than their preoperative baseline. The same trajectory was shown for self-reported physical activity, while anxiety and depression were shown to be way below the patient baseline 4 weeks postoperatively. Even more interestingly, fewer postoperative complications were recorded in patients who improved their walking ability during prehabilitation while people whose functional capacity declined during the pretreatment time had poorer outcomes. It might help considering the response to the prehabilitation regimen to be an additional screening tool for elderly patients undergoing surgery for cancer (Chan et al. 2016).

Several issues regarding the feasibility and effectiveness of this approach have still not been completely resolved. The lack of time, which often forces surgeons to bring elderly patients with CRC to the operating room sooner rather

than later because of impending obstruction or perforation, might reduce the feasibility for a very large number of patients. At the same time, lack of adherence to prehabilitation regimens is indeed higher in the elderly, above all in cases of inconsistent family or financial support. On the other hand, the results obtained before colorectal cancer surgery are so promising for restoring active life and independence in this frail group of patients that it may be worth a try, above all, for those patients who are able to wait 4–6 weeks before surgery (e.g., neoadjuvant therapy). Good clinical data and larger trials focused on elderly patients are needed to eventually shed light on this fascinating field.

Minimally Invasive Surgery

The aim of this paragraph is merely to address the main key message: MIS is safe and feasible in the elderly and it should be pursued because it promotes faster functional recovery. For the purpose of the discussion, we will mostly refer to the colorectal surgery field where MIS has been routinely used over the last two decades and where the vastest amount of literature has been produced in order to address its usefulness for senior adults.

The term MIS was coined by Dr. John Wickham, urologist, who wrote of it in the *British Medical Journal* in 1987 prophetically foreseeing that "in the next 30 years [. . .] surgeons who practice minimum invasion will do the most non-emergency surgery." The goals of MIS are to obtain the same disease-related and functional outcomes of an open operation while decreasing the surgical stress and consequently the associated morbidity and mortality.

Since the very beginning, MIS became a synonym of laparoscopic surgery, and in the early 1990s, it was introduced to treat benign colorectal diseases. Early studies showed that laparoscopy promoted improvements in return of bowel function, earlier oral intake, decreased opioid analgesia requirements, and decreased length of hospital stay, all while improving cosmesis and patient satisfaction (Dunker et al. 1998). One of the focuses of the use of MI techniques is not only to promote the return of bowel function, expedite oral nutrition, and reduce hospital stay but also to facilitate functional recovery. Such abilities as return to active life and return to independent living or bowel/urinary control are particularly necessary in elderly patients, where reaching those goals often means the difference between an operation's success and failure (Frasson et al. 2008).

Frasson et al. specifically focused on functional recovery after laparoscopic surgery, analyzing a series of 535 patients with colorectal disease randomly assigned to laparoscopic ($n = 268$) or open ($n = 267$) resection. Within the two groups, the outcomes of young patients (under 70 years of age) were compared with those obtained in patients $\geq$70 years old. The authors were able to show how laparoscopy in the elderly, even more than in younger patients, improves the preservation of functional status, permitting a higher rate of postoperative independence at discharge and faster postoperative recovery. Stocchi et al. (2000) were also able to demonstrate that independent status on admission (assessed in 37 patients undergoing laparoscopic-assisted colectomy and 38 undergoing open colectomy) was more frequently maintained at discharge in those undergoing laparoscopic-assisted colectomy (95% vs. 76%, respectively; $P = 0.025$).

Recently, Li Y et al. "sealed" the debate on possible benefits of laparoscopic surgery in octogenarians by publishing a meta-analysis of 11 comparative studies including 1,066 laparoscopic and 1,034 open colorectal resections in their pooled analysis (Li et al. 2016). The result of the meta-analysis is that laparoscopy is safe and carries a lower risk of infectious complications, both pulmonary and at the surgical site, shorter length of stay, and a reduced incidence of postoperative ileus while maintaining the same cardiovascular risk as compared to open surgery.

Enhanced Recovery Programs

Enhanced recovery or fast-track programs include preoperative patient education, no routine bowel preparation, no perioperative starvation, early removal of the nasogastric tube and urinary catheter, tailored anesthesia and postoperative

analgesia, and early mobilization with minimal fluid infusion.

The literature suggests that elderly patients have an advantage in functional recovery if enrolled in a fast-track program. Baek et al. (2013) analyzed a group of 337 patients (87 over 70 years of age and 250 under 70 years of age) who underwent laparoscopic colorectal surgery with a perioperative fast-track program. No significant differences were observed in terms of return of flatus, stool passage, progression of diet, complication rate (26% in the elderly patients vs. 32% in the young patients) or length of hospital stay (12 days for each group). These results were obtained regardless of significant differences between the two groups when considering age, presence of comorbidities (70% in the elderly vs. 44.7% in the younger patients), and ASA score. In particular, they observed a lower than expected cardiopulmonary complication rate, which they acknowledged was most likely due to the use of a low-pressure pneumoperitoneum (8 mmHg). The only significant differences were observed in readmission rate and emergency room visits (11.7% vs. 4%, respectively).

Pawa et al. (2012) achieved similar results, with a median length of stay of 6 days for a 558 patient group under 80 years of age, while a total of 8 days was recorded in a cohort of 130 patients $\geq$80 year ($P = 0.363$). No significant differences in 30-day readmission rate (8.6% of the whole population) were observed in the study.

"Fast-track protocol" has been often used as a synonym of the enhanced recovery after surgery (ERAS) protocol, but the two entities are not the same. The ERAS protocol, promoted through the ERAS® society, refers to a well-designed but necessarily strict list of items that need to be entirely fulfilled in order to obtain the desired effect (Gustafsson et al. 2011). But adherence to the long list of tasks is not easy to achieve and, as demonstrated by several studies and surveys, despite increasing awareness of the importance of structured perioperative management, the implementation of this complex protocol has been slow (Segelman and Nygren 2014).

The above considerations are even more relevant when considering elderly patients who can hardly follow complex processes and who present high variability within their own group.

In addition, some of the items reported in the ERAS protocol such as the use of epidural anesthesia and the absence of oral antibiotic with mechanical bowel preparation have been deeply questioned by the current literature, above all after the implementation of laparoscopy. Epidural anesthesia has been shown to be detrimental when associated to laparoscopic abdominal procedures (Halabi et al. 2014), while the combination of antibiotics and bowel preparation has been reported lowering postoperative infections (Chen et al. 2016).

While promoting accelerated recovery, one of the goals should be to reduce stressors and to decrease the body inflammatory response following surgery. Pursuing this aim, a recent systematic review by Watt et al. examined the impact on the magnitude of the systemic inflammatory response (SIR) for each ERAS component following colorectal surgery using objective markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). While analyzing 19 studies, including 1898 patients, the author showed that, with the exception of laparoscopic surgery, objective evidence of the effect of individual components of ERAS protocols in reducing the stress response following colorectal surgery was limited (Watt et al. 2015).

Based on the current evidence, we should conclude that elderly patients, more than a strict list of prescriptions, do benefit from minimally invasive surgery followed by a "controlled, tailored rehabilitation program including early progressive reintroduction of oral diet, ambulation and physical therapy, early removal of drains and catheters, minimal to nil opioid analgesia, and individualized/limited fluid management. Making the patients and the families engaged with the "controlled rehabilitation plan" via constant, effective communication should be a top priority for the whole care team.

Old Assumptions about Surgery and Poor Cancer Prognosis

In addition to emergency procedures, some other circumstances may result in a theoretical need for aggressive surgical treatment that will most likely

correlate with an elevated rate of disability. This is the case of highly aggressive malignancies like pancreatic cancer, low rectal cancer, or metastatic colon cancer.

Elevated postoperative morbidity and mortality, possible need for permanent bowel diversion or imperfect bowel continence, need for preoperative chemotherapy, and prolonged postoperative course make these scenarios difficult to face for physicians and families.

Pancreatic Cancer

Pancreaticoduodenectomy (PD) is considered one of the most challenging surgical procedures, and the complication risk may vary overall from 5% to 50%, while 5-year overall survival is approximately 15–20% when a malignancy is diagnosed (Riall et al. 2006). PD has been shown to be safely performed in the elderly (Di Carlo et al. 1998; Lightner et al. 2004; Makary et al. 2006; Brozzetti et al. 2006; Hatzaras et al. 2011; Ballarin et al. 2009) even if the higher rate of postoperative complications may be related to comorbidities. Nevertheless, some may debate that the high costs of this procedure, not questioned in younger patients, only bring minimal advantages due to superior postoperative morbidity and poor long-term survival. In order to address this issue, Turrini et al. (2013) prospectively gathered data from 932 patients from 37 institutions, undergoing PD for cancer stratified in <70 (control group), 70–79, and ≥ 80 years old. The three groups were found to be homogeneous in preoperative conditions except for higher incidence of biliary stenting and higher ASA (3–4) in the elderly groups. Senior adults were also statistically less prone to be treated with adjuvant chemotherapy after the surgery. By analyzing this large group of people, they found no difference in postoperative mortality or morbidity in the three groups, but elderly patients recorded a longer length of stay. More surprisingly the overall 1-year, 3-year, and 5-year survival rates of control group/70s group/80s group were 82.2%/75.7%/75.7%, 49.9%/41.8%/31%, and 38.7%/33.2%/0%, respectively ($P = 0.16$) showing no difference in the overall oncological outcomes. Only cancer-related features (vascular invasion and positive lymph nodes) and lack of adjuvant treatment were found to independently predict poor prognosis. The study is affected by a clear selection bias due to the fact that only fit elderly patients were offered massively invasive surgery, but this is exactly the point that should be made. Regardless, the authors managed to make it clear that optimal oncological care should not be withdrawn only based on age since long-term oncological outcomes are no different between fit elderly and the younger population.

The data were confirmed by Riall et al. (2011) who analyzed 9,553 Medicare patients with pancreatic cancer from the Surveillance, Epidemiology and End Results (SEER) database (Riall et al. 2011). They showed that as surgical resection rates increased significantly, 30-day operative mortality rates decreased from 9% to 5% from 1992 to 2005. Comparing patients who underwent a pancreatic resection to the group who did not have surgery, they noticed how participants were less likely to be resected when older. On the other hand, when a resection was performed, the hazard of death was significantly lower, regardless of age, compared with unresected participants.

The authors concluded that, despite previous reports of greater morbidity and mortality after pancreatic resection in older adults, the benefit of resection does not diminish with older age in selected people.

Stage IV Colorectal Cancer with Liver Metastasis

Stage IV colorectal cancer (CRC) is commonly considered a “death sentence,” above all when occurring in elderly patients. Several healthcare professionals have been quoting poor mid-to-long-term survival rates to prematurely withdraw medical and surgical care from this group of patients. Unfortunately, clinicians should also be aware that, even with more modern and tolerable chemotherapy regimens, 5-year survival in patients with colorectal cancer with liver

metastases receiving only palliative chemotherapy is 0–4% (Yun et al. 2007; Okuno 2007).

Guidelines from the National Comprehensive Cancer Network recommend that patients with stage IV CRC should undergo surgery to remove the primary cancer only if they are symptomatic (e.g., bleeding, obstruction, perforation) or have a potentially resectable metastatic localization. Liver resection remains indeed the only chance for long-term survival in patients with CRC liver metastases.

De Liguori Carino et al. (2008) analyzed data from 181 liver resections performed on 178 consecutive senior adult patients. The overall survival rate at 5 years was 31.5%. Similar results were reported by Nagano et al. (2005) who reported 34.1% 5-year survival in 202 elderly patients undergoing surgery for CRC liver metastatic disease.

Adam R. et al. compared 60-day postoperative complications and 3-year survival rate in a group of 999 > 70-year-old patients versus a control group of 6765 younger, consecutive patients who underwent liver resection for metastatic stage IV CRC (Adam et al. 2010). The elderly patients had a higher rate of postoperative mortality and morbidity, but, surprisingly, the 3-year survival rate was similar in the two groups (57.1% vs. 60.2%, respectively).

Unfortunately, liver treatment is usually performed after chemotherapy (named both adjuvant, after CRC surgery, and neoadjuvant, before liver surgery), but this is seldom prescribed to elderly patients due to presumed higher risk of cardiac and liver toxicity secondary to the 5-FU and oxaliplatin, respectively.

De Liguori Carino et al. (2008) were not able to confirm this presumption in their series as only 1 out of the 34 patients receiving FOLFOX developed liver failure. Postoperative complication rates were not found to be higher in patients who did receive preoperative treatment. Although no significant difference in postoperative complication rates is evident between the groups, postoperative mortality was increased after major hepatic resection, thus affecting long-term survival.

It can be concluded that, even for stage IV disease, there should be no upper age limit, but the surgical approach should be planned taking into consideration disease stage and symptoms, patient life expectancy, performance status and the presence of comorbidities (Ugolini et al. 2014).

Conservative Treatment Versus Undertreatment

As previously reported, worse oncologic outcomes in the elderly population are related to suboptimal treatments. The chain of events is most likely to start from the healthcare providers who assess the patients in the first place, as reported by a large survey of primary care physicians in France (Delva et al. 2011). Results showed that the patient's chronological age was highly associated with the decision not to refer patients with advanced cancer to oncologic specialties (odds ratio 0.55; 95% confidence interval 0.35–0.86; $p = 0.009$). But, even if elderly patients are referred to a specialist, it is very likely that a similar age discrimination will be noticed once again. A second survey of 1408 French medical and radiation oncologists showed that breast cancer specialists did not always prescribe potentially beneficial treatments based on chronological age alone (Protiere et al. 2010).

At the same time, we need to acknowledge that "standard of care" is not always synonym with "best possible option" when we deal with elderly cancer patients.

As previously mentioned, quality of life and restoration of independence should be taken sometimes over 5-year survival rate and recognized that "to do less" might be, at times, in the best interest of patients and families. Several strategies to promote conservative, organ sparing, oncologic surgery have been developed in the different surgical fields over the course of the years (Saclarides et al. 1992; Veronesi et al. 1997). While these techniques were initially designed for young patients with early-stage cancer (who would benefit from treatments minimally altering their lifestyle), they seem to perfectly fit with elderly patients' needs.

Balance between "standard of care," "conservative treatment," and "undertreatment" is a fine equilibrium. A tight integration among professionals of different fields can help maintaining the balance of keeping the patients', and not the physicians', best interest at the center of the healthcare process.

Breast Cancer

Breast cancer is the most common neoplasia among women, and age is one of the most important risk factors in developing this disease (Alberg and Singh 2001). It is estimated that 21–30% of cases occur in women older than 70 years (Wanebo et al. 1997). Despite the magnitude of the issue, there is little solid evidence for the management of this specific group of patients, leading to treatments based only on prior incomplete knowledge.

Breast cancer clinical practice is, indeed, mostly based on clinical trials which recorded the exclusion of these patients from the studied population; therefore, there are still many fields in which level 1 evidence is lacking. In addition, physicians are more likely prone to treat elderly patients with cancer following their own "gut feeling," overtreating in some cases and undertreating in some others.

There have been no specific guidelines for the management of elderly patients until 2007, when the International Society of Geriatric Oncology (SIOG) created, for the first time, a dedicated task force to provide precise recommendations to treat elderly women with breast cancer (Wildiers et al. 2007). SIOG guidelines were then integrated with the European Society of Breast Cancer Specialists (EUSOMA) in 2012, and a comprehensive document was published (Boganzoli et al. 2012). This is, to this day, the best source of knowledge to obtain the fundamental information on this topic and should be used by every breast cancer specialist in their daily practice.

Despite this effort, several issues still remain unsolved, as shown by the previously described surveys, and undertreatment of breast cancer in elderly women is more than hypothetical.

Richards et al. (2015) recently presented data from 17,129 women $\geq$70 year from two UK cancer registry regions Richards et al. (2015). Analysis was restricted to patients with stage III disease and estrogen receptor (ER)-positive tumors between 2002 and 2010. Effects of a regimen including primary endocrine therapy (PET) only, and no surgery, were retrospectively investigated. Authors were able to show that nonsurgical treatment of elderly women, with early breast cancer, increases the risk of breast cancer death regardless of age, comorbidity, and disease characteristics. During the same period, a number of randomized controlled trials (RCTs) aimed to compare the efficacy of PET against surgery in older patients. A Cochrane meta-analysis demonstrated the superior local control of surgical approach but no increased survival benefit (Hind et al. 2006). As a result of this, more recent studies have advocated the use of PET only for "the very frail or very old" (Wyld and Reed 2003; Chakrabarti et al. 2011). Unfortunately, two major biases were hidden in this "more conservative" treatment strategy. First, RCT-included patients were deemed, by the studies design, fit enough for surgical treatment, thus not "very old or very frail." In addition, since this data was published, tamoxifen has largely been replaced by the third-generation aromatase inhibitors (AI) as first-line treatment for both PET and adjuvant therapy, again limiting the value of the Cochrane review.

At the same time, improvements in surgical and anesthetic techniques have occurred, and breast surgery today, even in frail patients, carries a very low morbidity and a nonexisting mortality (National Mastectomy and Breast Reconstruction Audit 2011).

A more recent review of six randomized controlled trials and 31 nonrandomized studies (including the previously mentioned RCTs) confirmed the superiority of AI over tamoxifen and the pivotal role of surgery in cancer treatment (Morgan et al. 2014). Surgery showed both better overall survival and breast cancer-specific survival as compared to PET only (67% vs. 49%; $p < 0.01$, 90% vs. 85%; $p = 0.01$, respectively). This could be partially expected because of the likely difference in comorbidities and frailty, but

again, the main message is that treating indiscriminately every patient with the same strategy leads to worse oncological outcomes.

When surgery is performed tailoring the treatment seems no longer doable but mandatory. Giuliano et al., who first promoted only limited approach to axillary surgery (Giuliano et al. 2011), published a retrospective analysis of a series of 140 elderly patients affected by T1–2 N0 breast cancer who only underwent breast-conserving surgery with no lymph node biopsy/dissection (Chung et al. 2015).

After surgery the vast majority of patients did not receive chemotherapy (98% vs. 2%; $p < 0.001$), radiation (76% vs. 24%; $p < 0.001$), or hormonal therapy (59% vs. 41%; $p = 0.04$). Of 140 patients, 5 (4%) experienced a breast cancer-related event. The 5-year overall survival rate was 70%, while the 5-year breast cancer-specific survival rate was 96%. Authors concluded that patients in this subgroup were more likely to die of causes other than breast cancer, and not performing a sentinel node biopsy did not affect survival.

Rectal Cancer

Elderly patients' rectal cancer management is frequently influenced by many factors, which lead to undertreatment and, consequently, poorer outcomes. This was first demonstrated by Chang et al. (2007) in a group of 21,390 patients identified from SEER database (1991–2002). The authors showed that the rectal cancer-specific survival rates decreased as patients' age increased. Unfortunately, this was also associated with a decreased use of multimodal treatment and of radical resection, while local excision rate was found to be higher than the younger counterpart.

Despite elderly patients being often prevented from neoadjuvant chemoradiation (CRT), preoperative therapy has indeed been associated with better oncological outcomes when followed by surgery (Sauer et al. 2004; Maas et al. 2010). The result of medical treatment has been so remarkable that Angelita Habr-Gama and her group decided to explore the possibility of not operating on patients having a complete clinical response (cCR) after CRT. Authors were able to obtain, in this subgroup, similar 5-year disease-free and overall survival as compared to the standard of care (Habr-Gama et al. 2004). Moving forward, the same group of scientists implemented this "watchful waiting" approach in a series of 70 patients with cT2–4, cN1–2 low rectal cancer who underwent only extensive CRT (54 Gy + 6 cycles of 5-fluorouracil and leucovorin) (Habr-Gama et al. 2013). Overall, 35 patients (51%) did not require any surgical treatment and they were free from disease after 56 months of median follow-up. The mean age of the patients in the study was 60.2 ± 12.9 years old; thus, the study was not specifically addressed to elderly patients, but this might be an interesting solution for unfit-for-surgery senior adults. The same hypothesis has been explored by the Memorial Sloan Kettering Cancer Center group and a prospective study is currently enrolling patients (Smith et al. 2015).

A second interesting solution offered by the same two groups is to perform only a local excision (without a formal proctectomy) after neoadjuvant CRT (Perez et al. 2013; Garcia-Aguilar et al. 2015). It should be acknowledged that both studies reported oncological results that are, at the moment, significantly worse than CRT + proctectomy, but with lower postoperative complications and better quality of life. While still debatable, if this could be a novel standard of care for patients with an extended life expectancy, it might be a viable option in the elderly where restoration of independency plays a central role. Once again it is important to appreciate how those surgical treatments, which are considered the standard of care for the general population (level 1 evidence), might not apply to senior cancer patients. As an example, total mesorectal excision has been established and validated on the general population of rectal cancer patients; however, sufficient evidence has been gathered to prove if the opposite is true for older rectal cancer patients, where the increased operative mortality and morbidity exceeds the survival advantage. Patient selection seems again to be the key step in order to offer feasible solutions without perhaps under treating them (Garcia-Aguilar 2013).

Ovarian Cancer

Complete cytoreduction with adjuvant or neo-adjuvant chemotherapy has been established as the main treatment for advanced epithelial ovarian cancer (Bristow et al. 2002; Chi et al. 2006). Peak incidence of ovarian cancer is 61 years old, which means that a high proportion of patients are elderly. Concerns visibly rose when facing the evidence that elderly patients are less likely to be optimally debulked (Cloven et al. 1999), receive standard therapy less often (Markman et al. 1993; Sundararajan et al. 2002; Uyar et al. 2005) , and are less able to tolerate medical cancer treatments (Moore et al. 2008).

Ovarian cancer prognosis is poorer for older women because the treatment is often substandard (Sabatier et al. 2015). Elderly women with ovarian cancer management are extremely challenging. On one side the goal is to achieve complete cytoreduction and improve survival, on the other side, complication rates are much higher; this can lead to severe outcomes including death.

Chi et al. (2008) have proposed a nomogram to evaluate survival in this group of patients, but few data are available (Diaz-Montes et al. 2005).

The role of the surgical strategy is to improve outcomes, regardless of the immediate perioperative morbidity and mortality. Chéreau et al. (2011) reported on 172 patients undergoing surgery for ovarian cancer from 2001 to 2009; 143 patients were <70 years old and $29 > 70$ years old Chéreau et al. (2011). Despite a limited sample size, the authors were able to show that two-year disease-free survival (DFS) was 57% for the group <70 and 35% for the group >70. The 5-year DFS was also reduced in the elderly group (40% vs. 23%, respectively). There was no difference in the rate of complete and optimal cytoreduction; however, a lower rate of pelvic/para-aortic lymphadenectomy and peritoneal surgery was noted in the elderly group. Several studies already underlined the detrimental impact of a limited lymphadenectomy independent from the extension of cytoreductive surgery (Chang et al. 2007; Chan et al. 2007; Rouzier et al. 2010). A publication by Aletti et al. (2006), it was determined that the decision to perform lymph node assessment depends on surgeon's choice, low residual disease, ASA grade and the absence of carcinomatosis. Regrettably, once lymphadenectomy has been decided upon, the main independent criterion to perform a complete lymphadenectomy versus lymph node sampling was shown to be limited to patient age under 65 years. More objective criteria have also been advocated by different authors, but the ultimate reality is that ovarian cancer surgical and medical management often requires extended and debilitating treatments in order to be effective Carli et al. (2010).

Recently, Lin et al. (2016) analyzed 7,938 elderly women from the SEER database Lin et al. (2016). Among this group, 2.9% received no treatment, 15.4% underwent surgery only, 24.8% received chemotherapy only, 41.8% underwent primary debulking surgery and chemotherapy in an optimal timeframe, and 15.1% had primary debulking surgery and chemotherapy, but timing or chemotherapy scheme were suboptimal. Those who underwent surgery only had similar survival as those who received no treatment (2.2 compared with 1.7 months), whereas those who received chemotherapy only, had a better overall survival (14.4 months). Optimal treatment was associated with the longest survival time ($P < 0.001$, median overall survival 39.0 months). The authors also concluded that, despite the fact that survival time associated with optimal treatment has increased over the past decade, the proportion of women who received optimal treatment decreased over time.

Currently no alternatives with more limited impact but similar outcomes have been recommended to effectively treat ovarian cancer. On the other hand, despite the redundant evidence in favor of this risk predictive tool, elderly women with ovarian cancer are prevented from the best available treatment, merely due to their chronological age.

Lung Cancer

The median age at diagnosis of non-small cell lung cancer (NSCLC) is approximately 70 years in Western countries (SEER database 2015). Once again, despite the high incidence of lung cancer in

the elderly, it is well known that these patients are underrepresented in clinical trials, and, therefore, it is difficult to reach evidence-based clinical recommendations for them (Sacher et al. 2013). Numerous studies have proven the feasibility of surgical treatment of elderly patients with lung cancer and even in octogenarians (Fanucchi et al. 2011; Rivera et al. 2011). However, the likelihood of elderly patients with early-stage disease not receiving any treatment is significantly increased with age (Wang et al. 2012). In 2010 and again in 2014, the European Organization for Research and Treatment of Cancer (EORTC), in collaboration with the International Society of Geriatric Oncology (SIOG), created an experts panel that generated a consensus paper for the management of elderly NSCLC patients.

First, the implementation of screening and minimally invasive techniques has significantly decreased mortality rate (Bravo Iniguez et al. 2016). McKenna et al. reported a large series of minimally invasive lobectomies with 1048 cases operated for primary lung cancer. The mean age was 72 years. Perioperative mortality was only 0.8%, and the morbidity rate was 15% (McKenna et al. 2006). This is a dramatic reduction from previously published data reporting a 7% mortality for open lobectomies (Ginsberg et al. 1983). As more authors commented, "to graphically illustrate the importance of these figures, an operative mortality of 7% equals one death for every 14 patients, while an operative mortality rate of 0.8% is one death in every 125 patients" (Pallis et al. 2014).

Secondly, segmental resection in early-stage NSCLC has shown to be an effective alternative to lobectomy that carries instead a higher risk of morbidity and mortality in the elderly population (Bravo Iniguez et al. 2014). Cheng et al. published a nonrandomized prospective, controlled study conducted to compare lobectomy with segmental resection for the treatment of elderly with stage I lung cancer (Cheng et al. 2012). A total of 184 patients were included in the study. The local recurrence and long-term survival rates were not significantly different between lobectomy and segmental resection. Among the patients who underwent segmental resection, those who had regional lymph node dissection showed a higher 3-year and 5-year survival rate than those undergoing selected lymph node resection (77.8% vs. 51.7%; $p = 0.042$; 55.6% vs. 27.6%; $p = 0.034$), but this was not significant in lobectomy. A subgroup analysis of patients with $FEV_1 < 1.5$ L showed that segmental resection, which preserves more normal lung segments, was more suitable for the elderly without decreasing the overall survival rate.

Thirdly, implementation of palliative care is an essential part of lung cancer treatment. Crucial data were reported by Temel et al. (2010) who analyzed the effect of early integration of palliative care in parallel to usual oncological care (Temel et al. 2010). Authors demonstrated an improvement of both health-related quality of life (HRQoL) and depression at 3 months when palliative care was started right from the beginning in addition to usual oncological treatment. Surprisingly, patients treated with early integration of palliative care lived 2.3 months longer than those treated with usual care.

Palliation of Symptoms: The Sooner the Better

When the report *Dying in America: Addressing Key End of Life Issues* (2014) was made public by the Institute of Medicine in 2014, it made clear that improving access to palliative care for seriously ill patients was a national priority.

"Palliative or supportive care" includes all actions that are not directly related to anticancer treatment and has the main goal to help managing cancer−/treatment-related psychological and physical symptoms. Early involvement of a "supportive care system" in the management of every frail patient should be promoted by the MDT (Naeim et al. 2014).

Surgeons play a pivotal role as providers of end-of-life care. It has been shown that among Medicare patients, almost one-third undergo surgery in the year before death, many in the last week of life (Kwok et al. 2011), while up to 25% of patients diagnosed as having stage IV cancer undergo a surgical procedure. As Lilley et al. (2016) pointed out, although surgeons routinely

care for seriously ill patients, the role of palliative care in surgery remains poorly defined.

Despite the wide room to establish roles of surgeons in palliative care teams, it seems to be recognized that timely strategies should be put in place early in the process. Temel et al. (2010) showed that lung cancer patients assigned to early palliative care experienced better QoL with lower rate of depression compared with ones only receiving care from their specialists. In addition to this, despite fewer patients receiving aggressive care, they had a longer survival when enrolled in early palliative treatment groups. Zimmer et al. (1984, 1985) were able to demonstrate that, if physicians and nurses with experience in the geriatric care were added to the equation, patients had fewer hospitalizations and nursing home admissions. Home-care team patients and caregivers reported significantly higher satisfaction.

To improve patients' and families' satisfaction, when end-of-life situations are approaching, shared decision-making seems to be the preferred model. It would be erroneous for physicians to misinterpret this process as simply obtaining an informed consent. Many surgeons struggle to balance the need for open discussions about prognosis with the desire to maintain hope; decision-making about palliative procedures poses a definitive challenge.

Miner et al. (2011) reported a higher rate of symptom resolution, lower morbidity, and longer survival using a shared decision-making approach. "Shared decisions" mean primarily to explain more accurately possible the present and future (possible) scenarios to patients and families. It has been shown that patients who are nearing the end of life and have an accurate prognostic understanding are more likely to prioritize comfort over potentially life prolonging but highly burdensome treatments.

Symptoms relief is a primary goal shared by patients and surgeons. However, patients have their own individual priorities for treatment. Family activities or events may be highly valued by patients over schedules and treatment plans. Modern, patient-oriented clinicians need to be willing to have them influencing the care process.

Cross-References

- ▶ Colorectal Cancer in Older Adults: Surgical Issues
- ▶ Early-Stage Breast Cancer in Older Adults
- ▶ Frailty in Cancer Patients
- ▶ Geriatric Screening in Cancer Patients
- ▶ Lung Cancer in Older Adults: Local Treatment
- ▶ Multidisciplinary Management of Liver, Pancreatic, and Gastric Malignancies in Older Adults
- ▶ Predictive Tools for Older Cancer Patient Management

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Principles of Radiation Therapy in Older Adults

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Sarah Hoffe, Nadia Saeed, and Jessica Frakes

Contents

Abstract

The specialty of radiation oncology has significantly evolved over the past few decades. Historically, large volumes of normal tissue were irradiated along with the tumor due to the prevailing techniques and equipment in the era of two-dimensional delivery. This led to an increased incidence of side effects, causing difficulty for elderly patients to tolerate treatment. Not only were toxicities higher but also the radiation dose could not be escalated due to uncertainty about tumor location and dose to the intended target. With the advent of computer integration into the radiation oncology clinic, the therapeutic window improved dramatically. For the first time, tumors could be visualized in three dimensions so that a new technique called 3D conformal radiation

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therapy (3D-CRT) evolved. The tumors could now be delineated such that the dose could be spatially encompassed with more precision than ever before. This led to significant improvements in local control for a variety of tumor types with fewer side effects, which are of particular concern in elderly patients, who usually present with a higher number of comorbidities that can limit treatment toleration. This chapter will discuss advances in radiotherapy and their significance for elderly patients. It will also discuss considerations for neoadjuvant, definitive, adjuvant, and palliative radiation in a geriatric population across tumor sites, with a focus on toxicity and tolerability.

Keywords
Radiation therapy · Geriatric oncology

Introduction

The specialty of radiation oncology has significantly evolved over the past few decades. Historically, large volumes of normal tissue were irradiated along with the tumor due to the prevailing techniques and equipment in the era of two-dimensional delivery. This led to an increased incidence of side effects, causing difficulty for elderly patients to tolerate treatment. Not only were toxicities higher but also the radiation dose could not be escalated due to uncertainty about tumor location and dose to the intended target (Stroom et al. 1998).

With the advent of computer integration into the radiation oncology clinic, the therapeutic window improved dramatically. For the first time, tumors could be visualized in three dimensions so that a new technique called 3D conformal radiation therapy (3D-CRT) evolved. The tumors could now be delineated such that the dose could be spatially encompassed with more precision than ever before. This led to significant improvements in local control for a variety of tumor types with fewer side effects, which is of particular concern in elderly patients, who usually present with a higher number of comorbidities that can limit treatment toleration. One example of where this technology integration has had a significant role of decreasing toxicity for elderly patients is in the setting of prostate cancer, where the integration of 3D-CRT has facilitated blocking of the normal tissues precisely in alignment with the position of the tumor (Soffen et al. 1992). This technique, called conformal avoidance, allows a beam's eye view of the volumetric relationships between structures so that an acceptable dose volume histogram (DVH) analysis that achieves the desired tumor coverage while also respecting the allowable dose that the specified volume of the normal organ can receive is achieved (Purdy 1997).

Each year since, more improvements have been developed so that radiation oncologists now have the ability to use 4D CT scans that can measure the position of the tumor as it moves with breathing (Keall 2004). This increased precision has led to the reduction of margins necessary to accurately encompass the tumor, greatly limiting the normal tissue reactions. Furthermore, each day when the patient undergoes radiation, the radiation oncologist now has the ability to ensure the patient's proper positioning by daily image guidance. This resulting image guided radiation therapy (IGRT) has resulted in more accurate daily treatment with less irradiation of the surrounding normal tissues (Bell et al. 2017).

Such imaging can be performed directly on the radiation delivery unit itself, either with kilovoltage x-rays or a conebeam CT. In the example of prostate cancer, these techniques allow the implantation via transrectal ultrasound of radiopaque markers directly into the prostate gland. Each day the patient comes in for treatment, the radiation therapist is able to image the real time position of the tumor and verify the measurements before delivery. This is important because the degree of bladder and rectal filling, as well as the effects of respiration, can significantly affect organ position. For elderly patients, avoiding long-term injury to the adjacent rectum by minimizing radiation proctitis is a central concern, thus IGRT strategies have become the standard of care for the safe delivery of high doses of external beam radiation therapy (EBRT) to the prostate (Gill et al. 2011).

The treatment landscape shifted further with the expansion of treatment tools to include intensity modulated radiation therapy (IMRT) (Purdy

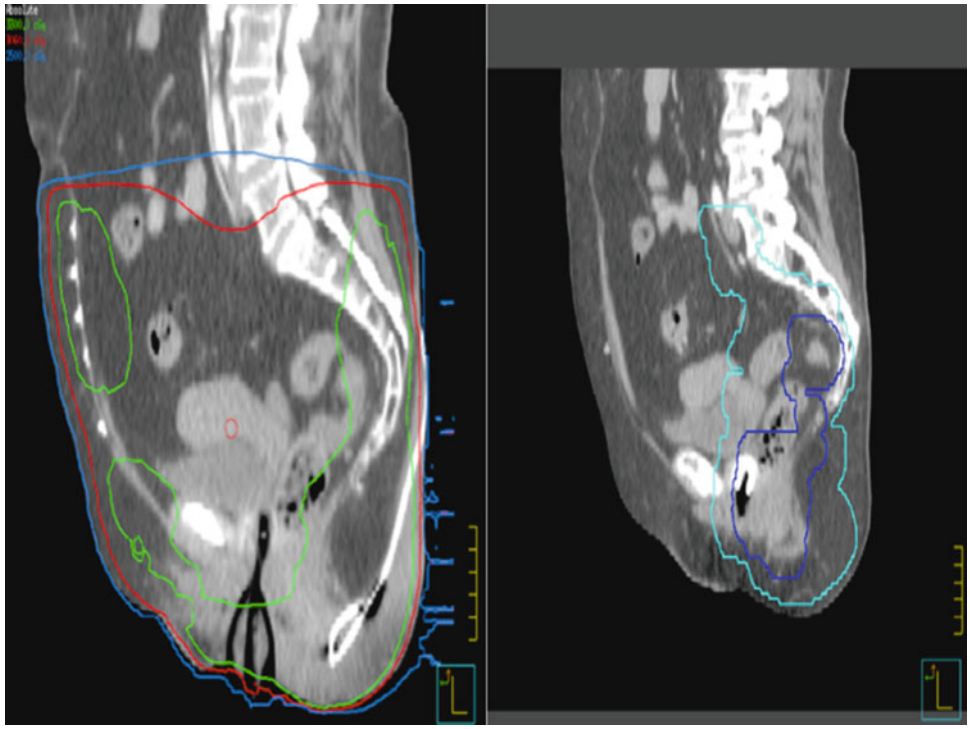

Fig. 1 IGRT: Conebeam CT overlaid with the simulation CT showing the positioning of a liver oligometastasis for SBRT

1999). With 3D-CRT, the dose is delivered with a uniform fluence across the treatment field. However, with IMRT, the physician can change the radiation beam into individual beamlets to focally escalate or de-escalate the dose. The dose is shaped by these individual computerized blocks that move during treatment delivery to create the specific intensity of the doses across the volume of interest. The result is to allow safe dose escalation to improve tumor control while minimizing the morbidity to the adjacent normal tissue (Fig. 1).

In the modern era, radiation therapy can be delivered with conventional fractionation with daily doses of 1.8–2.0 Gy (Gray, the unit of dose) over many weeks or with a newer type of high dose ablative delivery called stereotactic body radiation therapy (SBRT). With SBRT, doses up to 12 times the normal daily dose can be delivered to maximize tumor dose with rapid falloff of dose to the surrounding normal tissue. Research to date indicates there may be a novel mechanism of cell kill with SBRT such that there is apoptotic death of the endothelial cell microvasculature (Kolesnick and Fuks 2003). Although the exact mechanism of cellular injury is not known, clinically these 5-day or less regimens are associated with higher rates of local control. Such intensified treatment is only possible because of the advances in 4D CT, 3D-CRT, and IMRT, which now allow maximization of a conformal approach.

Further, imaging of the tumor has dramatically improved with the addition of scans that incorporate metabolic tumor information that can be fused directly to the planning CT scan for treatment. With many tumor types, a positron emission tomogram (PET) scan is fused to a CT scan and can be directly imported into the treatment planning system. This allows the radiation oncologist the ability to improve the accuracy of the target volume delineation; this certainty of tumor position leads to smaller planning target margins, which aids in normal tissue morbidity relief.

For some patients, internal radiation treatment with brachytherapy may be a better option. With

the example of prostate radiation, this can be delivered either with a low dose rate LDR technique of implanted radioactive seeds or a form of high dose rate HDR delivery (Magnuson et al. 2017).

These techniques have a role for patients with low risk disease as definitive treatment alone or in combination with IMRT for higher risk disease. For those elderly patients who may have difficulty assuming the treatment position for 5 days a week for 9 weeks, brachytherapy may have an enhanced therapeutic ratio.

Consideration of avoiding toxicity is thus significantly heightened in the elderly. Design of treatment fields must take into account how long the patient can tolerate a certain position per day and how many weeks will be needed to deliver the intended dose. For elderly patients, the life expectancy, goals of treatment, and the potential for least acute and late side effects are all factors to be expectantly weighed.

Anticipation of acute toxicity revolves around what organs will be in the radiotherapy field and review of what doses they will receive according to the DVH. With the arsenal of modern treatment planning techniques, modification and adaptation of treatment is more readily accessible than ever before. Incorporation of IMRT and IGRT has been shown across many clinical treatment sites to limit morbidity by virtue of decreasing the volume of healthy tissue irradiated to a high dose. Nonetheless, patients are seen weekly in the radiation oncology clinic to assess the individual's toleration of treatment. Assessment of the skin for erythema and desquamation is routine. This is performed in conjunction with assessment of other normal tissue effects referable to the body part being irradiated. In addition, many patients receive concurrent chemotherapy with the radiation, thus expanding the assessment each week to evaluate for an expanded array of acute symptoms specific to the agents and doses being received. Nutritional support is critical during radiation therapy and, for the elderly patient, this can often mean the difference between treatment toleration and hospitalization. With a multidisciplinary team including a dietician, weight loss can be rapidly evaluated and managed with oral supplements. For elderly patients who may have baseline sarcopenia, vigilance of nutritional status is paramount.

Once the acute effects of radiotherapy have healed, the patient treated with curative intent returns for ongoing surveillance. During these visits, carefully tailored probing of the function of those normal tissues within the treatment field may elicit suggestion of late radiation damage. Each normal tissue has a tolerance dose for radiotherapy, which is considered the "safe" dose for the majority of the population. However, within the population, there are subsets of patients who have increased radiosensitivity of their healthy tissues that may manifest as significant toxicity. Monitoring of those tissues within the field is indicated since radiation damage may not be clinically apparent for years after treatment.

If an elderly patient does develop evidence of a late complication, multidisciplinary evaluation is often needed to place the effect within the full context of the elderly patient's life and social support environment. Supportive care with the appropriate modality based on organ site is done with the intent of improving the microvascular tissue environment. With some delayed injuries, hyperbaric oxygen therapy can improve the local healing of the tissue irradiated, causing notable gains in function (Bennett et al. 2016). However, such therapy takes multiple weeks to deliver in an enclosed space and is not necessarily the most comfortable environment for an elderly patient.

In short, technological advances over the last few decades have revolutionized the delivery of radiation therapy, increasing the escalation of high-dose irradiation to the tumor and lower dose to the surrounding normal tissues. These improvements have expanded options for elderly patients with cancer to include the potential of noninvasive radiation. Depending on the site, radiation therapy can be used as a neoadjuvant, adjuvant, or definitive form of therapy. In this chapter, we will explore some specific examples of how such treatment may have an expanded role for elderly patients.

Neoadjuvant Radiotherapy

Treatment of gastrointestinal tumors often involves trimodality therapy such that chemotherapy and radiotherapy are delivered, either sequentially or concurrently, prior to surgical resection to maximize the potential for local control and to enhance complete excision of the tumor with negative margins for an R0 resection. Prior to the era of conformal therapy, large field irradiation was associated with increased rates of acute toxicity. With integration of advanced technologies, radiation therapy for GI cancers can be delivered with more normal tissue sparing than ever before.

The current standard of care based on data from the CROSS Trial is for concurrent chemoradiation prior to esophagectomy for locally advanced disease (Shapiro et al. 2015). Such concurrent chemoradiation has the potential for significant esophagitis during treatment, which could lead to feeding tube placement as well as the potential for radiation pneumonitis, which could affect the perioperative surgical risks. IMRT has been shown not only to decrease the rates of grade $\geq$3 acute treatment-related toxicity (Shridhar et al. 2015) but also to improve the outcomes with better overall survival, locoregional control, and noncancer death (Lin et al. 2012). With IMRT techniques, it is now possible to endoscopically place fiducial markers to denote the superior and inferior extent of tumor prior to measurement of the tumor's position with breathing on the 4D CT scan such that the gross tumor volume can receive a higher dose than the surrounding clinical volume (Fernandez et al. 2013; Dhadham et al. 201614).

Higher dose >51 Gy data now suggests that this may lead to improved outcomes (Zhang et al. 2005). Since the likelihood of attaining a pCR increases with dose, (Geh et al. 2006) with these new dose escalated techniques improved outcomes for patients with locally advanced tumors may be increasingly possible. Indeed, Donohoe et al. have reported a 71-month median survival for those esophageal patients attaining a pCR versus 17 months for those without a pCR, $P < 0.0001$ (Donohoe et al. 2013). For elderly patients, these treatment improvements are important to consider for patients who are medically inoperable (Li et al. 2015).

As in esophageal cancer, integration of preoperative radiation strategies is associated with improved local control and less acute as well as chronic toxicity in patients with locally advanced rectal cancer (Kapiteijn et al. 2001; Sauer et al. 2004). These improvements in local control are significant for elderly patients who are medically unable to undergo surgical resection, while the decreased toxicity is particularly beneficial in a geriatric population that tolerates side effects more poorly due to a higher presence of comorbidities. Moreover, similar to treatment of locally advanced esophageal cancer, patients treated with concurrent chemoradiation prior to surgery who attain a pCR have improved 5-year disease free survival (DFS) compared to those who do not, 83.3% pCR versus 65.6% non pCR, $P < 0.0001$ (Maas et al. 2010). In the last few decades, comparison of long-course chemoradiation over 5.5 weeks has been compared with short-course external beam irradiation over one week and found to be equivalent (Bujko et al. 2006). In addition, a short course of endorectal brachytherapy has been reported to have equivalent local control outcomes with conventional external beam treatment but with less toxicity given the dose is to the tumor and adjacent mesorectum only (Vuong and Devic 2015). Thus, for the elderly patient, delivery of a short course of pelvic or endorectal radiation alone prior to surgery has the advantage of improving outcomes for patients in whom chemotherapy may be contraindicated or for whom longer-treatment durations would pose challenging. Finally, with the emergence of tumor-regression criteria, there is now an alternative for those elderly patients who achieve an excellent clinical response and in whom rectal surgery may be contraindicated called nonoperative management. (Beets et al. 2015; Smith et al. 2015).

Patients with pancreatic cancer often present with disease that is not amenable to upfront resection, termed either borderline resectable (BRPC) if the tumor abuts the blood vessel or locally advanced (LAPC) if the tumor is encasing the vessel (Schwarz and Katz 2015).

In elderly patients, standard neoadjuvant therapies of systemic chemotherapy followed by chemoradiation may be difficult to tolerate so advanced techniques have now paved the way for integration of a short course of high-dose radiation termed stereotactic body radiation therapy (SBRT). Since the earliest pancreatic SBRT studies (Koong et al. 2004; Hoyer et al. 2005) were introduced in the early 2000s, significant progress has been made to optimize the number of fractions, manage the respiratory associated target motion, and precisely deliver the high dose directly to the gross tumor volume (Pollom et al. 2014). A recent prospective multi-institutional trial (Herman et al. 2015) reported rates of grade $\geq$2 gastritis, fistula, enteritis, and ulcer of only 2%. Indeed, pancreatic SBRT has become exceedingly well tolerated and represents a convenient choice for the elderly patient with multiple comorbidities since the treatment is typically delivered within one week.

Definitive Radiation Therapy

Incorporation of radiation advances has led to exploration of high-dose radiation alone for the treatment of oligometastases. Many elderly patients present with isolated liver metastases but are not candidates for invasive procedures due to their medical comorbidities. Liver SBRT for metastatic disease thus emerges as an attractive option for this group given available data citing excellent local control and minimal morbidity (Rusthoven et al. 2009; Lee et al. 2009; Rule et al. 2011; Meyer et al. 2016). Definitive SBRT has also been reported as effective for those elderly patients with pancreatic cancer who have unresectable disease, decline surgery, or have comorbidities that preclude surgery, with data from the University of Pittsburgh showing no acute or late grade 3+ toxicities (Kim et al. 2013).

In addition to the potentially curative delivery of ablative SBRT to eradicate metastases, there is also the future possibility that focal SBRT to an isolated local site, by virtue of effects on the immune system leading to resolution of distant metastases termed the abscopal effect (Zeng et al. 2013), may lead to enhanced systemic control in an elderly population where chemotherapy may not be a choice given the patient's underlying medical status. The potential of immune-SBRT in patients is already being explored and, pending completion of ongoing trials, could become an excellent option for elderly patients if their local as well as distant disease could be improved by a noninvasive modality.

Oligometastases to the brain offer particularly challenging circumstances to elderly patients who may already be experiencing declining cognitive function. Conventional whole brain radiation treatments for brain metastases are associated with acute effects of increased fatigue and potential late effects of neurocognitive injury with associated deficits (Li et al. 2008; Chang et al. 2009). For elderly patients with limited brain metastases, an approach of stereotactic radiosurgery (SRS) offers highly conformal, high ablative doses without diffuse CNS injury, offering significant sparing of the normal brain tissue. Reports of patients $>$65 years treated with SRS have indicated excellent local control (Noel et al. 2005) and may provide the most appropriate option for these patients with very limited disease in a suitable anatomic location. Unfortunately, elderly patients with inoperable primary glioblastoma multiforme (GBM) undergo much higher volumes of brain irradiation due to the nature of their infiltrative brain tumors. Recent data suggests that incorporation of a patient's MGMT gene methylation status could be useful to select elderly patients for regimens including radiation and temozolomide (Stupp et al. 2005; Brandes et al. 2009; Wick et al. 2012; Malmstrom et al. 2012).

In addition to SBRT integration for patients with metastatic disease, elderly patients who are not optimal surgical candidates with early stage non-small cell lung cancer may also derive significant benefit from this definitive radiation alone approach, with 3-year survival rates of 45% (Haasbeek et al. 2010). Even when the disease is more advanced and concurrent chemoradiation regimens are planned, more tailored techniques can improve toleration for elderly patients (Schild et al. 2007). Patients with more advanced primary lung cancers benefit from a conformal approach

with daily IGRT. In particular, data has emerged that involved-field radiotherapy to the gross disease only is associated with improved outcomes in the elderly population (Yu et al. 2008). Radiation to a moving tumor in the thorax can be associated with the toxicities of radiation pneumonitis, pericarditis, and esophagitis. Limitation of the volumes irradiated with avoidance of healthy tissue can facilitate the tolerance of elderly patients to definitive combined modality and definitive therapy regimens.

Elderly men with prostate cancer benefit from advanced radiation modalities as well, with increased choices titrated to stage of disease ranging from brachytherapy alone to IMRT/IGRT alone to a combination of both modalities. Offering treatment to such elderly patients can be tailored to their life expectancy and geriatric assessment. Indeed, data indicates that low-risk cancers in men >75 with comorbid conditions that are significant do not benefit from aggressive treatment (Daskivich et al. 2011). Similarly, for those patients with higher-risk disease, assessment of the Charlson comorbidity index for patients receiving external beam radiation in combination with brachytherapy and androgen blockade predicts overall survival and can be utilized in treatment decision-making (Hjalm-Eriksson et al. 2017). For those patients who elect to receive treatment, IMRT has shown less grade-3 proctitis (Dearnaley et al. 1999).

With advanced head and neck cancers, advanced modalities have a particularly critical role in treating elderly patients. Historically, head and neck radiation was associated with large-field irradiation that was associated with increased rates of long-term toxicities such as xerostomia, feeding tube dependence, and dysphagia (Prameela et al. 2016). Now, with IMRT, the high-dose regions can be carefully sculpted such that they encompass the primary and nodal tumor volume while keeping the mean dose to the normal tissues below the level at which significant toxicity occurs (Mendenhall et al. 2006; Nutting et al. 2011).

These improvements facilitate more elderly patients being offered organ preservation strategies with concurrent chemotherapy and radiation therapy. The focality of high dose to the PET/CT defined gross tumor volumes has also been associated with improved outcomes, enhancing the therapeutic ratio for this patient population. Finally, with daily imaging, the volume of tissue irradiated can be decreased as the patient responds to therapy. This new strategy is called adaptive radiation and allows real time tracking of tumor response during the weekly therapy so that adjustments can be made that will increase the volume of normal tissue preserved from the high-dose regions (Veresezan et al. 2017).

In addition to better computerized treatment planning and delivery techniques, novel radiation delivery modalities are being explored to further improve outcomes. In recent years, proton therapy administration has been increasing, with clinical trials evaluating whether this modality is significantly superior given its much higher cost (Mishra et al. 2017). Although data is still accumulating, there are some treatment sites in particular, such as primary liver tumors, where proton therapy may have a resonant niche. With primary liver malignancies such as hepatocellular carcinoma (HCC), there is underlying liver dysfunction, which limits the tolerance of the liver (Kimura et al. 2017; Fukuda et al. 2016). For elderly patients in whom there may be underlying comorbidities that preclude consideration of liver transplant or resection, focal liver proton therapy may be especially attractive. With protons, the physical characteristic of the radiation beam is different than that of the traditional photon beam such that there is a Bragg peak, beyond which the radiation dose stops, unlike the photon beam which has low dose delivered along the exit path (Skinner et al. 2011). This feature of protons decreases the volume of normal liver irradiated such that the risk of radiation-induced liver disease is lowered. For elderly patients, as liver proton data matures, this may become an important option.

In addition to EBRT approaches, there are expanding indications for brachytherapy as both curative and palliative treatment in many tumor sites in addition to prostate cancer. For primary and second liver tumors, for example, injection of millions of radioactive spheres can directly irradiate the liver malignancy and minimize the dose to the healthy parenchyma. HCC tumors traditionally undergo radioembolization for palliation, but

there are expanding roles of selectively irradiating a limited volume of the liver to an extremely high dose in an attempt to eradicate very focal disease (Kallini et al. 2016). The advantages of these liver-directed radioactive sphere strategies for elderly patients are limitation of short duration of side effects to fatigue, nausea, and pain with outpatient delivery.

Many elderly patients may have difficulty travelling to outpatient radiation facilities given a living situation in an institutional facility. For these patients, shorter duration of treatment is of particular concern. With nonmelanoma skin cancer incidence rising with increasing age, this becomes a difficult management problem for the infirm patient who is wheelchair bound and so frail that navigating transfer to the radiation treatment couch daily may pose a contraindication. For these patients, short-course brachytherapy may be advantageous with recent evidence showing excellent and good cosmetic results in 94.8% of patients (Delishaj et al. 2016).

Finally, there is new data evaluating the role of the patient's individual tumor histology to influence a personalized radiation dose choice, which could lead to more organ preservation approaches for radiosensitive tumors (Torres-Roca 2012). Within the spectrum of GI cancers, we look to squamous cell carcinoma of the anus for an example. Early work from Nigro et al. (1981) demonstrated that anal cancer represented a far more radiosensitive histology than rectal adenocarcinoma and could be treated definitively, not preoperatively. Data over the past 30 years has refined the treatment paradigm such that IMRT dose-painted definitive chemoradiotherapy is now the standard of care with significantly less acute toxicity than prior techniques (Kachnic et al. 2013). The recognition of the inherent differences in individual tumor radiation sensitivity has led to an appreciation that the future may be to consider the appropriate genomically adjusted radiation dose (GARD) for each patient (Scott et al. 2017). Incorporating this concept into future trials will help identify those elderly patients with radiosensitive tumors that may benefit from a noninvasive radiation approach.

Adjuvant Radiation

One of the best examples of adjuvant irradiation is following lumpectomy for invasive ductal carcinoma of the breast to complement breast preservation. In the setting of early stage breast cancer, the Oxford overview reported postoperative radiation therapy to the whole breast has been associated with a twofold decrease in first recurrence even in older patients (EBCTCG 2011). For patients with early stage invasive breast cancer $\geq$70, breast conservation therapy showed an absolute decrease in ipsilateral tumor recurrence of 7% with over 10 years of median follow-up compared with lumpectomy alone and tamoxifen (Hughes et al. 2004, 2013). Yet, although the whole breast radiotherapy is well-tolerated, elderly patients have sought shorter course fractionation schedules, and data has emerged to support this option as well. Indeed, such hypofractioned regimens have shown no difference in long-term local control or cosmesis (Bentzen et al. 2008; Haviland et al. 2012; Whelan et al. 2010). Advanced radiation techniques, such as treatment in the prone position or with the deep inspiration breath hold technique, have evolved to decrease the amount of normal lung and heart irradiated, which particularly may benefit elderly patients (Kirova et al. 2009; Grann et al. 2000; Smyth et al. 2015).

In addition to whole breast approaches, partial breast radiation has been investigated as an option for breast preserving therapy in selected patients. For elderly patients, delivery of a single fraction of radiation immediately following lumpectomy in the operating room, termed intraoperative radiation therapy or IORT, is especially attractive. Data to support this approach has been reported by investigators from the TARGIT and ELIOT trials. In the TARGIT trial, over 2,000 patients were randomized to receive either a 20 Gy dose of IORT or to standard whole breast irradiation, with 5-year results showing only a slight increase in local recurrence for the IORT group (3.3% vs. 1.3%, $P = 0.042$), which may be key to the decision-making of elderly women (Vaidya et al. 2014; Vaidya et al. 2010). Similarly, in the ELIOT trial, over 1000 patients $\leq$75 were treated with

standard whole breast techniques or single 21 Gy fraction of IORT following lumpectomy (Veronesi et al. 2013), with results showing worse local control in the IORT group, 4.4% versus 0.4%.

Accelerated partial breast radiotherapy can also be performed after surgery, either with external beam or brachytherapy approaches, and evidence to support its effectiveness has now matured (Vicini et al. 2016). As there has not been any difference in overall survival and since some series of APBI patients have noted less acute and chronic toxicity, this option may have a role in those appropriately selected elderly patients at low risk for locoregional recurrence of their disease.

Similar to breast cancer adjuvant strategies, postoperative treatments for patients with endometrial cancer have improved so that women experience less normal tissue morbidity. Within this spectrum of malignancy, tumors that are defined as high-intermediate risk based on age, depth of myometrial invasion, and grade benefit from postoperative radiation, including elderly women with stage I disease (Keys et al. 2004; Scholten et al. 2005). Further studies have refined the optimal extent of radiation, comparing pelvic radiation with intravaginal brachytherapy alone. In the PORTEC-2 trial, women >60 with stage IB G 3 and stage IC G1–2 and IIA G1–2 were randomized to pelvic external irradiation to vaginal brachytherapy (VB) alone (Nout et al. 2012). Although the results showed no significant differences in locoregional or distant recurrence at 5 years, the vaginal brachytherapy alone was associated with better quality of life and less toxicity. For elderly women, the strategy of VB with its improved normal tissue toxicity profile significantly enhances the therapeutic ratio.

Strategies to decrease normal tissue toxicities have also been explored in the adjuvant therapy of resected pancreatic head adenocarcinoma. Incorporation of adjuvant irradiation is currently controversial, with conflicting European data supporting systemic chemotherapy alone (Neoptolemos et al. 2001; Oettle et al. 2013) compared with US data from the RTOG (Regine et al. 2011; Berger et al. 2012). For those elderly patients receiving adjuvant irradiation, contouring should be done according to consensus guidelines (Goodman et al. 2012) with consideration of techniques involving IMRT and IGRT to decrease toxicity (Hajj and Goodman 2015).

Palliative Radiation

Palliative radiation has the potential to reduce pain and improve quality of life without curative intent for end-stage metastatic cancer. The patterns and indications for palliative radiation in an elderly population warrant discussion. There has been data to suggest that patient age influences the likelihood that the patient receives radiotherapy with palliative intent, and specifically that elderly patients are less likely to be administered palliative radiation by their provider. This is a trend that appears to be consistent in palliative care services offered to elderly cancer patients, with some data suggesting that older patients are less likely to be referred or to use a Palliative Care Specialist (Burt and Raine 2006). Wong et al. evaluated Age-related trends in receipt of palliative radiation in 63,221 patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database with metastatic cancer of the lung, breast, prostate, or colon/rectum between 2000 and 2007 (Wong et al. 2014). Increasing age was significantly associated with a steady decrease in administration of palliative radiation: for patients 66–69 years, 70–74 years, 75–79 years, 80–84 years, and over 85 years, the rates of palliative radiotherapy receipt were 42%, 38%, 32%, 24%, and 14%. Multivariate analysis showed similar results, with 7%, 15%, 25%, and 44% decreased rates of radiation receipt for patients 70–74 years, 75–79 years, 80–84 years, and over 85 years compared to 66–69 year old patients (all $P < 0.0001$). Murphy et al. similarly found that likelihood of receiving palliative radiotherapy decreased with increasing age group from 65 to older than 85 for elderly patients with colorectal, lung, breast, or prostate cancer in their analysis of 51,610 Medicare patients (Murphy et al. 2013). Results from these studies indicate a need for more research investigating the

indications and rationales for decreased administration of palliative radiotherapy in an elderly population that can potentially benefit from its use.

Research has also been done to identify factors associated with greater likelihood of receipt of palliative radiation among elderly patients. Guadagnolo et al. performed an analysis of elderly Medicare patients who received palliative radiation for lung, breast, prostate, colorectal, or pancreas cancers from the SEER database from 2000 to 2007 (Guadagnolo et al. 2013). Elderly patients who had an earlier year of death, had lung cancer as the cause of death, were younger, were male, were not black, were married, had a Charlson comorbidity index of 0, were part of the southern SEER region, lived in an urban environment, had a neighborhood income level in the highest quartiles, and did not receive hospice care were more likely to receive palliative radiation. Moreover, of the 15,287 (7.6%) patients who received palliative radiation, almost 20% (2,721) received more than 10 days of treatment. The authors found that patients who did not receive of hospice care, patients who were treated in a freestanding facility, and Caucasian patients were more likely to receive more than 10 days of palliative radiation in the last 30 days of life.

There is also evidence to suggest that elderly cancer patients are as likely to benefit from palliative radiotherapy as younger patients, and therefore that age is not an appropriate factor to use in determining administration of radiation therapy for palliation. Campos et al. examined response to palliative radiation for painful bone metastases in 558 patients and found no significant differences in pain scores or analgesic intake between patients 65 years or older, 70 years or older, and 75 years and older compared with younger patients at 1, 2, or 3 months following radiation (Campos et al. 2010). Instead, there was a significant correlation between response and performance status, indicating this could potentially be a useful indicator in determining which patients can tolerate palliative radiotherapy for bone metastases. Westhoff et al. found similar results in 1,157 patients treated with palliative radiation for painful bone metastases (Westhoff et al. 2014). The authors compared pain response based on changes in pain score and medication and quality of life between patients less than 65 years ($n = 520$), patients 65–74 years ($n = 410$), and patients 75 years and older ($n = 227$). They found that there were no significant differences in pain response based on age group, and there was comparable overall quality of life between elderly and younger patients, indicating that age should not prohibit receipt of palliative radiation for bone metastases.

In a subgroup analysis of a phase III trial showing significantly better outcomes from palliative chemoradiation compared to palliative chemotherapy alone in poor prognosis patients with unresectable, locally advanced stage III non-small cell lung cancer except those with 2 or worse performance status, Strom et al. studied the effect in patients based on age (Strom et al. 2015). Patients in the experimental group received 42 Gy in 15 fractions, in addition to the four courses of carboplatin and vinorelbine that all patients received. Separating patients into those 70 and older and those less than 70, the authors found significantly increased 2- and 3- year survival in both age groups, and better preserved health-related quality of life and less hematologic toxicity in the older age group, although the increase in overall survival associated with radiation was only significant for the younger age group. These data are promising and suggest that palliative radiation can be feasible and beneficial in a geriatric population in this setting.

Future Directions

In addition to advances in computerized radiation treatment planning systems, novel machine delivery units are also continuing to evolve. Recent interest has focused on the functional information derived from MRI units that are mounted to the radiation emitting linear accelerator. With the ability to image the tumor and surrounding normal tissue on MRI scanners in real time during treatment delivery, there is optimism that this capability will further enhance the therapeutic ratio. For elderly patients, this would

increase the potential for conformal avoidance of healthy tissue, particularly for targets that move with respiration. The increased certainty of both tumor location and normal tissue location would translate to an ever-greater degree of precision such that smaller margins could be used for treatment planning. The resulting sparing of normal tissue could further enhance the ability to dose escalate the gross disease. Moreover, there is the potential to adjust the treatment fields as the course of radiation progresses over subsequent days given the functional assessment of in vivo response. All of these future therapies await data from trials to determine optimization, but, for the elderly population, this could increase the prioritization of noninvasive EBRT as the treatment modality of choice. Increased confidence in tumor location may also come from continued advances in diagnostic imaging. Novel ways to extract mineable data from the images themselves is emerging as the new field of radiomics (Lambin et al. 2012).

These imaging features may be able to direct the delivery of dose painting with the deliberate accounting for discrete habitats within the tumor. For elderly patients this would mean relative sparing of normal tissue adjacent to tumor that requires a lower dose. The future may thus be shaped around more actionable intelligence about the discrete biological features of each patient's individual tumor so that truly personalized radiation can be delivered for each patient. In a frail elderly population, that would be of the highest clinical concern.

Conclusion

In summary, radiation therapy has evolved over the past few decades to include advances in tumor targeting, location, and delivery highly relevant to an elderly patient population. These improvements have increased the safety of both EBRT and brachytherapy and offer elderly patients a highly effective, well-tolerated outpatient treatment. Personalization of technique, treatment position, and fractionation schedule can be more readily adapted to the special needs of a fragile elderly patient. Whether such treatment is indicated in the neoadjuvant, adjuvant, definitive, or palliative setting, patients can benefit from the incorporation of advanced technologies. Further optimization may be possible in the future with the expected developments of increasingly sophisticated imaging equipment on the radiation delivery unit itself.

Cross-References

- ▶ Aging and Cancer Biology
- ▶ Digestive Organ Aging and Cancer
- ▶ Frailty in Cancer Patients
- ▶ Head and Neck Tumors in Older Adults: Systemic Treatments and Combination with Local Strategies
- ▶ Lung Cancer in Older Adults: Local Treatment
- ▶ Mitochondria, Oxidative Stress, Cancer, and Aging
- ▶ Multidisciplinary Management of Liver, Pancreatic, and Gastric Malignancies in Older Adults
- ▶ Neurological Aging and Cancer
- ▶ Organizing the Clinical Integration of Geriatrics and Oncology
- ▶ Pain Management in Older Cancer Patients
- ▶ Predictive Tools for Older Cancer Patient Management
- ▶ Respiratory Organ Aging and Cancer

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Principles of Chemotherapy in Older Adults

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Stuart M. Lichtman

Contents

Abstract

The aging of the population and the resultant increase in older patients with cancer make the study of this vulnerable group an important focus of cancer care. Older patients are the largest consumer of pharmaceuticals and have the highest incidence of drug toxicity and

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adverse events. It is critical for clinicians to have adequate information regarding these therapeutic issues. This chapter will discuss some basics of pharmacology and aging and drug metabolism of specific agents.

Keywords
Chemotherapy · Pharmacology · Pharmacokinetics · Polypharmacy · Toxicity · Assessment

Introduction

Age is the single most important risk factor for developing cancer with 60% of all newly diagnosed malignant tumors and 70% of all cancer deaths occurring in persons 65 years or older. It has been estimated that by the year 2030, 20% of the US population (70 million people) will be older than age 65 years. The median age range for diagnosis for most major tumors is 68 to 74 years, and the median age range at death is 70 to 79 years. The mortality rate is disproportionately higher for the elderly population. There are several potential reasons for this, including more aggressive biology, competing comorbidity, decreased physiologic reserve compromising the ability to tolerate therapy, physicians' reluctance to provide aggressive therapy, and barriers in the elderly person's access to care (Williams et al. 2015). The elderly patient with cancer often has an elderly caregiver or is socially isolated. The older patients have not been participants in clinical trials, and the data necessary to help clinicians care for these patients is lacking. All of these factors contribute to the difficulty of caring for these complex, heterogeneous, and vulnerable patients (Rao and Cohen 2016). The field of Geriatric Oncology has become increasingly recognized as an important component of cancer care and cancer research.

Geriatric Assessment in Oncology

The identification of problems in older patients is critical in prognostication and decisionmaking. Researchers in geriatric oncology have demonstrated that the traditional method of routine history and physical is inadequate in determining elder-specific issues (Extermann et al. 1998, 2000). Clinicians have not been trained to ask the appropriate questions and appropriate interpret the available data. Medical oncologists have used performance status scales such as the Karnofsky and ECOG (Eastern Cooperative Oncology Group) scales to help stratify patients for treatment and as part of clinical trial eligibility. This has been a valuable tool and, for the general oncology population, has been helpful and has withstood the test of time. However, this simple approach is not adequate in the complex, heterogeneous older population. Performance status often does not reflect the functional status of older patients (Extermann et al. 1998). Clinicians will appropriately refer to published clinical trials and established national and international guidelines to assist to decisionmaking and deciding on treatment options. Unfortunately, older patients have been grossly underrepresented in clinical trials, and data reporting has been inadequate (Lichtman 2012a; Hutchins et al. 1999). This includes registration trials for new drugs (Scher and Hurria 2012; Talarico et al. 2004). When they do participate, they are an exceptional group of elders who have passed the often-stringent eligibility requirements and usually have minimal to no comorbidity and an excellent performance and functional status. Therefore, the available data usually do not reflect the average patient seen in practice. The result is that there is a paucity of data to make true evidence-based decisions. In order to obtain this important information, researchers in geriatric oncology have been developing geriatric assessment scales appropriate for the oncology patient. There is a need to assess basic information. Functional assessments include activities of daily living (toileting, feeding, dressing, grooming, ambulation, bathing) and instrumental activities of daily living (using the telephone, shopping food preparation, housekeeping, laundry, transportation, and ability to take medication accurately). Dependence in these areas has shown to be a prognostic factor for poor outcomes and treatment-related toxicity (Audisio et al. 2008; Hurria et al. 2011b; Korc-Grodzicki et al. 2015).

The presence of a geriatric syndrome (delirium, dementia, incontinence, falls, pressure ulcers, malnutrition, osteoporosis, hearing and vision difficulties, and sleep disorders) also has a negative impact (Reuben et al. 1992). The study of the overall evaluation of the older patient has been an extrapolation of the established Comprehensive Geriatric Assessment (CGA) methods. The CGA is a multidisciplinary, interdisciplinary diagnostic process focusing on the medical, psychosocial, and functional capabilities to develop a coordinated and integrated plan for treatment and follow-up (Wildiers et al. 2014). It is recognized that a CGA as performed by geriatricians is not practical in the usual outpatient oncology setting. Researchers are trying to streamline the approach by determining the most important questions in terms of oncologic care and then validating this approach in various settings. A position paper published by the International Society of Geriatric Oncology (SIOG) highlighting issues in this field and discussed the domains which need to be evaluated and the important questions to be addressed (Wildiers et al. 2014). In terms of predictive models, one area that has developed a significant amount of important data is the risk of therapy-related toxicity. Two models have been developed. The Cancer and Aging Research Group developed a predictive for significant (grade 3+) hematologic toxicity (Hurria et al. 2011b). The power of this model is that it has been shown to be better than clinical judgment in predictive value. The study also demonstrated that those older patients with the lowest scores (0–3) still had a 25% risk of $\geq$ grade 3 toxicity. The CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) score is able to distinguish several risk levels of severe toxicity. It predicts separately hematologic and nonhematologic toxicity (Extermann et al. 2012). Oncology-specific geriatric assessments are also being developed to predict other outcomes (Kenis et al. 2014). These scales include the G8, Flemish version of the Triage Risk Screening Tool (fTRST), Groningen Frailty Indicator, and Vulnerable Elders Survey-13 (Bellera et al. 2012; Kenis et al. 2014). Another important consideration is recognizing frailty. The frail patient can be thought of an individual who have a higher susceptibility to adverse outcomes, such as mortality and institutionalization. From an oncology perspective, it often indicates a patient who has dependence in activities of daily living and if given standard therapies will often not complete the treatment, have excessive toxicity, and therefore will not benefit. The frailty phenotype was established by the work of Fried et al. (2001). Clinicians need to recognize this group to avoid excessive toxicity and suffering (Rockwood et al. 2005). Predictors of mortality can be helpful to clinicians to weight the risk vs. benefits of therapy, particularly adjuvant treatment. The website ePrognosis (www.eprognosis.com) is one such example. Gait speed has been shown to be a powerful predictor of survival (Studenski et al. 2011) and is clearly simple to evaluate. Geriatric assessment can also be helpful in predictions of delirium (Korc-Grodzicki et al. 2014). These scales and predictive models also have been shown not to be time-consuming to the medical staff and are often self-administered by the patient. The functional components such as gait-speed, get up, and go testing can be done by nursing. Newer technologies are beginning to be utilized to capture and evaluate this information (Kelly and Shahrokni 2016).

Physiology of Aging and Drug Therapy

There are a number of physiological changes which accompany aging (Lichtman 2006; Lichtman et al. 2007a). Drug compliance is an important issue particularly with the marked increase in oral anticancer therapies which compound the problem of polypharmacy (Lichtman 2015; Nightingale et al. 2015). Studies have emphasized that obesity is a significant problem in elderly and should be considered in trials (Campbell et al. 2012; Gibson et al. 2014; Renfro et al. 2016). Other variables to be considered are the effect of age and diet and genetic polymorphisms (Walko and McLeod 2014). Polypharmacy can also affect metabolism due to the potential of drug-drug interactions. There is an age-related reduction in GFR which is not reflected by an increase in serum creatinine levels

because of the simultaneous loss of muscle mass which occurs with age. Two common equations used clinically are the Cockcroft-Gault and Jelliffe equations. It should be noted that many older patients who have a serum creatinine in the normal range for a particular laboratory have renal insufficiency (Launay-Vacher et al. 2007b). Dosing recommendations for older patients and those with renal insufficiency have been published (Launay-Vacher et al. 2007a, 2015; Lichtman et al. 2007b). Appropriate dose modifications can result in safe and effective outcomes (Lichtman et al. 2016). The study of the pharmacokinetics of chemotherapy in older patients has truly been lacking. Patients reported generally do not have significant comorbidity and may not be truly representation of the average patient seen in practice. There is very little prospective pharmacokinetic data. Future study is required.

Research

Research is being performed by a growing number of investigators at institutions across the nation, as well as internationally. The International Society of Geriatric Oncology, founded in the year 2000, fosters the mission of developing health professionals in the field of geriatric oncology, in order to optimize treatment of older adults with cancer, through education, clinical practice, and research. The Society's publication, the *Journal of Geriatric Oncology*, is the first journal devoted solely to the field. The Cancer and Leukemia Group B (now, the Alliance for Clinical Trials in Oncology) Cancer in the Elderly Committee has supported furthering research in geriatric oncology through clinical trials and secondary data analyses (Hurria et al. 2010, 2011a). The Cancer and Aging Research Group has developed an instrument to predict chemotherapy toxicity, initiated and supported trials to validate this methodology in different clinical settings, and, most importantly, mentored junior investigators in geriatric oncology and study novel clinical trial designs (Hurria et al. 2014). The Gynecologic Oncology Group Elderly (now NRG oncology) taskforce is supporting the first prospective trial in older women with ovarian cancer and planning further studies in other diseases and modalities. The American Society of Clinical Oncology (ASCO) also has a number of initiatives in geriatric oncology. These include a Geriatric Oncology Issue Exploration Team, educational materials including ASCO University, sessions at the Annual Meeting including a Geriatric Oncology track, the BJ Kennedy Award for Excellence in Geriatric Oncology, articles in the ASCO Post and a Geriatric Oncology component of the Cancer Education Committee. ASCO has also published a position paper encouraging research in older patients to increase the available of evidenced-based data (Hurria et al. 2015). One area of great interest is rethinking clinical trial design. It is important that clinical trials prospectively obtain important patient data such as baseline functional status. The issue of eligibility, appropriate endpoints, and toxicity evaluation need to be reconsidered for older patients (Wildiers et al. 2013; Lichtman 2012b; Kim et al. 2015) . Data analysis and clinical trial reporting also has to adapt for appropriate evaluation and interpretation. These issues are imperative to obtain quality data, so clinicians have the ability to make meaningful decisions.

The care of the older cancer patient is a complex endeavor. It requires careful thought and evaluation. Goals of therapy need to be carefully considered. A multidisciplinary approach is preferred. Geriatric oncology needs to move to the forefront of oncology care. These vulnerable patients need to be the focus of our endeavors.

Pharmacokinetic Evaluation in Older Patients

There is a question whether there is a need to study pharmacology in older patients. If we say that it is not necessary, then we are saying that current clinical trials structure is adequate for older patients. It is definitely not as indicated by the under representation of these patients in trials. In terms of drug trials, the pharmacokinetics of chemotherapy has been primarily studied in the "typical" patients, that is, those patients without

significant comorbidity and good performance and functional status. End-organ dysfunction studies have been performed on many drugs such as irinotecan, paclitaxel, gemcitabine, and pemetrexed (Venook et al. 1998, 2000, 2003; Mita et al. 2006). To date there are few studies which have shown a difference between the "typical" patients and elderly. Few age-related changes have been reported. Pharmacokinetic differences, when present, have not been clinically relevant. In addition, there are virtually no studies which look at changes in pharmacokinetics over multiple cycles. Heterogeneity makes studies in the elderly difficult and results in too much variability to be clinically applicable. Some differences in clinical toxicity are often been a result of drug scheduling not age (Lichtman et al. 2007a). An example is 5-fluorouracil toxicity differences if administered weekly, bolus monthly, or infusion.

One rationale in the past to do pharmacokinetics studies was the avoidance of toxicity. Hematologic toxicity has been minimized due to hematopoietic growth factors. Dose-limiting toxicity is often due to nonhematologic toxicities which are not related to significant differences in pharmacokinetics, i.e., neuropathy from oxaliplatin.

One main issue is that we need to consider which subset elderly patients need to be included when deciding on pharmacokinetics studies. Are they the healthy, vulnerable, frail, anemic, hypoalbuminemic, those dependent in activities of daily living or instrumental activities of daily living and multiple comorbidities? Many older patients have had previous chemotherapy and radiation for treatment of other cancers. In addition, comorbidity may cause further change in organ function and change the patients' sensitivity to toxicity, i.e., diabetes-neuropathy, atherosclerotic heart disease-cardiomyopathy. We should be studying pharmacokinetic tests in these different elderly populations. The factors to be studied should also include oral therapy, compliance, biologic therapy, and drug interactions. The other factors which should be included in data acquisition include longitudinal effects of treatment, changes in cognition, changes in function with treatment, dependency, chronic toxicities, scheduling differences which can affect toxicity, and correlation of toxicity and function. The inclusion of pharmacogenomics is also critical (Shah 2004). In evaluating toxicity, questions which need to be answered are our toxicity scales adequate for older patients? Do they capture enough information, particularly function, such as the effect of neuropathy on activities of daily living and instrumental activities of daily living?

Therefore, pharmacokinetics should be studied, but the trials need to be novel and include these aforementioned factors. Regulatory agencies should require the inclusion of older patients before drugs can be approved, or an appropriate subset should be analyzed to at least provide safety data (Hurria et al. 2015; Lichtman 2012a).

Clinical Trial Design

A number of barriers limit the participation of older patients in clinical trials. Often, for various reasons, clinicians do not offer a clinical trial to eligible older patients. Cognitive dysfunction also interferes with patient understanding of complicated informed consent documents, impairments that affect as much as 36% of adults aged 85 and older and that rules out trial enrollment. There are a number of design issues which need to be addressed. There are specific issues which are particularly pertinent to the older patients including function, comorbidity, and social supports. Clinical investigators and biostatisticians need to develop novel trials to optimize the data derived from these studies. Suggestions have been proposed to "geriatricize" the standard oncology drug design. We have to meld the standard oncology outcomes of disease specific and overall survival with geriatric outcomes of evaluating function, cognition, toxicity, nutrition, and dependence, i.e., quality vs quantity of life. ASCO has published position papers on specific needs to improve the evidence base to improve cancer care of older patients (Hurria et al. 2015; Wildiers et al. 2013). To meet the needs of these vulnerable cancer patient, which will be the majority, these clinical design considerations need to be incorporated in studies as soon as possible. The reluctance to alter our standard designs must be overcome, or

the progress that is urgently needed will never occur. A review of commonly used chemotherapy drugs follows and discusses the issue of pharmacology.

Chemotherapy: Pharmacology

Alkylating Agents

Alkylating agents have been the foundation of therapy for decades, particularly for breast cancer and hematologic malignancies. Their main dose-limiting toxicity is hematologic. The large interindividual variability in terms of bone marrow reserves is well known among older patients depending on comorbidity. Metabolism represents the main route of elimination for most compounds. Hepatic enzymatic processes are often involved. Cytotoxic effects correspond to metabolites rather to parent compounds.

Melphalan

Melphalan is administered to elderly patients for treatment of multiple myeloma. Drug excreted unchanged in the urine represents about one third of the administered dose (Reece et al. 1988). Positive correlation has been observed between melphalan area under the curve (AUC) and the degree of renal insufficiency (Vigneau et al. 2002). However, renal insufficiency did lead to a limited decrease in melphalan clearance compared to the interindividual variations in systemic clearance (Tricot et al. 1996).

High-dose chemotherapy is being increasingly utilized for the treatment of multiple myeloma in older patients (El Cheikh et al. 2011; Klepin and Hurd 2006). Doses up to 200 mg/m^2 by intravenous (iv) infusion has become a standard. Higher toxicity, mainly myelosuppression, has been observed in patients over the age of 70 years (Jantunen et al. 2006). There is no recommendation of melphalan dosing based on renal function, but there is a consensus that reduction of the melphalan dose should be considered in patients with glomerular filtration rate of $<$30 ml/min.

Cyclophosphamide

Metabolism of cyclophosphamide to active metabolites is initiated by cytochrome P450 (subfamily 3A and 2B) mainly in the liver. An accumulation of toxic alkylating metabolites is expected in renal insufficiency justifying a dose reduction of 20–30% depending on the degree of the renal insufficiency. Cyclophosphamide is administered in combination of methotrexate and 5-fluorouracil for treatment (CMF) of breast cancer. A prospective study in patients $>$70 years old concluded that the dose of CMF in patients above 70 years should not exceed 75% of the standard dose. The combination of cyclophosphamide and doxorubicin for the treatment for breast cancer was evaluated (Dees et al. 2000). There was a moderate evidence of age-related decrease in nadir absolute neutrophil count (ANC). Pharmacokinetics analyses did not demonstrate age-related differences in the either cyclophosphamide or doxorubicin plasma exposure, but only the pharmacokinetics of the parent drug (unchanged cyclophosphamide) was explored. The available evidence indicates that dose modification is not required due to age alone.

Bendamustine

Bendamustine is a novel chemotherapeutic agent comprised of a bifunctional mechlorethamine alkylating group, a purine-like benzimidazole ring, and a butyric acid side chain. The drug has been shown to be a potent cytotoxic agent, with in vitro studies demonstrating extensive and durable DNA damage. In a pharmacokinetic trial, bendamustine was administered as a 60-min 120 mg/m^2 intravenous infusion on Days 1 and 2 of six 21-day cycles (Owen et al. 2010). Pharmacokinetic models were developed, with covariate assessment. Following a single dose of bendamustine HCl, concentrations declined in a triphasic manner, with rapid distribution, intermediate, and slow terminal phases. The intermediate $t_{1/2}$ (40 min) was considered the pharmacologically relevant (beta elimination) $t_{1/2}$ since the initial

phases accounted for 99% of the AUC (area under the curve). Age, sex, mild/moderate renal, or mild liver impairment did not alter pharmacokinetics.

Fluoropyrimidines

Fluoropyrimidines are one of the most widely used groups of agents in the medical treatment of solid malignancies. There are marked intraindividual variations in plasma levels of the parent drug and metabolites, and toxicities can vary widely among individuals. In the elderly, these drugs are commonly reduced in dosage often arbitrarily (Raghavan and Suh 2006).

Studies Suggesting an Effect of Age on Toxicity

Stein et al. reported increased toxicity with age on a phase III trial of the Gastrointestinal Study Group treatment of metastatic colorectal cancer (Stein et al. 1995). This was based on a logistic regression analysis using age, gender, treatment, performance status, and length of therapy. These conclusions are also supported by data derived from a meta-analysis of 6 randomized trials of patients with colorectal carcinoma with a total of 1219 patients comparing infusional 5-fluorouracil with bolus 5-fluorouracil (toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. Meta-Analysis Group In Cancer 1998). Older patients and those with poorer performance status had significantly higher risks of diarrhea, mucositis, nausea, and vomiting and older female patients having the highest incidence of this toxicity. Grade 3 or greater hematologic toxicity was sevenfold more common with bolus 5-FU (31 versus 4%, $p < 0.0001$) (toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. Meta-Analysis Group In Cancer 1998).

Studies Suggesting that Age Is Not Determinant of Toxicity

An overview of 7 phase III trials involving 5-fluorouracil with either leucovorin or levamisole showed that no interaction between age and outcome could be identified. Age greater than 70 years correlated with the occurrence of treatment-related leucopenia with borderline significance (Sargent et al. 2001). In an attempt to minimize the bias of patient selection for protocol study, Delea et al. retrospectively examined a 5% sample of Medicare patients who had undergone colorectal surgery. There was no difference in the incidence of hospitalization, but drug dosage and comorbid conditions were not identified (Delea et al. 2002). In a retrospective analysis of clinical trials testing FOLFOX 4 (5-fluorouracil, leucovorin, oxaliplatin), older age was not associated with increased overall incidence of grade ≥ 3 toxicity or 60-day mortality except there was a higher incidence of grade 3 neutropenia and thrombocytopenia. The benefit of FOLFOX4 did not differ by age (Goldberg et al. 2006). In an intergroup study with adjuvant 5-fluorouracil for high risk stage II and stage III colon cancer, the secondary analysis of this trial demonstrated that the elderly are as likely to tolerate the benefit from adjuvant chemotherapy as are younger patients (Haller et al. 2005). In an evaluation of the Surveillance Epidemiology and End Results Medicare-linked database for resected stage III colorectal cancer, adjuvant 5-fluorouracil was well tolerated even among the very old patients without a major comorbidity (Schrag et al. 2001). A retrospective analysis of European trials has showed equivalent benefit and toxicity in "fit" elderly patients as younger patients (Folprecht et al. 2004).

Capecitabine

Studies have compared capecitabine with 5-fluorouracil in patients with a median age over 60 years . From this literature it appears that capecitabine at the recommended dosage of 1250 mg/m^2 twice daily for day 1–14 every 21 days is better tolerated than 5-fluorouracil administered as per Mayo schedule 425 mg/m^2 day 1–5 every 28 days. Hand-foot syndrome is more common with the capecitabine therapy and myelosuppression more common in the 5-flurouracil therapy. Feliu et al. studied prospectively 51 patients with

advanced colorectal cancer who were older than 70 years of age with doses adjusted based on creatinine clearance. Only 12% of patients experienced grade 3 or 4 treatment-related adverse events such as diarrhea, hand-foot syndrome and thrombocytopenia. No treatment-related deaths were reported. The median dose intensity was 88% of predicted (Feliu et al. 2005). Sharma et al. studied the effect of fixed dose oral capecitabine 2000 mg twice daily on days 1–14 every 3 weeks in patients with advanced colorectal cancer with a median age of 72 years. Grade 2 and 3 treatment-related toxicities were diarrhea 34%, fatigue 27%, stomatitis 15%, and hand-foot syndrome 22%. The median overall survival was 11.2 months and the response rate was 28%. The patients with the higher pretreatment levels of serum folate experienced the greater treatment toxicities over the entire treatment period ($p = 0.04$) (Sharma et al. 2006). The toxicities reported could be just a consequence of impaired renal function that occurs with aging. In a prospective evaluation, Cassidy and colleagues have found that patients with moderate renal impairment at baseline (estimated creatinine clearance 30–50 ml/min) experienced a higher incidence of grade 3 or 4 toxicities. Therefore the authors recommended a lower starting dose in patients with moderate renal impairment at baseline (calculated creatinine clearance 30–50 ml/min) and a contraindication in patients with severely impaired creatinine clearance at baseline (<30 ml/min). For patients with normal or mildly impaired renal function at baseline, the standard starting dose is well tolerated (Cassidy et al. 2002). In efforts to further improve the therapeutic index, studies have been performed which alter the schedule to 7 days on and 7 days off. This schedule may be preferable in older patients in terms of toxicity and compliance (Gajria et al. 2011).

Data has been published giving conflicting results as to whether fluoropyrimidines are more toxic in elderly patients. A main determinant of this difference is the schedule utilized. It is clear that the weekly 5-FU regimen is better tolerated than the monthly regimen (Haller et al. 2005). Infusional therapy likely has a more favorable toxicity profile (Folprecht et al. 2004). Intravenous fluoropyrimidines should be given by a weekly schedule or by the published infusional regimens. Recent data suggest no reason to dose reduce fluoropyrimidines unless there is severe renal dysfunction, poor performance status, prior radiation therapy, or comorbidity. The dose of capecitabine should be adjusted to creatinine clearance and a starting dose of no greater than 1000 mg/m^2 twice daily be strongly considered. The interaction with coumadin needs to be emphasized in older patients (Camidge et al. 2005).

Platinum Compounds

Oxaliplatin

The kidneys eliminate approximately 30–50% of the drug. Clearance of total and free platinum is decreased in patients with renal impairment. However, in studies of patients with mild to moderate renal impairment (GFR >20 ml/min), no increased toxicity was seen (Takimoto et al. 2003). Clearance of ultrafilterable platinum after administration of oxaliplatin is not influenced by impairment of hepatic function, sex, or age (Graham et al. 2000).

Principal dose-limiting toxicities are peripheral neuropathy and bone marrow suppression. Few studies have been performed specifically in the elderly population. The retrospective meta-analysis of 3742 patients (614 greater than or equal to 70 years) performed by Goldberg of patients receiving FOLFOX was mentioned previously (Goldberg et al. 2006). A retrospective review of 44 patients median age 78 concluded that treatment in this population was feasible with manageable toxicity (Aparicio et al. 2003). The combination of oxaliplatin/capecitabine has been studied in patients over 70 years. No relationship was seen between response and patient age, ECOG performance status, or the ability to perform activities of daily living (ADL) or instrumental ADL (IADL) (Feliu et al. 2006; Comella et al. 2005). The rate of neurotoxicity secondary to oxaliplatin-based chemotherapy has not been shown to be any greater in the elderly than in younger patients; a bi-fractionated protocol was developed in attempt to minimize this side effect. Grade 3 sensory neuropathy occurred in 6% of patients. ADL and IADL scores did not change significantly during

treatment (Mattioli et al. 2005). Other trials with oxaliplatin combinations in patients over 70 years showed acceptable toxicity and efficacy (Berardi et al. 2005). Future studies need to perform prospective evaluations of neuropathy, and aging needs to be performed with an emphasis on the possibility of functional impairment and long-term toxicity.

Cisplatin

Cisplatin has triphasic elimination and shows the half-life of the initial phase is 20–30 min and second-phase half-life is 48–67 min, with a terminal half-life of 24 h. Cisplatin pharmacokinetics is dependent on normal renal function due to the contribution of renal elimination for cisplatin (Reed et al. 1996). But, the nonreversible plasma protein binding of cisplatin should be also considered as an elimination process since only the unbound plasma cisplatin concentrations represent the active fraction. Plasma protein binding of cisplatin is larger than that of other platinum compounds (e.g., carboplatin). However, renal function should be considered as the major pharmacodynamic parameter since renal insufficiency represents the major toxicity together with magnesium wasting, nausea and vomiting, peripheral neuropathy, auditory impairment, and myelosuppression. Severe nausea and vomiting has been markedly reduced as a significant toxicity by the premedication of patients with a serotonin receptor type-3 antagonist. Intravenous hydration has reduced acute nephrotoxicity to 5%, but intensive hydration regimens may be difficult in older patients (Daugaard and Abildgaard 1988). Dose modification based on age alone is not required. It needs to be emphasized that patients receiving cisplatin in clinical trials are a highly selected group with minimal comorbidity. Calculation of renal function is critical using one of the available formulae but should be used with caution (Marx et al. 2004).

Carboplatin

Carboplatin has a similar mechanism of action compared with cisplatin, with antineoplastic activity against cervical, lung, and ovarian cancers. Carboplatin is completely eliminated through the kidneys. The Cockcroft-Gault, Calvert, and Chatelut formulas allow for accurate and safe dosing, taking into account renal function changes with age and a targeted AUC (Calvert and Egorin 2002). Carboplatin exhibits biphasic elimination with an initial half-life of 1.1–2 h and final half-life of 2.6–5.9 h with creatinine clearances greater than 60 mL/min. Because of the low incidence of nonhematologic toxicity, it can replace cisplatin in the palliative setting, particularly in older patients. Obesity, which is more common in the elderly, may affect the calculation of renal function (Launay-Vacher et al. 2007a; Lichtman et al. 2007b),

Anthracyclines

Anthracyclines are part of regimens for the treatment of many malignancies encountered in the elderly. Toxicity that is observed more frequently is a form of cardiomyopathy that manifests itself during the therapy with doxorubicin in the greatest part of the cases (Von Hoff et al. 1982), and it has been reported that the incidence of congestive heart failure following treatment with anthracyclines increases progressively with age after 70 years (Balducci and Beghe 1999). This may explain why many elderly patients are either excluded from chemotherapy treatment or receive less aggressive chemotherapy. Dose modification of the adjuvant AC regimen due to obesity is not necessary (Rosner et al. 1996). For anthracyclines, some studies suggest that the drug's peak concentration correlates with efficacy when toxicity is most likely a function of both peak and exposure (Aoki et al. 1998). The limited sampling strategies developed for several anthracyclines would facilitate the implementation of pharmacokinetic studies. One example is the case of epirubicin. The studies described a triexponential model for epirubicin behavior. In one study, variability in clearance could be attributed to gender and also to age in women (Wade et al. 1992). If severe renal impairment leads to a decrease in epirubicin clearance, no dose reduction guidelines have been proposed. The pharmacokinetic profile of epirubicin is modified in case

of hepatic impairment (Camaggi et al. 1985). Dosing modifications based on aspartate aminotransferase levels have been proposed (Twelves et al. 1992).

Liposomal Anthracyclines

Liposomal formulation completely alters the pharmacokinetics, pharmacodynamics, and toxicity profile of these agents. Palmar-plantar erythrodysesthesia syndrome is seen more frequently with these drugs; conversely, mucositis, alopecia, and cardiac toxicity are markedly diminished compared with nonliposomal formulations (Safra et al. 2000). The reduced toxicity of this class of drugs may be particularly beneficial in older patients with anthracycline- sensitive diseases (Biganzoli et al. 2006; Theodoulou and Hudis 2004).

Antimicrotubule Agents (Spindle Poisons) in Elderly Cancer Patients

Vinca Alkaloids

Vincristine is excreted primarily by the liver and requires dose reduction, or even avoidance, in liver failure (Donelli et al. 1998). There are no data for dose modification based on age alone.

Vinorelbine is a semisynthetic vinca alkaloid and causes less neurotoxicity than the older compounds in this group. It is highly bound to human platelets (78%) (Urien et al. 1993), and thrombocytopenia seems to correlate with increased hematologic toxicity, probably due to an increased unbound fraction, although high inter- and intraindividual variability in AUC (20–65%) can be present (Gauvin et al. 2002). Vinorelbine undergoes substantial hepatic elimination, but dose modification might only be necessary in patients with severe liver dysfunction, when the liver volume has been replaced by tumor by more than 75% (Robieux et al. 1996). There are conflicting data on the effect of age on pharmacokinetics of intravenous vinorelbine (Sorio et al. 1997). In the largest study, creatinine clearance and hepatic clearance were independent factors of vinorelbine clearance, while age was not (Wong et al. 2006). Several studies in breast and lung cancer and non-Hodgkin's lymphoma (NHL) show that full dose vinorelbine (e.g., 25–30 mg/m^2 weekly with rest points) has a very favorable tolerance profile (Sorio et al. 1997; Monfardini et al. 2005), and improved quality of life has been demonstrated in a large phase III trial in NSCLC in the elderly (median age 74 years) (effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group 1999). Although there are conflicting data on the impact of age on vinorelbine exposure, several trials show that vinorelbine is generally well tolerated in elderly cancer patients. There is no evidence that dose modification is required on the basis of age.

Taxanes: Paclitaxel and Docetaxel

Paclitaxel

The majority of paclitaxel is protein bound (97%), and it is extensively metabolized in the liver by the cytochrome P450 system and is excreted in bile, more specifically by the cytochrome P450 isozymes CYP2C8 and CYP3A. Awareness of drug interactions is needed when given concomitantly with drugs metabolized by the same pathways, e.g., ketoconazole (Sonnichsen and Relling 1994). It is preferable not to use paclitaxel in liver dysfunction because of significantly increased AUC and toxicity (mostly neutropenia) (Venook et al. 1998), but if it is necessary, the dose should be greatly reduced. A CALGB trial shows a modest but significant decrease in clearance of total paclitaxel with increasing age (Lichtman et al. 2006). This decrease seems partly induced by decreased clearance of the formulation vehicle CremophorEL (Smorenburg et al. 2003). Moreover, unbound paclitaxel might be a better predictor of clinically relevant exposure than total paclitaxel. Many studies have shown the feasibility and efficacy of administering paclitaxel in elderly patients with various cancer types. Both weekly and 3-weekly regimens have been studied. The every 3-week regimen can be used in fit elderly patients such as those with ovarian and bladder cancer (Uyar et al. 2005). There is a preference for weekly

administration in some patients, particularly breast cancer, as this causes less hematological toxicity without loss of efficacy (Akerley et al. 1997; Seidman 2005), possibly as a result of the more effective antiangiogenic activity in this fractionated regimen.

There are somewhat conflicting data on the impact of age on paclitaxel clearance. Moreover, the importance of unbound versus total paclitaxel clearance is not fully determined. However, several trials indicate the feasibility of both every 3 week weekly paclitaxel in elderly patients. There is no basis for a dose reduction based on age alone for any standard dose or schedule. Neurotoxicity has emerged as a significant toxicity and seems to be more significant in older patients (Lichtman et al. 2011; Tew et al. 2010).

Docetaxel

The majority of docetaxel is protein bound (94%), and it is extensively metabolized in the liver by the cytochrome P450 system (CYP3A4) and is excreted in bile, resulting in increased toxicity when administered to patients with impaired liver function (Venook et al. 1998). There is a large interpatient variability in exposure (AUC) and drug clearance. Hepatic CYP3A4 is by far the strongest predictor of total docetaxel clearance and together with AAG (alpha1-acid-glycoprotein) accounts for 72% of the interpatient variation in clearance (Hirth et al. 2000). In serum, docetaxel is extensively bound to albumin, lipoproteins, and *alpha*-1-acid glycoprotein (AAG); indeed, the latter is the main determinant of docetaxel serum binding variability. There have been attempts in elderly patients to predict variation in AUC of docetaxel through correlations with plasma (AAG) or urinary cortisol ratio (Extermann 2004). Many studies have investigated the efficacy and toxicity of docetaxel in relation to age, mainly in breast cancer (Maisano et al. 2005) and lung and prostate cancer (Tannock et al. 2004) . In a specific phase I trial in elderly cancer patients treated with docetaxel every 3 weeks, maximal tolerated dose was not reached at 80 mg/m^2, and accrual was continued. On the other hand, another phase I trial in elderly breast cancer patients was stopped after four patients at the first level of 75 mg/m^2 every 3 weeks because of excessive toxicity. The Japanese population might be more vulnerable due to ethnic differences in metabolism; the MTD in a phase I trial was 30 mg/m^2/week. As with paclitaxel, weekly dose docetaxel regimens have been investigated and seem to decrease toxicity without loss of efficacy except maybe in prostate cancer where 3-weekly might be slightly more effective than weekly docetaxel (Tannock et al. 2004). Neutropenia was limited with weekly regimens, but fatigue was often invalidating. Various dosages (e.g. 20–35 mg/m^2 weekly or 60–100 mg/m^2 every three weeks) and regimens (rest weeks at various time points) have been used.

There is no significant data to support dose modification based on age alone. Docetaxel pharmacokinetics is at most only minimally influenced by age. Any age-related changes are minimal compared to interpatient variability in metabolism. However, elderly patients are somewhat more vulnerable to side effects, but also here, interpatient variability is larger than age-related variability. Improvement in predicting unbound docetaxel clearance and toxicity by pharmacogenomic-based treatment optimization will hopefully improve correct dosing for the (elderly) cancer patients. In principal, standard regimens of docetaxel can be used, e.g., 30–36 mg/m^2 weekly with a rest week at regular time points or 75 mg/m^2 3-weekly. The choice between weekly and 3-weekly can depend on the setting (e.g., in prostate cancer, 3-weekly at 75 mg/m^2 is the standard) and on potential side effects.

Purine Analogs

Fludarabine

The elimination half-life of this drug ranges from 6.9 to 12.4 h. The total body clearance of this agent is related to both the serum creatinine and the creatinine clearance. After initial dephosphorylation, the subsequent metabolite, 2-fluoro-araA, is eliminated primarily by renal excretion, with approximately 60% of the administered dose excreted in the urine within 24 h after administration (Lichtman et al. 2002). Dose modifications

based on varying degrees of renal dysfunction have been proposed (McEvoy 2000). The most significant toxicities with fludarabine are related to the therapy-related myelosuppression from this agent, as well as the impact on cellular immune function. The severity of fludarabine-related neutropenia is related not only to the total body clearance of this agent but also to AUC and half-life β. No association was found between age and the incidence of either hematologic toxicity or infection during the first cycle of fludarabine therapy. However, patients with an estimated creatinine clearance of <80 ml/min had an increased risk of toxicity during their treatment course (Martell et al. 2002). Fludarabine may be used efficaciously and safely in an older patient population. Response rates tend to be lower in these older patients as compared to a younger cohort. Dose reductions are recommended in the setting of reduced creatinine clearances, in an effort to limit treatment-related toxicities.

Cytarabine

Cytarabine is rapidly metabolized in the liver to inactive metabolites, and 90–96% is excreted in the urine (Launay-Vacher et al. 2005). Due to increase neurotoxicity in patients with renal insufficiency, dose adjustments are required for high-dose therapy.

Gemcitabine

Pharmacokinetic data indicate that small age- and sex-related differences exist. These differences corresponded to differences in mean half-life for men at 42 min versus 61

min in the over 65 age group and women at 49 min versus 73 min in the over 65 group. Despite these differences, dosing guidelines are the same based on age and sex for gemcitabine. Toxicities primarily include neutropenia and thrombocytopenia. Dosing modifications for hepatic and renal dysfunction have been reported (Venook et al. 2000). Gemcitabine as a single agent displays minimal toxicity in older patients.

Pemetrexed

Pemetrexed is primarily excreted unchanged in the urine (70–90% in the first 24 h). It is contraindicated in patients with CrCl <45 mL/min. In patients with impaired renal function, pemetrexed plasma clearance positively correlated with GFR, which resulted in increased drug exposures. Pemetrexed 600 mg/m^2 was well-tolerated (with vitamin supplementation) in patients with GFR >80 mL/min. In patients with GFR 40–79 mL/min, a dose of 500 mg/m^2 along with vitamin supplementation was tolerated (Mita et al. 2006). Further studies are needed to determine dosing in renally impaired patients.

Camptothecins

Topotecan

Topotecan is a topoisomerase I inhibitor approved for the treatment of recurrent or refractory ovarian cancer and small cell lung cancer, and it has activity in myelodysplastic syndromes and acute myeloid leukemia. Topotecan renal clearance accounts for 30% of its elimination, and it has a half-life of 3 h. A large interindividual variability was observed, with clearance varying from 9.1 to 42.51 per hour (mean 21.0). Topotecan clearance was related to serum creatinine level and age (Montazeri et al. 2000). Dose adjustments are required in patients with moderate renal impairment. Severe myelosuppression can occur if doses adjustments are not made. A specific dose modification based on creatinine clearance has been recommended, particularly for older patients (O'Reilly et al. 1997). A review of patients with small cell lung cancer showed no difference in efficacy and minimal toxicity differences in patients 65 years and older compared with younger patients (Garst et al. 2005).

Irinotecan

Irinotecan is a topoisomerase I inhibitor approved for the treatment of metastatic colorectal cancer alone or in combination with 5-FU and leucovorin. It has activity in glioblastoma multiforme, non-small cell and small cell lung cancer, and gastric, esophageal, and pancreatic cancer. It can be given as a weekly and every-3-week dose. The weekly and once-every-3-week regimen showed similar efficacy and quality of life. Patients age 70 years or older independently

predicted occurrence of grade 3/4 diarrhea. Treatment with the every-3-week schedule was associated with a lower rate of grade 3/4 diarrhea (Fuchs et al. 2003). SN-38, the major metabolite of irinotecan, is approximately 1000 times more potent than the parent compound. The major toxicity of irinotecan therapy is delayed diarrhea and myelosuppression. Late diarrhea may be caused by intestinal accumulation of SN-38. The biliary concentration of SN-38 may be predictive of gastrointestinal toxicity, leading to the proposal of a biliary index as a surrogate measure to predict the severity of diarrhea (Mick et al. 1996). Delayed diarrhea was increased in patients with advanced age. Pharmacokinetic parameters, such as mean irinotecan, SN-38, SN-38G, Cmax, AUC0-24, and biliary index values in patients 65 years or older, were within 3% of those in younger patients. In addition, response rates do not vary based on age (Rothenberg et al. 1999). It is recommended that patients over the age of 70 years, patients with prior pelvic irradiation, and patients with poor performance status start at reduced doses (Rougier et al. 1998).

Etoposide

Etoposide is a topoisomerase II inhibitor used in the treatment of refractory non-Hodgkin's lymphoma, lung cancer, germ cell tumors, and a multitude of other malignancies. It is typically given through the intravenous route, although oral therapy is also used. Oral therapy occasionally poses problems with oral absorption and tolerance (Souhami et al. 1997). Etoposide displays biphasic or triphasic pharmacokinetic characteristics with an initial half-life of 0.6–2 h (mean, 0.25–2.5) and a terminal half-life of 5.3–10.8 h (mean, 2.9–19). Etoposide absorption is highly variable estimated at 50% but ranging from 25% to 75% (Dorr and Von Hoff 1994; McEvoy 2000). Impaired renal function leads to a decrease in drug clearance rates. Increasing age has been correlated to increased free etoposide concentrations during oral therapy correlating with leucopenia (Miller et al. 1997). Poor performance status may place older patients at higher risk for grade 4 dose-limiting toxicities such as myelosuppression and mucositis (Miller et al. 1997). Etoposide is eliminated to some degree via hepatic CYP P450 metabolism, but dosage adjustments based on liver dysfunction are controversial. The pharmacokinetics of oral etoposide in patients with liver dysfunction do not differ from patients with normal liver function (Aita et al. 1999).

Conclusion

The data presented will hopefully be able to aid clinicians in the treatment of elderly patients. Unfortunately, prospective data, particularly pharmacokinetic data, correlated with patient's functional status and clinical status does not exist. Particularly for those patients aged 80 years and older, extrapolation and, most importantly, good clinical judgment are an absolute necessity. In general, age-related differences in pharmacokinetics have been demonstrated on a consistent basis. Pharmacokinetic changes that are seen are usually a reflection of end-organ dysfunction (hepatic, renal), hypoalbuminemia, and anemia. The more important clinical issue is the increased toxicity that is seen particularly in those patients with poor function. Also, there is data which already exists from completed clinical trials which has never undergone an analysis by age. This situation needs to be remedied by a reanalysis and journal editors insisting that submitted publications include an age-related analysis where appropriate. Clinical trials evaluating and defining the treatment needs and the goals of therapy in elderly cancer patients are being performed. Methods for identifying high-risk individuals for developing side effects from chemotherapy are being developed. Chemotherapy approaches for several common malignancies, both in the adjuvant setting and for metastatic disease, are changing rapidly at this time. Optimizing therapeutic strategies for cancer patients who are over 65 years of age remains a challenge. Choosing the correct regimen and dose for the older patient can be extremely difficult as there are no accepted algorithms to guide management decisions in this patient group. Older cancer patients who have an adequate performance status and functional status and a reasonable life expectancy should receive the same therapies as younger patients. For those older

patients with a poor performance status or functional status, single-agent reduced-dose chemotherapy options and nonchemotherapeutic approaches should be considered, together with palliative and supportive care options. Pegfilgrastim and filgrastim can reduce the incidence of neutropenia and its sequelae (Smith et al. 2006). The effectiveness of growth factor support has often made nonhematologic toxicity dose limiting. The National Comprehensive Cancer Network has published Senior Adult Oncology guidelines, which can greatly aid the physicians treating (VanderWalde et al. 2016). Investigators need to be encouraged to develop appropriate clinical trials for older patients which will be acceptable to these vulnerable individuals and their families.

Cross-References

- Acute Myeloid Leukemia in Older Adults
- Chronic Lymphocytic Leukemia in Older Adults
- Colorectal Cancer in Older Adults: Systemic Treatments
- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Decision Making and Safety Issues in Older Cancer Patients
- Diffuse Large B-Cell Lymphomas in Older Adults
- Drug Interactions in Aging and Cancer
- Early-Stage Breast Cancer in Older Adults
- Head and Neck Tumors in Older Adults: Systemic Treatments and Combination with Local Strategies
- Integrating Geriatric Oncology into Clinical Pathways and Guidelines
- Low-Grade Lymphomas (Other than CLL/SLL) in Older Patients
- Lung Cancer in Older Adults: Systemic Treatment
- Multidisciplinary Management of Liver, Pancreatic, and Gastric Malignancies in Older Adults
- Multiple Myeloma in Older Adults
- Ovarian Cancer in the Older Woman
- Pharmacology of Aging and Cancer
- Research Methods: Epidemiologic Research in Geriatric Oncology
- Research Methods: Outcomes and Survivorship Research in Geriatric Oncology
- Research Methods: Quality of Life and Patient-Reported Outcome Research in Geriatric Oncology
- Research Methods: Clinical Trials in Geriatric Oncology
- Research Methods: Systematic Reviews and Meta-Analysis in Geriatric Oncology
- Research Methods: Translational Research in Geriatric Oncology
- Research Methods: Using Big Data in Geriatric Oncology
- Systemic Treatment of Metastatic Breast Cancer in Older Adults

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Principles of Cancer Targeted Therapy in Older Adults

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Andrea Luciani

Contents

Abstract

More than half of patients newly diagnosed with cancer are aged >65 years, and as this group is underrepresented in clinical trials there is less evidence on which to base treatment decisions. Geriatric assessment as well as the careful evaluation of comorbidities can help oncologist to better define the clinical complexity of older individuals, in particular the estimation of life expectancy and the risk of toxicity. In this context, the precision medicine (PM) could be extremely important in the approach to cancer treatment management. Precision medicine is defined by the National Cancer Institute as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease." Knowledge of the molecular profile of the tumor is necessary to guide selection of therapy for the patient. Several molecules, as tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor, monoclonal antibodies, angiokinase inhibitors, and mammalian target of rapamycin inhibitors (mTOR inhibitors), were developed and are now available for the use in clinical practice. Even if the toxicity profile of these drugs is somewhat less than that of conventional chemotherapy, data on older patients are poor and often they are extrapolated from large randomized trials that did not have a planned elderly specific analysis. Except for bevacizumab in colorectal cancer and some TKIs as sunitinib

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in renal cell carcinoma, the recommendations for the use of these molecules in clinical practice are made using indirect data.

Keywords
Elderly Geriatric-assessment Target-therapy Precision-medicine

Introduction

More than half of patients newly diagnosed with cancer are age >65 years. Although this number is expected to increase as the world population ages, there is less evidence on which to base treatment decisions for older patients with cancer, because this group is underrepresented in clinical trials (Crome et al. 2011). Because chronologic age alone is a poor descriptor of heterogeneity of the aging process, a systematic (and maybe evidence-based) way of describing the heterogeneity is needed to help oncology treatment decisions. A comprehensive geriatric assessment (CGA) can fill this knowledge gap as it has the ability to predict severe treatment-related toxicity in some form of tumors, to predict OS, and to influence treatment choice (Hurria et al. 2005).

Comorbidity, defined as a medical condition that exists along with an index condition, is a main issue in older patients with cancer. Comorbidities could impact the cancer management in various ways. They can act as confounders that complicate the diagnosis and treatment of cancer; they mediate cancer treatment effects and pose competing risks for morbidity and mortality. The presence of moderate to severe comorbidities is of greatest prognostic importance among patients with localized and potentially curable cancer, such as early-stage breast or prostate cancer; in contrast, comorbidities have little impact on overall survival in more lethal and aggressive cancers where mortality is dominated by the primary disease (Jorgensen et al. 2012; Read et al. 2004).

Comorbidities can alter the risk/benefit ratio of many treatment decisions. In a study using SEER-Medicare Database, older adults with resected stage III colorectal cancer with comorbidities were less likely to be referred to a medical oncologist for consideration of adjuvant chemotherapy and less likely to be given chemotherapy when seen by an oncologist (Bradley et al. 2008; Dy et al. 2006). In a context of complexity, as geriatric oncology, the precision medicine (PM) could be extremely important in the approach to cancer treatment management. PM, also called "personalized medicine," is defined by the National Cancer Institute as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease." PM in oncology was born with the advent of molecularly targeted agents (MTAs) almost two decades ago and is mainly based today on the DNA molecular information of the patients' tumors (Table 1). Knowledge of the molecular profile of the tumor is necessary to guide selection of therapy for the patient. For example, the Oncotype Dx assay (from Genomic Health) for breast cancer; Development of single-gene or multigene expression signatures of response or resistance to particular drug treatments (for example, HER2 and estrogen receptor) to identify patients with breast cancer who are likely to benefit from adjuvant paclitaxel treatment, or ERCC1 expression as a marker of resistance to platinum-based chemotherapy (Le Tourneau et al. 2016). Clinical trial requiring a genomic alteration for enrollment has increased in the past years; however, the number has to be improved (Roper et al. 2015).

The Use of Target Agents in Older Patients

Non–Small Cell Lung Cancer

As median age at diagnosis is 70 years old, non–small cell lung cancer (NSCLC) is a disease of older patients Two classes of drugs had a major clinical development in the last 10 years: tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor and monoclonal antibodies (MoAb) directed against vascular endothelial growth factor (VEGF).

Table 1 Recommendations for the use of target therapy in older patients

Drug	Disease	Efficacy	Safety	Data	Practical considerations in elderly
Gefitinib	NSCLC	Effective	Good toxicity profile in elderly patients	Elderly specific data	Well tolerated; monitor for rush and diarrhea
Erlotinib	NSCLC	Effective	Increased toxicity	Elderly specific data	Extreme caution; close monitoring for toxicity
Afatinib	NSCLC	Effective	Increased toxicity	Elderly data from subgroup analysis	Monitor toxicity. Dose reduction is an option
Crizotinib	NSCLC	Limited	Limited	Pivotal trial	Likely reasonable option, although data are limited
Nivolumab	NSCLC	Limited	Limited	Retrospective data	Reasonable option. Limited data
Nintedanib	NSCLC	Limited	Limited	No elderly trials	Use with caution
Bevacizumab	NSCLC	Available; effective	Available; increased risk for HTN	Subgroup analysis	Monitor for HTN; screen for vascular risk factors
Ramucirumab	NSCLC	Limited	Limited	No elderly trials	Use with caution
Sorafenib	Advanced HCC	Limited; appears effective	Limited; appears safe	Elderly specific data	Monitor for GI and skin toxicity
Everolimus	ER-positive MBC; HER2-positive	Effective	Caution; higher incidence of treatment-related deaths in elderly patient	Elderly specific data	Close monitoring for stomatitis, diarrhea, and anemia
Trastuzumab	Breast cancer; HER2-positive	Limited	Limited	Retrospective data	Use in elderly patients with regular cardiac monitoring
Pertuzumab	MBC; HER2-positive	Available; effective	Limited; increased toxicity in all patients	Pivotal trial	Use in elderly patients without cardiac risk factors
T-DM1	HER2-positive MBC	Limited	Limited	Pivotal trial	Favorable safety profile
Vemurafenib	BRAF-mutant advanced melanoma	Limited	Limited	Pivotal trial	Monitor for skin toxicity, fatigue, arthralgia
Dabrafenib	BRAF-mutant advanced melanoma	Limited	Limited	Pivotal trial	Monitor for skin toxicity, fever, fatigue, arthralgia
Ipilimumab	Advanced melanoma	Available	Available	Pivotal trial; elderlyspecific data	Immune-related adverse events: Dermatologic, endocrine, GI
Sunitinib	mRCC	Available	Available; increased toxicity	Elderly specific data	Monitor for GI toxicity, HFS, HTN, fatigue; first-line dose modification may be appropriate

(*continued*)

Table 1 (continued)

Drug	Disease	Efficacy	Safety	Data	Practical considerations in elderly
Pazopanib	mRCC	Available	Available; favorable toxicity profile in elderly patients	Pivotal trial	Monitor for GI toxicity, HTN, anorexia
Sorafenib	mRCC	Available	Available	Pivotal trial	Monitor for skin toxicity, diarrhea, fatigue, and rare serious AEs (HTN, cardiac ischemia
Everolimus	mRCC	Available	Available; well tolerated	Elderly specific data	Monitor for stomatitis, rash, fatigue
Temsirolimus	mRCC	Available	Available; well tolerated	Pivotal trial	Monitor for rash, fluid retention, hyperlipidemia, hyperglycemia
Axitinib	mRCC	Available	Limited	Pivotal trial	Monitor for HTN, diarrhea, fatigue
Cabozantinib	mRCC	Limited	Limited	No elderly specific trial	No data. Use with extreme caution
Nivolumab	mRCC	Limited	Limited	Retrospective data	Reasonable option. Limited data
Cetuximab	mCRC	Available; effective	Limited	Pivotal trial	Monitor for rash, GI toxicity
Panitumumab	mCRC	Available; effective	Limited	Pivotal trial	Well tolerated; monitor for skin toxicity, diarrhea, hypomagnesemia
Bevacizumab	mCRC	Available; effective	Available; increased risk for HTN	Elderly specific data	Monitor for HTN; screen for vascular risk factors
Aflibercept	mCRC	Available; effective	Available; increased risk for toxicity	Pivotal trial	Cautious use in elderly patients, given toxicity profile
Regorafenib	mCRC	Available; effective; smaller benefit than in younger patients	Available; increased toxicity	Pivotal trial	Cautious use in elderly patients, given toxicity profile and small benefit
Trastuzumab	Advanced gastric cancer	Limited	Limited	Pivotal trial	Use in elderly patients without cardiac risk factors
Ramucirumab	Advanced gastric cancer	Limited	Limited	Pivotal trial	Lack of data to support use

Modified from Kelly et al. (2014)

AE adverse event, *ER* estrogen receptor, *GIST* GI stromal tumors, *HCC* hepatocellular carcinoma, *HER2* human epidermal growth factor receptor 2, *HFS* hand-foot syndrome, *HTN* hypertension, *MBC* metastatic breast cancer, *mCRC* metastatic colorectal cancer, *mRCC* metastatic renal cell carcinoma, *NSCLC* non–small cell lung cancer, *T-DM1* trastuzumab emtansine

Bevacizumab

Bevacizumab demonstrated a survival benefit for patients with adenocarcinoma histology (12.3 vs. 10.3 months, HR for death 0.79; $p = 0.003$). A subset analysis of ECOG 4599 showed an higher rate of toxicity for elderly patients in the experimental arm (87% vs. 61%, $P < 0.001$) and nonsurvival advantage (11.3 vs. 12.1 months;

$P = 0.4$) (Sandler et al. 2006). The AVAIL trial compared cisplatin plus gemcitabine alone or plus bevacizumab at two dosage (7.5 and 15 mg/Kg). The primary end point, progression free survival advantage, was met for the bevacizumab arm (Reck et al. 2009). In the subgroup analysis of 304 patients aged 65 years or older (median age 68 years) in the AVAIL trial, the lower dose of bevacizumab (7.5 mg/kg once every 3 weeks) yielded an improvement in progression-free survival (HR, 0.71; *P* 0.023). In the Safety of Avastin in Lung study 623 patients older than 65 years (mean age 70.6) had incidence of adverse events (AEs) and overall survival comparable to that of younger patients (Leighl et al. 2010).

Erlotinib

There are no prospective trials in older patients. In a retrospective age-specific analysis of the BR.21 study, where erlotinib improved survival vs. placebo in second- or third-line setting, 112 had received erlotinib and 51 had received placebo (Wheatley-Price et al. 2008). The median OS was 7.6 months compared with 5 months for those who received placebo (*P* 0.67), and for young patients, the median OS was 6.4 months versus 4.7 months (*P* 0.0014). Despite the same results in terms of progression free survival between older and younger patients, the former suffered of worse toxicity with worse rash, fatigue, and dehydration. An open-label phase II study evaluated survival in chemotherapy-naïve patients aged 70 years with advanced NSCLC treated with erlotinib. The 1- and 2-year survival rates were 46% and 19%, respectively (median, 10.9 months). The presence of an EGFR mutation correlated with prolonged survival (*P* 0.027). The EURTAC trial was a phase III compared erlotinib with chemotherapy in first-line advanced EGFR-mutated NSCLCa. Erlotinib showed a significant improvement in median PFS in both young and older patients with a worse toxicity profile in the latter group (Rosell et al. 2012). A phase II single arm trial showed promising results of the association erlotinib/bevacizumab in NSCLC EGFR mutated patients with a median progression-free survival of 16.0 months (95% CI 13.9–18.1) with erlotinib plus bevacizumab versus 9.7 months (5.7–11.1) with erlotinib alone (hazard ratio 0.54, 95% CI 0.36–0.79; log-rank test $p = 0.0015$) (Seto et al. 2014). A phase III trial is currently ongoing to explore the activity of the combination against monotherapy with erlotinib.

Gefitinib

The only elderly specific trial is the INVITE study (Phase II Iressa versus vinorelbine [INVITE]) that explored the first-line use of gefitinib compared with vinorelbine in patients aged 70 years or more. The PFS was similar in both arms (2.7 vs. 2.9 months; *P* 0.310). Gefitinib was well tolerated, and grade 3 to 5 adverse events were less frequent in the gefitinib arm (12.8% vs. 41.7%) (Crino et al. 2008). The Iressa Pan Asia study (IPASS; first line IRESSA versus carboplatin/paclitaxel in Asia) was not an elderly specific trial, and showed a PFS benefit for gefitinib vs. platinum doublet chemotherapy (24.9% vs. 6.7%) especially in EGFR mutated patients. Other small series show the effectiveness and feasibility of gefitinib in the population of people with more than 70 years age (Takahashi et al. 2014).

Afatinib

Afatinib demonstrated superior PFS vs. doublet cisplatin chemotherapy in advanced NSCLC in two large trial, lux lung 3 (LL3) and lux lung 6 (LL6). A subgroup analysis on patients with more than 65 years old of both studies was performed (Fein et al. 2016). A total of 220 patients were randomized; 134 in LL3 and 86 in LL6. In Del19-positive patients, afatinib significantly improved OS versus chemotherapy in LL3 (41.5 vs. 14.3 months, HR1⁄40.39 [95% CI: 0.19e0.80], p1⁄40.0073) and demonstrated a trend toward improved OS in LL6 (34.1 vs. 21.1 months, HR1⁄40.57 [95% CI: 0.24e1.36], p1⁄40.20). The AE profile in patients aged more than 65 years was similar to that observed in the overall population.

Crizotinib

Crizotinib is an oral small-molecule TKI that targets the echinoderm microtubule-associated protein-like 4 (ELM4) anaplastic lymphoma kinase (ALK) fusion oncogene rearrangement that is found in 5% of patients with advanced lung adenocarcinomas. Crizotinib has been demonstrated

Table 2 New drugs in NSCLC

Study	Design	N	Elderly	RR	ΔPFS/OS	HR os
Lume lung 1	N-DTX vs DTX	1307	≥65.30%	4.7 versus 3.6%	2.7/2.3 mo (adeno))	0.75
Revel	R-DTX vs DTX	1253	≥65.38%	23 versus 14%	1.5/1.4 mo	0.76
Checkmate 0.17	Nivo vs DTX	272	≥65 <75.33% ≥75.8%	20 versus 9%	0.7/2.8 mo	0.59
Checkmate 0.57	Nivo vs DTX	582	≥75.7%	19 versus 12%	−1.9/2.8 mo	0.73

to be superior versus chemotherapy in second-line setting in advanced NSCLC (Shaw et al. 2013). No large data on elderly patients are available.

Nintedanib

Nintedanib is an oral angiokinase inhibitor that targets the proangiogenic pathways mediated by VEGFR1–3, fibroblast growth factor receptors (FGFR) 1–3, and platelet-derived growth factor receptors (PDGFR) α and β. In the LUME Lung 1 trial nintedanib plus docetaxel was superior to docetaxel alone in second-line setting in advanced adenocarcinoma of the lung with a HR for PFS that was 0.85 (95% CI 0.75–0.96, $p = 0.0070$) and HR for OS that was 0.75 [95% CI 0.60–0.92] $p = 0.0073$. Patients with more than 65 years old were 30% of the population without a planned subgroup analysis (Reck et al. 2014) (Table 2).

Ramucirumab

Ramucirumab is a fully human IgG1 monoclonal antibody that specifically binds to the VEGFR-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and receptor activation. In REVEL trial patients with advanced NSCLC were randomly assigned to receive docetaxel plus ramucirumab or docetaxel. Median overall survival was 10.5 months in the ramucirumab group compared with 9.1 months in the control group (stratified HR 0.86, 95% CI 0.75–0.98; $p = 0.023$). Ramucirumab had an overall good safety profile, however patients with more than 65 years old, were only 38% of the population and the trial was not designed to have a subgroup specific analysis (Garon et al. 2014).

Nivolumab

Nivolumab is a fully human IgG4 PD-1 immune-checkpoint–inhibitor antibody that disrupts PD-1–mediated signaling and may restore antitumor immunity. Checkmate 0.17 and 0.57 were two trials in which nivolumab was compared with docetaxel in second-line setting in NSCLC in squamous and adenocarcinoma histology, respectively (Borghaei et al. 2015; Brahmer et al. 2015). In both studies, patients with more than 75 years were 8% and 7%, respectively. A safety analysis across all registration trials, stratified by age, was presented at ASCO 2016 meeting. About 414 patients out of 1020 were 65 years old or more and only 11% of them experienced grade 3–4 toxicities.

Breast Cancer

Trastuzumab

Trastuzumab is a humanized monoclonal antibody targeting the extracellular domain of human epidermal growth factor receptor 2 (HER2). Trastuzumab demonstrated benefit in adjuvant setting in several trials without any toxicity concern in elderly patients with more than 70 years old and without any relevant cardiovascular comorbidities. Several studies have established the benefit of trastuzumab in adjuvant setting (Piccart-Gebhart et al. 2005; Romond et al. 2005). Cardiotoxicity is the main adverse event of trastuzumab and becomes challenging when the regimen contains also anthracyclines. The trastuzumab-related cardiotoxicity is not dose dependent and is usually reversible. An analysis of SEER-Medicare and the Texas Cancer Registry (TCR) on women more than 66 years with a diagnosis of stage I–III breast cancer identified 2203 trastuzumab-treated patients (23.1%) (Chavez-MacGregor et al. 2013). These patients were more likely to develop cardiac heart failure (CHF) than nontrastuzumab users (HR, 1.95; 95% CI, 1.75–2.17) and patients older than 80 years had the highest risk of CHF

(HR, 1.76; 95% CI, 1.48–2.09). Coronary disease (HR, 1.82; 95% CI, 1.34–2.48) and hypertension (HR, 1.24; 95% CI, 1.02–1.50) were associated with increased risk of CHF. About 68.8% of the events occurred within the first 12 months after initiation of treatment. In hormone-sensitive, HER2-positive patients with metastatic breast cancer, the TANDEM study (A study to evaluate the efficacy and safety of herceptin plus anastrozole vs. arimidex alone in patients with metastatic breast cancer) was not an elderly designed trial; however, the combination of trastuzumab and anastrozole was superior to anastrozole alone with no relevant differences on the rate of grade 3 and 4 cardiac events between the two groups.

Pertuzumab

In the CLEOPATRA study, Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in previously untreated HER2-positive metastatic breast cancer, the median age was 54 years (range 22–82), 15.7% of patients were age >65 years and 2% were age >75 years. A PFS advantage for docetaxel trastuzumab-pertuzumab arm was evident across all age groups (Baselga et al. 2012).

Trastuzumab Emtansine

In the EMILIA (An open-label study of trastuzumab emtansine [T-DM1] vs. capecitabine lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer) the major benefit of T-DM1 was in younger population; however, the small proportion of elderly patients did not allow to evaluate the impact of T-DM1 on older population (2.5% had more than 75 years old) (Verma et al. 2012).

Lapatinib

Lapatinib is an orally active small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor type 1 (EGFR). In a nonelderly designed trial, lapatinib plus capecitabine was superior with respect to capecitabine alone in women with metastatic breast cancer (HR for time to progression was 0.49 (95% confidence interval, 0.34 to 0.71; P <0.001) (Geyer et al. 2006). Diarrhea is the main issue in patients receiving lapatinib and those older than 70 years experienced more grade 3 events than younger women (33% vs. 19%) (Crown et al. 2008).

Colorectal Cancer

Metastatic colorectal cancer is actually treated with several biological agents. Some of them require the assessment of specific biomarkers. As for lung and breast cancer, there are two types of biological agents, monoclonal antibodies and small molecules.

Bevacizumab

The first biological agent used for colorectal cancer was bevacizumab which demonstrated, in association with irinotecan and fluorouracil, to be superior to fluorouracil alone in first-line setting in metastatic colorectal cancer (median OS 20.3 months vs. 15.6 months, HR for death of 0.66 (P <0.001) (Hurwitz et al. 2004). In the BRITE observational cohort study, 896 patients ≥65 years, out of 1953 advanced colorectal cancer patients, were evaluated for the safety and effectiveness of bevacizumab-based first-line therapy. Arterial thromboembolic events (ATEs) increased with age and the overall survival was worse in elderly patients. Hypertension, the main side effect of bevacizumab should be monitored. The BRITE registry reported 1.5% to 3.4% 60-day mortality rate for patients with CRC age ≥ 65 years who developed or worsened an hypertension (Kozloff et al. 2010). In AVEX trial, elderly patients unsuitable for oxaliplatin- or irinotecan-based chemotherapy with a median age of 76 years (range 70–87) were randomly assigned to receive bevacizumab plus capecitabine (n = 140) or capecitabine only (n = 140) (Cunningham et al. 2013). Progression-free survival was significantly longer for bevacizumab arm (median 9.1 months [95% CI 7.3–11.4] vs. 5.1 months [4.2–6.3]; hazard ratio 0.53 [0.41–0.69]; p <0.0001). In a German observational study, patients received bevacizumab 5–10 mg/kg every 2 weeks or 7.5–15 mg/kg every 3 weeks in combination with chemotherapy (Hofheinz et al. 2014). About

480 (27%) of 1770 patients who were 70 years old or more had worse median overall survival than younger patients (median OS for patients aged <70 vs. ≥70 years and <75 vs. ≥75 years were 25.8 vs. 22.7 months (HR: 1.28, 95% CI: 1.11–1.47; 2-sided log-rank test p <0.0008; and 25.8 vs. 20.8 months, respectively (HR: 1.48, 95% CI: 1.23–1.80; 2-sided log-rank test p <0.0001). The efficacy and safety of bevacizumab plus S-1 was tested in elderly patients with previously untreated mCRC in a phase II trial (the median OS was 25.0 months, and the RR was 57%).

Panitumumab

Panitumumab is a fully humanized recombinant monoclonal immunoglobulin G2 kappa antibody against EGFR. The PRIME study reported the efficacy of adding panitumumab to infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) in the first-line setting of K-ras WT mCRC with an improvement in PFS (9.6 vs. 8.0 months, respectively; hazard ratio [HR], 0.80; 95% CI, 0.66 to 0.97; P 0.02). This was not elderly specific trial; however, the toxicity of panitumumab for patients more than 65 years was relevant. Panitumumab as single agent was explored in a series of frail elderly patients defined by the authors as patients not able to receive chemotherapy. The median PFS and OS were 6.4 months (95% confidence interval [CI]: 4.9–8 months) and 14.3 months (95% CI: 10.9–17.7 months), respectively. The most frequent grade 3 AE was skin rash, with an incidence of 20%. A Spanish phase II study on frail elderly patients confirmed these results.

Cetuximab

Cetuximab is a chimeric monoclonal immunoglobulin G1 antibody that binds to the EGFR. Cetuximab plus FOLFIRI and FOLFIRI alone. The median age of the population was 61 years with a range of 24–79. The hazard ratio for progression-free survival among patients with wild-type–KRAS tumors was 0.68 (95% CI, 0.50–0.94), in favor of the cetuximab–FOLFIRI arm. In a retrospective multicenter study on irinotecan pretreated patients, the age group 66 years and older included 250 patients (50.3%) with a median age of 70 years (range 66–88). 36.7% of patients required supportive treatment independently from age. No significant difference between both age groups (p = 0.51) there was in the rates of hospitalization. Elderly patients had higher grades of toxicities compared to younger ones (p 0.05). Patients >65 years had significantly more comorbid conditions and a higher CCI (Charlson Comorbidity Index), compared with the younger patients group (p = 0.001). Patients 18–65 years showed a PFS of 5.9 months as compared with 6.1 months for patients >65 years (p = 0.99, log-rank test). CCI and age had no negative influence on PFS.

Aflibercept

Aflibercept is an antiangiogenic agent that blocks the activity of VEGFA, VEGFB, and placental growth factor. In the VELOUR study (Aflibercept versus placebo in combination with irinotecan and 5-FU in the treatment of patients with metastatic colorectal cancer after failure of an oxaliplatin-based regimen) (Van Cutsem et al. 2012), the median age was 61 years (range, 21–82 years). The addition of aflibercept to FOLFIRI increased PFS relative to placebo plus FOLFIRI (hazard ratio, 0.758; 95% CI, 0.661–0.869; P 0.0001). Median PFS, based on independent assessment of radiologic progression, was 6.9 months in the aflibercept arm and 4.7 months in the control arm. No subgroup analysis on elderly patients was planned.

Regorafenib

Regorafenib is an oral, small-molecule multikinase inhibitor. In the CORRECT Study Group (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy), regorafenib demonstrated superior overall survival when compared to placebo in heavily pretreated patients (Grothey et al. 2013). The magnitude of OS benefit was a statistically significant 1.4-month favoring regorafenib over placebo. Median age was 61 (range 54–67) and only ECOG PS 0–1 patients were enrolled. About 285 older patients (≥65 years old) had progression free survival but not overall survival benefit compared to younger patients.

Renal Cell Carcinoma

Biological target agents with activity in renal cell carcinoma (RCC) include antiangiogenic multi-TKIs, mammalian target of rapamycin inhibitors (mTOR inhibitors), and immunotherapy.

Sunitinib

The superiority of sunitinib versus interferon in metastatic RCC was demonstrated in a phase III multinational trial (Motzer et al. 2007). A retrospective pooled data analysis investigated the efficacy and safety of sunitinib in 1059 patients who received sunitinib in either the first-line or cytokine-refractory metastatic RCC setting. About 202 (19%) patients were ≥70 years old with a median age of 73 years (range: 70–87). In patients who received sunitinib on schedule 4/2, the incidences of fatigue, dizziness, dehydration, and hand–foot syndrome were not significantly different between the two age groups, while constipation, asthenia, anorexia, and erythema were significantly more common in older patients. When given in a continuous daily dosing sunitinib caused more nausea, hyponatremia, arthralgia, and pruritus in older patients. Overall, the older patients were more likely to have a highest severity of grade 3. A series of 185 older patients receiving an adapted regimen, i.e., 37.5 mg/day for a 4/2 weeks schedule, were retrospectively analyzed. The median progression-free survival (PFS) was 11 months and discontinuations because of therapy-related adverse events occurred in 25 patients treated with standard regimen (20.3%) vs. 15 with adapted regimen (24.2%), respectively (P 0.679) (De Giorgi et al. 2014a, b; Hutson et al. 2014). Another retrospective analysis in six Italian centers evaluated 68 patients (median age 74 years, range 70–88) treated with sunitinib (Brunello et al. 2013). Hematological toxic effects were mostly grade 1–2 and so were non-hematological toxic effects, with the only reported grade 4 toxic events being neutropenia. The most common nonhematologic adverse events were fatigue (80.9%, 55 patients), mucositis (61.8%, 42 patients), and hypertension (58.8%, 40 patients).

Axitinib

Axitinib is a potent and selective second-generation inhibitor of VEGF receptors 1, 2, and 3. The AXIS trial (Axitinib as second line therapy for metastatic renal cell cancer) showed a significant improvement in median PFS, favoring axitinib when compared with sorafenib in second-line therapy in RCC (Rini et al. 2011). In the study, age is not a baseline prognostic factor for overall survival, and there were no concern about safety in older as well in younger patients (Motzer et al. 2013a).

Pazopanib

Study VEG105192 was a placebo-controlled, randomized, double-blind, global, multicenter, phase III study that compares pazopanib vs. placebo in patients with advanced RCC (Sternberg et al. 2010). The prespecified subgroup analyses showed that PFS was improved for patients treated with pazopanib compared with placebo regardless of MSKCC risk category, sex, age, or ECOG PS (HR range, 0.40–0.52; P 0.001 by log-rank test for all). The most common grade 3/4 AEs in the pazopanib arm were hypertension (4%) and diarrhea (4%). Arterial thrombotic events occurred in 3% of pazopanib-treated patients compared with none in the placebo group. The COMPARZ trial was a randomized, open-label, phase 3 trial of pazopanib versus sunitinib (Motzer et al. 2013b). Overall, 39% of patients were older than age 65 years. The median progression-free survival was 8.4 months with pazopanib (95% confidence interval [CI], 8.3–10.9) and 9.5 months with sunitinib (95% CI, 8.3–11.1). Investigator-assessed objective response rates were similar between the two groups (33% in the pazopanib group and 29% in the sunitinib group, $P = 0.12$). Patients who received pazopanib had a higher risk of increased levels of alanine aminotransferase or bilirubin of any grade and significantly less fatigue and foot soreness.

Sorafenib

Sorafenib is an antiangiogenic, antiproliferative vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI). Sorafenib

demonstrated this activity in RCC in the TARGET trial that compared sorafenib to placebo in patients resistant to standard therapy (Escudier et al. 2007). Hundred and fifteen out of 902 patients (13%) were 70 years old or more. A subgroup analysis showed similar benefit for younger as well as older patients with regard to progression free survival and clinical benefit. More grade 3 and 4 toxic effects were reported in older sorafenib-treated patients than in younger sorafenib-treated patients (for grade 3 events, 40.0% vs. 29.4%, respectively; and for grade 4 events, 5.7% vs. 7.3%, respectively). Older patients had slightly more gastrointestinal symptoms and fatigue than younger patients. There were no unexpected adverse events attributable to advanced age. Older patients discontinued sorafenib mostly because of gastrointestinal (5.7%, or 4 patients) and dermatologic (4.3%, or 3 patients) issues. Sorafenib treatment improved quality of life among older and younger patients (Eisen et al. 2008). The analysis of a large Sorafenib-RCC (Sor-RCC) Integrated Database on 4684 patients enrolled in eight company-sponsored clinical trials and expanded-access programs showed no difference across age subgroups in terms of clinical benefit and adverse events (Procopio et al. 2013).

Temsirolimus

Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR) kinase. In the ARCC trial, temsirolimus was compared in previously untreated patients with advanced RCC, to interferon alfa or the combination of both. Compared with interferon alone, treatment with temsirolimus alone was associated with a hazard ratio for death of 0.73 (95% confidence interval [CI], 0.58–0.92; $P = 0.008$), with a median survival of 7.3 months in the interferon group, 10.9 months in the temsirolimus group, and 8.4 months in the combination-therapy group. Older patients ($\geq$65 years old) in the temsirolimus alone arm were 31% and the effect of temsirolimus on overall survival was greater among younger patients (Hudes et al. 2007). Temsirolimus was better tolerated than IFN in older patients.

Everolimus

Everolimus is an orally administered inhibitor of the mammalian target of rapamycin (mTOR). In a nonelderly international, multicenter, double-blind, randomized phase III trial (RECORD-1), everolimus was compared with placebo for the treatment of metastatic renal cell carcinoma in patients whose disease had progressed on treatment with VEGF receptor tyrosine kinase inhibitors (Motzer et al. 2008) and showed a median progression-free survival 4.0 [95% CI 3.7–5.5] vs. 1.9 [1.8–1.9] months. Stomatitis, fatigue, and pneumonitis were more frequent in everolimus arm. About 36.8% were $\geq$65 year and 17.5% were $\geq$70 year of age. Elderly patients had the same benefit as younger patients for PFS. Toxicities in elderly patients were similar to those in the overall study population, being stomatitis the most common AE of any grade in everolimus-treated patients (Porta et al. 2012).

Cabozantinib

Cabozantinib is an oral, small-molecule inhibitor of tyrosine kinases, including MET, VEGF receptors (VEGFRs), and AXL. In the METEOR study, patients with pretreated RCC were randomly assigned in a 1:1 ratio to receive either cabozantinib or everolimus. Median age of the population treated with cabozantinib was 62 (36–83). The estimated median progression-free survival was 7.4 months (95% confidence interval [CI], 5.6–9.1) with cabozantinib and 3.8 months (95% CI, 3.7–5.4) with everolimus. The rate of disease progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio for progression or death, 0.58; 95% CI, 0.45–0.75; $P < 0.001$). The incidence of adverse events of grade 3 or 4 was 68% with cabozantinib and 58% with everolimus; the most common grade 3 or 4 adverse events with cabozantinib were hypertension (15%), diarrhea (11%), and fatigue (9%) (Choueiri et al. 2015). No data on older patients are available.

Nivolumab

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated

T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. In the CheckMate 025, pretreated RCC patients were randomly assigned to receive nivolumab or everolimus. Median age of the population was 62 years (23–88). The median overall survival was 25.0 months in the nivolumab group and 19.6 months in the everolimus group, with a hazard ratio for death (from any cause) with nivolumab versus everolimus as 0.73 (98.5% CI, 0.57–0.93; $P = 0.002$). The benefit of nivolumab was observed for patients with all age subgroups at least until 75 years. The most common treatment-related adverse events among patients who received nivolumab were fatigue (134 patients, 33%), nausea (57 patients, 14%), and pruritus (57 patients, 14%) with no concern about older age (Motzer et al. 2015).

Melanoma

The common target therapies for metastatic melanoma include BRAF inhibitors (Curtin et al. 2005), antibodies, anticytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and anti-PD-1.

Vemurafenib and Dabrafenib

These two small molecules are active in tumors with BRAF V600E or V600 K mutations. In the BRIM 3 trial, patients with unresectable, previously untreated stage IIIC or stage IV melanoma that tested positive for the BRAF V600E mutation were randomly assigned to receive vemurafenib or dacarbazine. The study was not elderly specific and the median age was 56 (21–86). The hazard ratio for death in the vemurafenib group was 0.37 (95% confidence interval [CI], 0.26–0.55; $P < 0.001$). About 160 out of 672 patients were older than 65 years, and they seem to have the same benefit in term of both overall survival and progression free survival with respect to younger patients. The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue. In another trial, patients were administered either oral dabrafenib (150 mg twice daily) and oral trametinib (2 mg once daily), or oral dabrafenib (150 mg twice daily) and placebo. The most common treatment-related adverse events were pyrexia, chills, fatigue, rash, and nausea in the dabrafenib and trametinib group; the HR for death was 0.71 (95% CI 0.55–0.92; $p = 0.0107$) in the combination group (Hauschild et al. 2012).

Ipilimumab

Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks CTLA-4. It showed its activity in a trial where patients were randomly assigned, in a 3:1:1 ratio, to ipilimumab plus gp100 peptide vaccine; ipilimumab alone; or gp100 alone. The median overall survival in the ipilimumab-alone group was 10.1 months (95% CI, 8.0–13.8) (hazard ratio for death with ipilimumab alone as compared with gp100 alone, 0.66; $P = 0.003$). Overall, 29% of patients were older than age 65 years. Ipilimumab can cause severe and potentially life-threatening immune-related toxicities; however, no difference in survival or safety data between younger and older patients was reported (Hodi et al. 2010).

Nivolumab

In the CheckMate 066 and CheckMate 037 study, Nivolumab monotherapy was superior to dacarbazine in metastatic melanoma without a BRAF mutation in terms of overall survival benefit and objective response, respectively (Weber et al. 2015; Wolchok et al. 2013). Adding nivolumab to ipilimumab resulted in better outcomes than ipilimumab alone in untreated melanoma (Postow et al. 2015). No specific data on elderly patients are available in this setting.

Hepatocellular Carcinoma

Sorafenib

Sorafenib is a an oral multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and Raf. It has become the standard of care in advanced hepatocellular carcinoma (HCC) after the results of the SHARP trial that showed a survival benefit of 3-months for sorafenib vs. placebo (10.7 months vs. 7.9 months; hazard ratio, 0.69; 95% confidence interval [CI], 0.55–0.87; $P < 0.001$) in treatment-naive patients

with advanced HCC (Childs Pugh class A) (Llovet et al. 2008). This was not an elderly specific trial (median age 64.9 ± 11.2). Two retrospective analyses on elderly patients (age ≥70) analyzed the efficacy and tolerability of sorafenib. In former, full doses of sorafenib were administered in 11 out of 60 patients (18.3%), with no significant change in the quality of life during the study (Montella et al. 2013). In the latter enrolled 51 individuals aged 70–83, Child-Pugh A or B, ECOG performance status 0 to 2 who were not suitable candidates for or had progressed after locoregional therapies. The most frequent Grade 3 adverse reactions were fatigue (15.7%), hand–foot syndrome (15.7%), abdominal pain (11.7%), and hyperbilirubinemia (11.7%). Dose reduction (from 800 to 400 mg/d) due to toxicity was required in 28 individuals (54.9%), mainly because of thrombocytopenia (15.7%). During treatment, IADL score decreased in 13 patients (25.5%) (Francini et al. 2014).

Gastric Cancer

Trastuzumab

Trastuzumab is overexpressed in 7–34% of patients with gastric cancer. The ToGA trial (ToGA Study: A study of trastuzumab in combination with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer) examined trastuzumab in combination with fluorouracil-platinum chemotherapy in advanced gastric adenocarcinoma. Patients assigned to trastuzumab plus chemotherapy had a median overall survival of 13.8 months (95% CI 12–16) compared with 11.1 months (10–13) in those assigned to chemotherapy alone (HR 0.74; 95% CI 0.60–0.91; $p = 0.0046$) (Bang et al. 2010). About 52% of the patients were age >60 years. Cardiac adverse events were rare with no difference between the trastuzumab plus chemotherapy and chemotherapy alone groups (17 [6%] vs. 18 [6%]).

Ramucirumab

Ramucirumab is a fully human IgG1 monoclonal antibody and VEGFR-2 antagonist. In RAINBOW (Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma) study, patients were randomly assigned to ramucirumab plus paclitaxel or placebo plus paclitaxel. Patients more than 65 years old were 38%. Overall survival with ramucirumab plus paclitaxel was significantly longer than with placebo plus paclitaxel (9.6 months vs. 7.4 months, HR 0.807 [95% CI 0.678–0.962]; $p = 0.017$); at the multivariable analysis age did not seem to influence survival outcomes (Wilke et al. 2014). In the REGARD trial (Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma), patients were randomly assigned in a 2:1 ratio, to receive best supportive care plus either ramucirumab 8 mg/kg or placebo. Treatment with ramucirumab resulted in a 52% reduction in the risk of disease progression or death from any cause; more patients in the ramucirumab group had grade 3 hypertension than those in the placebo group (Fuchs et al. 2014).

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Lung Cancer in Older Adults: Systemic Treatment
- ▶ Research Methods: Clinical Trials in Geriatric Oncology

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Pain Management in Older Cancer Patients

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Geneviève Gridel and Gilbert Zulian

Contents

Abstract

As a very frequent symptom, cancer pain in the elderly is an obvious signal for the need to improve the situation, both in physical terms and in terms of a more holistic approach. The multiplicity of causes and expressions of pain and the many means at our disposal for its management should not interfere with a rigorous diagnostic and therapeutic approach based on specific assessment and prognostic scales associated with a comprehensive geriatric evaluation. Thus, knowledge of the precise and safe handling of analgesics and other associated drug products, which can absolutely be offered to these vulnerable patients, is of paramount importance and must always be accompanied by a wish to combine this with consideration and multidisciplinary expertise while pursuing the objective of relief and the maintenance of a level of functional ability and quality of life that are acceptable to the patient.

Keywords

Elderly cancer · Pain management · Frailty · Multidisciplinarity · Holistic medicine

Introduction

In the holistic management of elderly cancer patients, each symptom has to be assessed and treated with a view to achieving the best possible quality of life. In this context, pain is a very frequent reason for consultation. After giving an overview of the many distinctive features of the characteristics of pain and its assessment in elderly patients with cancer, the broad principles of management and the different types of possible treatment will be presented in detail.

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Multidimensional Assessment of Pain in Geriatric Oncology

Geriatric oncology, since it was first described in 1983 (National Cancer Institute and National Institute of Aging (U.S.) 1984), is the expression and practical implementation of the acknowledgement that elderly subjects who increasingly face cancer need a multidisciplinary, specific, and customized approach and management. Increasingly, there are studies and clinical trials specifically dedicated to this problem and what emerges from these above all is the absolute necessity of correctly and comprehensively assessing these patients in order to tailor the treatment options to their level of vulnerability, both medical (comorbidities, polymedication, cognitive impairment, etc.) and psychosocial (isolation, need for partnership with home care facilities, etc.) (Falandry et al. 2011) with a view to improving their health status and quality of life. In this context, the comprehensive geriatric assessment is now recognized as an essential prerequisite in the management of elderly patients in oncology (Extermann et al. 2005). The progress made in terms of our knowledge of the aging process and associated frailties allows us to understand the great heterogeneity of elderly patients themselves, who we tend to classify in different categories of greater or less vulnerability or according to whether the aging process is smooth or pathological. Similarly, there is also great heterogeneity regarding pain, both in terms of its nature or mechanism as well as its expression and prevalence (real, reported, or diagnosed). In any event, different literature reviews or meta-analyses show that among the many symptoms presented by elderly cancer patients, pain is one of the most frequently mentioned (Teunissen et al. 2007). Furthermore, according to studies, its prevalence is considered to be equivalent to that found in young adults (Van den Beuken-van Everdingen et al. 2007) (i.e., affecting 20 to 50% of all cancer patients (Fischer et al. 2010)) or even greater as it is largely underestimated and undertreated) (Breivik et al. 2009). Some authors, on the other hand, find a higher incidence among the younger population who are believed to be subject to more frequent episodes of breakthrough pain (Green and Hart-Johnson 2010).Epidemiological data are not therefore all consistent since it is so difficult to standardize the precise assessment of pain. In any event, moderate to severe pain is believed to affect 80% of all patients in an advanced stage of cancer (Bruera and Kim 2003). Against this background, the management of pain in these frail patients is a priority, which increasingly needs to be personalized (Dalal et al. 2012).

Thus, it is absolutely essential that the precise assessment of pain must be rigorous, holistic, and repeated in order to achieve appropriate management. The most spontaneously used tools are self-assessment scales, which nevertheless in many cases must be combined with or replaced by hetero-assessment scales specifically developed for elderly subjects. Pain assessment must also be supplemented by the measurement of its impact on daily activities and overall quality of life and weighted by the patient's psychoaffective environment.

Severity of the Pain

In the area of self-assessment, the visual analogue scale (VAS) and the numeric scale (NS), which are most frequently used, are limited by the patient's powers of communication and abstraction. Only a minority of subjects in an advanced stage of cancer with both cognitive impairment and a deterioration of their general condition are able to use the VAS correctly. The numeric scale may be offered to patients who have difficulty understanding the principle of the VAS but who have retained their powers of abstraction. In its oral form, it can also be relevant for patients with physical handicaps. It is therefore often the simple verbal descriptor scale (SVDS) that, although less sensitive and less precise than the VAS, is preferred by medical staff and elderly patients. Indeed, elderly patients can describe their pain using familiar words. It is easy and quick to use. With the exception of subjects with very severe cognitive impairment, almost all patients are capable of completing it. The same is true of the faces pain scale, which is widely used in geriatric medicine and is

understandable and easy to use including for patients with severe cognitive impairment (Pautex et al. 2006). In certain situations, however, it is necessary to supplement these self-assessments, which are sometimes not very helpful, with observational scales. Numerous teams around the world who are confronted daily with the complexity of the management of elderly patients with cognitive impairment have highlighted the particular diagnostic and therapeutic features of this population (Buffum et al. 2007). Scales have been devised which are generally based on observation of the patient's behavior by the family or nursing staff which have to be repeated in different situations (resting, nursing, mobilization, etc.). These validated simplified behavioral scales include, depending on the country, the PAINAID scale (Pain Assessment in Advanced Dementia Scale) (Warden et al. 2003), developed in New Jersey, the PASLAC tool (Pain Assessment Checklist for Seniors with Limited Ability to Communicate) in Canada (Fuchs-Lacelle and Hadjistavropoulos 2004), or the Algoplus and Doloplus (Rat et al. 2014) scales for French-speaking Europe. Their limitations are mainly associated with the necessity of a multidisciplinary assessment, if possible with knowledge of the patient's normal behavior. These assessments also require the possibility of comparison with a baseline or previous condition. All these scales are often unsuitable for the assessment of acute pain.

It is therefore necessary to be very cautious and to follow certain rules of good practice so as to avoid the pitfall of inconsistency of assessment of the pain severity between the nursing staff and the patient, which inevitably leads to inappropriate pain management (Brasseur et al. 2006). For example, the reliability of self-assessment could be tested by rephrasing the instructions to the patient or by verifying the consistency of the result between the VAS, the SVDS, or the NS during a single consultation (Herr et al. 2011).

Location and Pathophysiological Characteristics

Once the severity of the pain has been measured, its locations, mechanisms, and causes have to be detailed in order the tailor the therapeutic options. One of the particular features of cancer pain is that it often affects several sites, with different pain mechanisms coexisting (Grond et al. 1996). By means of detailed questioning, of both the patients themselves, the family, caregivers, or nursing staff, the characteristics of the pain have to be defined as precisely as possible. The timing of the pain, its frequency, the existence of trigger, aggravating or alleviating factors, the date of onset, the existence of unpredictable episodes of searing pain, or, conversely, of reproducible episodes have therefore to be identified. The aim is to define the acute or chronic, nociceptive, neuropathic, or mixed characteristics of the pain and to recognize the existence of episodes of breakthrough pain. Among the multidimensional tools available is the "McGill Pain Questionnaire (Melzack 1975)," this is a self-assessment tool that allows the patient to link the severity of his or her pain to its subjective sensory and affective characteristics. Similarly, the DN4 questionnaire (Boussahira et al. 2005, Van Seventer et al. 2010) allows adjectives to be suggested to patients to allow them to describe their pain and to guide the clinician in whether or not to make a diagnosis of neuropathic pain. It is a specific diagnostic tool that is easy and quick to use.

Particular Medical, Psycho-Behavioral, and Social Characteristics of the Patient

In the assessment of pain, therefore, the objective, in particular in the case of elderly cancer patients, is to be as comprehensive and as multidimensional as possible. Certain scales have been created in order to measure the impact of the pain on the patient's functioning in daily life, which is an essential concept in the complex problems of geriatric oncology. The Brief Pain Inventory (Hølen et al. 2008) and the PROMIS-PI (Patient-Reported Outcomes Measurement Information System – Pain Interference) (Amtmann et al. 2010) are good examples of this. Even if these tools are not always easy to use in daily practice, they allow the assessment of a patient with pain to be fine tuned in certain complex situations and are good clinical research

tools. Once the pain and the main characteristics of the pain have been assessed, it is important to consider the patient's psychosocial environment and his or her pain coping strategies. The aim of this is to customize the choice of treatment, but also to be able to predict whether or not the pain will be well controlled. Indeed, the perception of pain and the quality of pain relief vary greatly from one patient to another, and some studies even show numerous cases of failure of pain relief in the absence of careful monitoring and regular adjustment of the analgesic treatment (Yennurajalingam et al. 2012).

It is therefore necessary to be familiar with all aspects of one's patient. Medically, the other symptoms should be assessed using the ESAS (Edmonton Symptom Assessment System) (Bruera et al. 1991). On a psychological level, the clinician has to look for anxiety or depression, whether or not this is in reaction to the pain. It is also necessary to understand the ability to adapt and the resilience of the patient with pain. On a social level, the patient's family situation (more or less supportive family members) (Im et al. 2009) and his or her ethnic origin and social background can influence the ability to tolerate pain or the response to treatment. As an example of this, we can cite the great variability in behavior in the face of pain according to a patient's ethnocultural origin (Chen et al. 2012), with the Asian culture in particular not showing or admitting to pain for fear of being regarded as weak and so as not to burden the family, while some Western cultures, in contrast, allow themselves to express their pain loudly. This detailed analysis should also make it possible to identify cases where the patient is completely overwhelmed by pain, physically, psychologically, emotionally, and socially. This is referred to as "unrelieved" pain, and specific therapeutic measures have to be considered (Syrjala et al. 2014).

Obviously, in order to complete the oncogeriatric assessment, it goes without saying that pain management has to take account of the specific comorbidities of the elderly patient and the impact of these on the pharmacokinetics, pharmacodynamics, and tolerability of the treatments under consideration.

Assessment of the Anticipated Efficacy of Treatment

All this attention to detail in the multidimensional assessment of pain in elderly patients with cancer is necessary as this rigor allows the best possible refinement of the proposed analgesic treatment and follow-up. In order to complete this assessment, it is beneficial to use pain prognosis scores, the aim of which is to predict the response to analgesic treatment. The objective is above all to screen patients at high risk of not responding effectively to treatment in order to define, particularly together with them, a policy and realistic pain relief targets from the outset, rather than promising them rapid and complete relief. Examples of this are the ESC-CP (Edmonton Classification System for Cancer Pain) (Fainsinger and Nekolaichuk 2008), which is based principally on the type of pain concerned, the level of psychological distress, past addictions, and cognitive function. The CPPS (Cancer Pain Prognostic Scale) (Hwang et al. 2002), for its part, takes the form of a formula defining a higher or lower probability score for response to analgesic treatment. This formula combines scores for pain intensity, the presence of mixed pain, the necessary doses of morphine, and how the patient copes emotionally. In all cases, it helps the clinician to make pain management more personalized and to guard against the temptation to escalate doses of analgesic, rather than viewing management from a more multimodal perspective in the case of patients considered to have a poor prognosis.

Pain Management in Geriatric Oncology

As has been extensively outlined above, a complete and detailed assessment of the pain suffered by a cancer patient, in particular when the patient is elderly and potentially frail, is the condition sine qua non which enables appropriate, personalized, and multidisciplinary pain relief treatment to be initiated and then to be managed (Fig. 1). In this context, the pain may be associated with either, in about 70% of cases, the disease itself (Gutgsell et al. 2003) or its treatment or the care associated

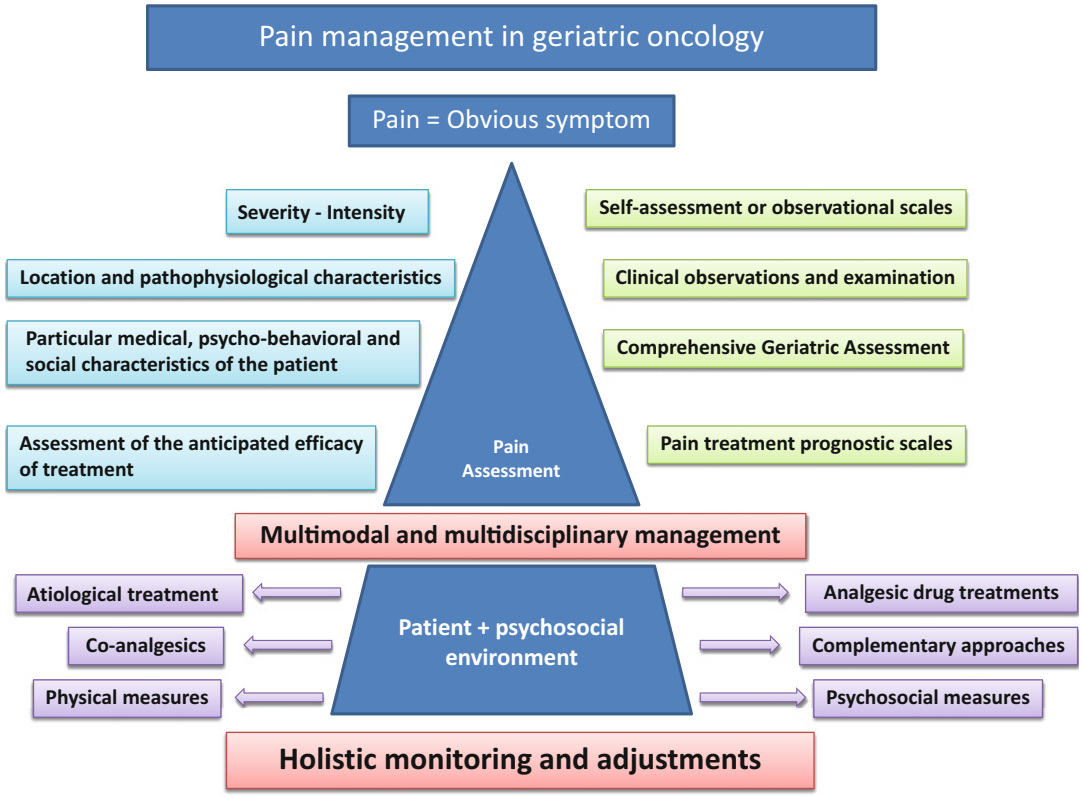

Fig. 1 Cancer pain management in the elderly: a multidisciplinary and holistic approach

with the cancer, or any other comorbidity, as is frequently encountered in this elderly population (approximately 8–15% of pain, generally pre-existing and receiving long-term treatment) (Barbera et al. 2013). The management of these patients still remains holistic, whether or not it combines general measures with specific drug treatments.

Etiological Treatment

In all cases, depending on the level of management desired by the patient and justified by the geriatric assessment, the specific treatment of the cancer remains a standard treatment for the pain associated with the disease itself. This cancer treatment can be viewed in terms of whether the objective is a cure or is purely symptomatic. Once this objective has been clearly defined, the methods of monitoring the efficacy/tolerability ratio of the treatment that has been started should be specified, with a regular reassessment of the symptomatic and functional benefit to the patient in terms of analgesia, as well as, naturally, the undesirable effects of the treatment. It must be borne in mind that the benefit of these treatments declines and the probability of serious complications arising increases with age (Balducci et al. 2015). These specific anticancer treatments are varied and can either involve drug treatment (chemotherapy, immunotherapy, or other targeted treatments) or be physical (radiotherapy) or surgical. Prescription of these remains the prerogative of specialists in oncology, but their indication should be established with caution, following multidisciplinary discussion, again with a view to a comprehensive prognostic assessment, taking account not only of molecular and cellular characteristics and the clinical spread of the disease, but also the functional abilities and initial autonomy of the patient, associated with all his or her comorbidities and psychosocial environment that affect compliance with and tolerability of the

treatment. For example, it can be mentioned here that the indication for radiotherapy for analgesic purposes in the case of bone metastases does have a place in geriatric oncology, but it should be borne in mind that on the one hand there is the possibility of a transient upsurge in the pain within the first 7 to 10 days and on the other that complete efficacy only occurs 3–4 weeks after the irradiation. Throughout this period, the elderly patient will have to be monitored particularly closely and is even at risk of major deconditioning which is essential to prevent and monitor.

Analgesic Drug Treatments

If an etiological treatment is unsuitable for the management of a particular patient, or else to supplement the analgesic effect of the latter, "classic" analgesics will naturally have to be used. This designation covers the analgesics of the WHO's three-step ladder. Prescription of these, for purely symptomatic purposes, is based in geriatric oncology on the same rules as for any other patient. These analgesics will therefore be administered starting with step 1 (paracetamol), then if this is ineffective moving straight on to step 3 (opioid treatments). In the context of oncology and in particular when pain management is associated with cancer, the analgesics in step 2 have little place, perhaps with the exception of buprenorphine. The need to be able to switch easily to strong opioids is explained on the one hand by the fact that pain in geriatric oncology frequently corresponds to nociceptive pain which will respond well to the mechanism of action of opiates and secondly by the fact that step 3 analgesics are more easily manageable and better tolerated than step 2 analgesics as they are available in much more varied pharmaceutical formulations and concentrations, allowing a much more delicate titration of the minimum effective dose and therefore a much more gradual and better tolerated adjustment of the doses required (Bandieri et al. 2016). A unique feature of patients in geriatric oncology is the fact that the therapeutic margin is especially narrow as the iatrogenic risk is increased by renal failure or the failure of other organs, malnutrition, or cognitive impairment.

For the record, step 3 analgesics include primarily morphine, oxycodone, fentanyl, and hydromorphone. All these drug products are pure μ, κ, and δ receptor agonists. Buprenorphine, on the other hand, classified in step 2 by the WHO, is a partial μ agonist and κ antagonist. It has a greater affinity than does morphine, but its activity is weaker. While it has good analgesic efficacy when used alone, its combination with pure opioids is contraindicated as it counteracts their analgesic action. Its role for elderly subjects lies in particular in its purely hepatic metabolism, which makes it a drug of choice in the case of renal failure.

Generally speaking, and in geriatric oncology in particular, the introduction of opioid treatment is a source of uncertainty and concerns for the patient (Potter et al. 2003). Patients should always be reassured as to the fact that this molecule (and its derivatives) is absolutely not reserved for end-of-life treatment, but is a standard analgesic which is also completely safe to use when it is prescribed in accordance with recommendations. The principles for prescription of these drugs are based on a fundamental concept, namely that of titration, where the minimum effective dose is sought, or else the lowest dose that allows sufficient efficacy to be achieved with the fewest possible undesirable effects. In order to obtain this, one starts with very low doses (generally one half, but even as little as one fourth of the dose recommended for a young adult, i.e., 2.5 mg of oral morphine per dose in an elderly subject instead of 10 mg in adults), up to a maximum of 6 times per day, with the frequency having to be reduced according to the patient's renal function and his or her psychological or cognitive vulnerability (Caraceni et al. 2012). As with young adults, back-up doses will be provided for, in order to adjust the fixed basic dose every 2 to 3 days if necessary, which can then be converted to a retard form if symptoms remain unchanged (Bruera et al. 1998). This gradual titration, if carried out correctly in accordance with the adage "start low, go slow," usually allows an appropriate balance to be achieved between efficacy and tolerability, including in frail elderly patients. It will be recalled that these molecules can also be antagonized by naloxone if necessary.

With regard to the tolerability of these opioid treatments, their undesirable effects have to be known in order to anticipate them and to treat them as early as possible, which will improve patient comfort and adherence to the treatment. These side effects include in particular:

- Constipation: this is by far the most common side effect and should be routinely averted whenever opioid treatment is introduced. Laxative treatment generally remains necessary in the long term. In the event of resistance to conventional first-line treatments, the use of methylnaltrexone may be necessary.
- Nausea and vomiting: these symptoms can usually be avoided if titration is carried out very gradually in accordance with the rules described above, but one should never hesitate to avert this undesirable effect at the least complaint by the patient. Rapid-release formulations are likely to encourage the onset of nausea and a switch to longer-release formulations as soon as analgesic stability appears to have been achieved is a good way of improving digestive tolerability of opioid treatment.
- Pruritis: this symptom, again, is often transient and can be treated with antihistamines if it is reported by the patient.
- Drowsiness: this almost always occurs when the treatment is started and whenever the dose is increased. It is a transient effect about which the patient and his or her carers should be warned and which wears off after 48–72 h, especially when a stable dose is achieved.
- Delirium and hallucinations: these manifestations, which are always overwhelming for the patient and carers, are uncommon and above all are multifactorial in the majority of cases (Morita et al. 2001). However, if they persist despite the correction of other associated risk factors, they are a recognized indication for rotation to alterative opioids.
- Respiratory depression: very often feared when dealing with opioids, it is, in fact, extremely rare and, as has been shown in several studies over the last few years, morphine remains the best symptomatic treatment for dyspnea. Thus, whether it is prescribed for analgesia or for the relief of dyspnea, there is no reason to fear the development of respiratory depression, provided the rules of good prescribing have been observed (Clemens et al. 2008).
- Opioid-induced hyperalgesia: a concept that is not yet widely described in the literature, and probably underdiagnosed, this is a situation that requires gradually increasing basic doses, but in which backup doses increase the pain, which distinguishes it from dependency. Currently, the best therapeutic strategy in this case remains opioid rotation, probably with methadone having special status (see below). Another recommendation would be to add in antineuropathic pain treatment, given the similarity between this syndrome and neurogenic pain (Bannister 2015).

Thus, while morphine remains the drug of choice, it may be replaced by another opiate in certain cases. This rotation can be justified by certain pain characteristics (oxycodone accepted in mixed nociceptive-neuropathic pain) or in the case of organ failure (fentanyl indicated in renal failure), or in order to choose a more appropriate route of administration (fentanyl transdermal patch), or, finally, in order to obtain stronger analgesia with an equal volume (hydromorphone) in rare cases of minimum effective doses in elderly subjects. Likewise, the route of administration of choice remains the oral route (Wiffen et al. 2013), which can be replaced by parenteral routes (IV or subcutaneous), transdermal, or transmucosal routes when the clinical context requires this, as in the specific treatment of episodes of acute breakthrough pain with transmucosal fentanyl (Simon and Schwartzberg 2014). However, these opioid rotations should not become routine and remain reserved for three main indications (Fine and Portenoy 2009):

- The presence of major side effects that cannot be controlled by standard measures, or the persistence of neurotoxicity.
- Suboptimal pain control despite well-managed titration, together with the appearance of side effects as an indication of poor tolerability of the dose attained.

– A change that is necessary for logistical reasons such as a change of the route of administration, the development of a new comorbidity or organ failure that is a contraindication to the drug in current use, or possibly financial considerations steering the new choice toward a less costly drug that is expected to have an identical result.

In the area of strong analgesics, the use of methadone sometimes proves necessary. This is a μ-receptor agonist and NMDA (N-methyl-D-aspartate) receptor antagonist. Its anti-NMDA properties make it a useful alternative, in particular if opioids are poorly tolerated or in the case of difficulties of pure opioid dose adjustment when associated hyperalgesia is suspected. Its routes of administration are many and varied and its unique pharmacokinetics, with rapid efficacy but a long half-life, but above all with wide inter-patient variability, make it complex to manage. In particular, the choice of a starting dose in the context of rotation from a strong opioid remains relatively empirical and must be made on a case-by-case basis (McLean and Twomey 2015). This unique feature, combined with its numerous drug interactions and its specific side effects such as prolongation of the QT interval, makes it a drug that requires complex management, prescription of which must be restricted to specialists.

Finally, a new treatment option related to strong opioids is the use of tapentadol, a synthetic opioid that is a μ-receptor agonist and noradrenaline reuptake inhibitor (NRI) which gives it beneficial analgesic properties, in particular in the case of mixed pain. Its efficacy and tolerability appear to be comparable to those of morphine and oxycodone. A recent meta-analysis (Wiffen et al. 2015) did not find that it has additional benefits compared to current standard treatments, but this drug represents an attractive treatment option in the management of pain in elderly cancer patients.

Co-analgesics

As has already been described above, pure analgesic treatments, including those in step 3 of the WHO ladder, remain indicated in elderly patients, provided that the rules of good prescribing and gradual dose adjustment are observed. That said, it is always advisable to try as far as possible to combine them with other types of drug product which have a different mode of action, but the analgesic action of which is able to supplement or potentiate the effect of the first, thereby aiming for a less substantial increase in the necessary doses, while remaining alert to the many possible drug interactions.

These supplementary treatments include, first and foremost, specific treatments for neuropathic pain. This pain, associated either with the disease itself or with the side effects of its treatment, must be identified using the diagnostic tools described above. Pharmacological management of neuropathic pain is the same as for young patients, but with the dosages adjusted according to renal and hepatic function (Attal et al. 2010; Dworkin et al. 2010). The standard drug products recommended for first-line treatment therefore remain the antiepileptics (gabapentin, pregabalin) and then the antidepressants, SRIs or dual SRI-NRIs, or even tricyclic antidepressants, tolerability of which, in particular neuropsychological tolerability, is not always good in elderly patients. In every case, a precautionary strategy should be adopted, starting with low doses and increasing them very gradually.

In the context of geriatric oncology, corticosteroids are obviously a vital part of this analgesic strategy for the control of the inflammatory component of pain. In fact, the most recent meta-analyses do not provide a good level of proof of a pure analgesic effect (Haywood et al. 2015), but the indication for corticosteroids is still accepted, in particular for neuropathic pain on compression (spinal or peripheral nerve) or for headaches caused by intracranial hypertension, as well as their general stimulatory and orexigenic effect which indirectly affects the response to the rest of the analgesic treatment (Paulsen et al. 2014). In this context, they are still recommended for elderly subjects in the same doses as for young adults (0.5–1 mg/kg/day of prednisone in the attack phase), with preference always given to short courses rather than long-term treatment that again fosters numerous complications. The

increased susceptibility of elderly patients to develop undesirable effects will be noted, in particular neuropsychological effects (irritability, sleep problems, and mood disorders), cardiac effects due to water and sodium retention, metabolic effects, in particular in terms of blood glucose, infections and functional effects with a loss of autonomy which may be increased by quadriceps muscle loss, or even increased skin fragility precipitating the development of sores in patients with underlying malnutrition. This functional impact, with a risk of falls, can be extremely detrimental and considerably worsen the patient's overall prognosis.

In addition, the particular place of anti-osteoclastic drugs such as bisphosphonates in the treatment and prevention of metastatic bone pain should be mentioned here (Wong et al. 2012). Their effect is not immediate, but a real benefit in the medium term is shown in the literature, justifying their use both for analgesia and in order to delay the development of bone pain.

In the area of coanalgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) should also be mentioned, bearing in mind above all that their systemic use is very limited in elderly subjects because of their renal toxicity (Hemett et al. 2014; American Geriatrics Society Panel 2009), although there is the possibility of temporary topical administration (in the form of a patch, cream, or gel), in particular for their local anti-inflammatory effect for general, non-cancer-related pain (muscle and joint pain, for example).

Finally, regarding systemic treatments, the place of ketamine is still uncertain. This anesthetic, used in subanesthetic doses, has been shown empirically to have an effective analgesic action against cancer pain that is not controlled by opioids. No precise recommendation can be made at the present time and its place in the treatment of cancer pain in the elderly is not proven (Bell et al. 2012).

With regard to topical treatments, mention should also be made, in ENT indications in particular, of the relief provided by applications of lignocaine or even topical morphine. For peripheral neuropathic pain, TENS (transcutaneous electrical nerve stimulation) can also provide supplementary treatment. The purpose of this type of stimulation is to stimulate the afferent nerve fibers of tactile sensitivity in order to limit and inhibit the communication of nociceptive signals that use the same physiological pathway.

Another strategy for supplementing the action of analgesics is the prevention of foreseeable exacerbations of pain, in particular during nursing care or other invasive procedures. In this connection, the use of a 50% nitrous oxide and 50% oxygen mixture, including in elderly patients, is well known (Krakowski et al. 2010). This technique allows complex and extremely painful wound care procedures to be carried out in conditions that are more acceptable to the patient, while avoiding the use of too high doses of back-up opiates. This treatment is now routinely offered in geriatric oncology, not forgetting the precautions for use associated with possible cognitive problems or difficulties of compliance of patients who have to hold the mask themselves.

However, it will be borne in mind that episodes of breakthrough pain or incidental pain are described as less common in the very elderly population and may be well controlled by opioid doses adjusted after careful titration (Mercadante et al. 2015).

Remaining in a more technical area, the elderly cancer patient may, subject to comprehensive geriatric assessment and prior consideration of the prognosis, be a good candidate for surgical procedures (vertebroplasty, cementoplasty), interventional radiological procedures, or even local/regional anesthetic blocks for specific lesions and in order to achieve functional improvement. The indications for these techniques still need to be assessed on a case-by-case basis in a collective and, above all, interdisciplinary spirit.

Finally, taking a more holistic view of patient pain, this symptom cannot be considered while overlooking the psychological component, either initially or at any rate reactive. In certain cases, the combination of purely analgesic treatment with anxiolytics proves necessary in order to control this symptom more completely. Despite their undesirable effects and their potential impact on

alertness, in this case benzodiazepines remain the class of drugs of choice, with the selection being made on the basis of the half-life (6–12 h: alprazolam; 10–20 h: lorazepam) and the dose and frequency of administration being adjusted according to the patient's cognitive status and organ failures.

Complementary Approaches, Physical Measures, and Holistic Management

As has just been suggested, treatment of the pain suffered by elderly cancer patients in fact goes far beyond merely prescribing the best possible opioid analgesic, possibly in combination with other synergistic approaches. The patient's pain must obviously be considered from a holistic perspective, linking the condition of old age, possibly already severely tested by life or other comorbidities, with the status of cancer patient. The pain, which is often exacerbated at the time an announcement is made (of the diagnosis, a recurrence, or progression of the disease), is a very sensitive indicator of the impact of the disease on the patient's quality of life. In light of this, it merits being linked to the idea of suffering. With the eye of a philosopher, Paul Ricoeur draws a clear parallel between these two concepts, defining them as follows: "Pain: affects experienced as located in particular organs of the body or in the whole body" and "Suffering: affects relating to reflexivity, language, relationship with oneself, relationship with others, relationship to the senses, to questioning". With this perspective, it is therefore essential to use the pretext of pain to in fact consider overall suffering (sometimes described as "total"). Questioning should therefore not apply solely to the treatments to be administered, but also to the way that announcements are made, to the necessity of going through patients' questions concerning the disease, sometimes expressed in the form of pain, with them and to offer psychological follow-up, even going so far as to offer cognitive behavioral therapy in the case of recurrent pain that is difficult to describe or is resistant to different treatments that are tried.

With this in mind, an increasing part is now played by complementary approaches such as sophrology, reflexology, hypnosis, but also touch massage, or even certain techniques from nonconventional medicine (acupuncture). These techniques are only available in certain centers, but they are approaches that should not be ignored, with discussion beforehand with patients, whose response to these types of treatment is very varied.

More conventionally, the role of physiotherapy is essential throughout the period of management of elderly cancer patients, not only to strengthen or develop existing motor functions, but also with the general aim of preserving functional abilities for as long as possible and for the prevention of multiple bone and joint pain which is the inevitable accompaniment to any degeneration of a patient's general condition. The work of the physiotherapist is often accompanied by that of the occupational therapist, whose suggestions are very often able to prevent the escalation of medication by means of physical, environmental, and material improvements at the time of any potentially painful procedure or installation.

From a multidisciplinary perspective, one could add that the management of pain in elderly cancer patients is in fact based on the team as a whole, which also includes psychosocial assessment of the patient's support network.

Indeed, this multidimensional and rigorous management of pain in elderly cancer patients is the key to being able to ensure that their quality of life is maintained and this management model can be summarized according to the following stages (Hui and Bruera 2014):

- Pain screening at each consultation in order to diagnose it as early as possible.
- More in-depth assessment in order to characterize the pain according to severity, semiological characteristics, associated prognostic factors, and above all incorporation within a multidimensional assessment of the elderly, vulnerable patient.
- Formulation of a multidisciplinary, multimodal treatment plan, combining possible pharmacological, analgesic, or coanalgesic measures with nonpharmacological measures.
- Education of the patient and of his or her family and friends in the management of the

treatment, its side effects, and the treatment objectives.
- Close monitoring throughout, with adjustments as often as necessary, both in order to improve the analgesic efficacy and considering a reduction in the treatment if necessary on the basis of the overall progress of the patient and of the disease.

Close adherence to this advice and the multidisciplinary nature of the management of these frail patients therefore remain, in both the area of analgesia and in all the areas affecting the health of elderly patients, the cornerstones of holistic and compassionate medicine.

Conclusion

In recent years, many campaigns have conveyed the idea that pain is not inevitable, thereby fostering much progress in terms of pain assessment and management. This symptom is in fact an obvious signal for the need to improve the situation, both in physical terms and in terms of a more holistic approach. The multiplicity of causes of pain and the many means at our disposal for its management should not interfere with a rigorous diagnostic and therapeutic approach. Thus, knowledge of the precise and safe handling of analgesics and other associated drug products, which can absolutely be offered to these vulnerable patients, is of paramount importance and must always be accompanied by a wish to combine this with consideration and multidisciplinary expertise while pursuing the objective of relief and the maintenance of a level of functional ability and quality of life that are acceptable to the patient.

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Digestive Symptoms Control and Nutrition Issues in Older Cancer Patients

56

Matti Aapro

Contents

Abstract

Cancer and its treatment can be related to various digestive symptoms: nausea and vomiting, diarrhea, constipation, and stomatitis/mucositis. In an older patient, these issues can be more difficult to tolerate and lead to various types of decompensation. In this chapter, we discuss their management and nutritional issues more specific to older patients.

Introduction

Cancer and its treatment can be related to various digestive symptoms: nausea and vomiting, diarrhea, constipation, and stomatitis/mucositis. In an older patient, these issues can be more difficult to tolerate and lead to various types of decompensation.

Digestive Symptoms Management

Nausea and Vomiting (Based on Roila et al. 2016)

This may reflect an underlying obstruction (peritoneal carcinomatosis or mass), a gastrointestinal infection (including appendicitis or diverticulitis), or the consequence of medical treatments ((chemo)therapy, opioids) or radiation therapy. It is important to always consider all the

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causes of vomiting and not attribute it automatically to one cause. In an elderly person, there may be less abdominal reaction, and on clinical examination, the (rebound) tenderness may well be missing.

Many treatment options exist to avoid chemotherapy-induced nausea and vomiting. These are applied in a preventative fashion, usually depending on the type of chemotherapy the patient receives (Figs. 1 and 2). Regrettably, evidence-based guidelines are lacking for chemotherapies given over several days or weeks. The recent demonstration of the benefit of olanzapine in some settings raises questions about the tolerability and appropriate dose of this agent, particularly in elderly patients.

Radiation-therapy induced nausea and vomiting has also various risk levels depending on the site of radiation; the risk classification is mainly based on incidence of emesis in clinical studies and expert opinions, and use of S_HT3 receptor antagonists, dopamine receptor antagonists, and dexamethasone will depend on the clinical situation.

Opioid-related nausea and vomiting is poorly studied, and while S_HT3 receptor antagonists are often used, many experts suggest the use of very low doses of drugs like haloperidol.

Diarrhea (Based on Bossi et al. 2018)

Diarrhea, when not related to the underlying cancer, has several causes, and one should always rule out infectious causes in cases of severe diarrhea (at least search for Clostridium difficile).

Some chemotherapies are related to diarrhea, with fluoropyrimidines, irinotecan, and signal transduction inhibitors being the most frequent agents inducing this symptom. In addition, various immunotherapies are related to severe diarrhea (colitis).

A well-tolerated diarrhea can be managed with loperamide, oral hydration, and dietary measures. In case of severe diarrhea or neutropenic enterocolitis, with or without fever, appropriate antibiotics and in-hospital observation are mandatory. Octreotide may be introduced in certain settings.

Constipation (Based on Larkin et al. 2018)

A clinical definition of chronic (sometimes termed functional) constipation requires the presence of any two of the following symptoms for at least 12 weeks in the previous 12 months (not necessarily consecutively):

- Straining during bowel movements
- Lumpy or hard stool
- Sensation of incomplete evacuation
- Sensation of anorectal blockage or obstruction
- Manual evacuation procedures to remove stool
- <3 bowel movements per week

Constipation is often related to opioid usage, but it is also a common side effect of S_HT3 receptor antagonists. A frequently mentioned issue is insufficient hydration of the patients.

Appropriate use of laxatives is often essential in the prevention and relief of constipation. There is limited evidence to support the use of one laxative over another. Osmotic laxatives include PEG (Macrogol), Lactulose: Magnesium, and sulfate salts.

Stimulant laxatives are anthranoid plant compounds (senna, aloe, cascara) usually taken in the evening or at bedtime. Care must be taken to avoid overstimulating effects.

Polyphenolic compounds like bisacodyl and sodium picosulfate work similarly to anthranoid laxatives.

Suppositories and enemas are a preferred first-line therapy when digital rectal examination identifies a full rectum or fecal impaction. Enemas (such as hyperosmotic saline) and suppositories increase water content and stimulate peristalsis to aid in expulsion, and both work more quickly than oral laxatives.

Nestlé Nutrition Institute

Self-MNA®

Mini Nutritional Assessment

For Adults 65 years of Age and Older

Last name: First name:

Date: Age:

Complete the screen by filling in the boxes with the appropriate numbers.
Total the numbers for the final screening score.

Screening

A Has your food intake declined over the past 3 months? [ENTER ONE NUMBER] *Please enter the most appropriate number (0, 1, or 2) in the box to the right.*	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake	☐
B How much weight have you lost in the past 3 months? [ENTER ONE NUMBER] *Please enter the most appropriate number (0, 1, 2 or 3) in the box to the right.*	0 = weight loss greater than 3 kg 1 = do not know the amount of weight lost 2 = weight loss between 1 and 3 kg 3 = no weight loss or weight loss less than 1 kg	☐
C How would you describe your current mobility? [ENTER ONE NUMBER] *Please enter the most appropriate number (0, 1, or 2) in the box to the right.*	0 = unable to get out of a bed, a chair, or a wheelchair without the assistance of another person 1 = able to get out of bed or a chair, but unable to go out of my home 2 = able to leave my home	☐
D Have you been stressed or severely ill in the past 3 months? [ENTER ONE NUMBER] *Please enter the most appropriate number (0 or 2) in the box to the right.*	0 = yes 2 = no	☐
E Are you currently experiencing dementia and/or prolonged severe sadness? [ENTER ONE NUMBER] *Please enter the most appropriate number (0, 1, or 2) in the box to the right.*	0 = yes, severe dementia and/or prolonged severe sadness 1 = yes, mild dementia, but no prolonged severe sadness 2 = neither dementia nor prolonged severe sadness	☐
Please total all of the numbers you entered in the boxes for questions A-E and write the numbers here:		☐

Fig. 1 Self assessment part 1

Now, please CHOOSE ONE of the following two questions – F1 or F2 – to answer.

Question F1

Height (cm)	Body Weight (kg)			
147.5	Less than 41.1	41.1 – 45.3	45.4 – 49.6	49.7 or more
150	Less than 42.8	42.8 – 47.2	47.3 – 51.7	51.8 or more
152.5	Less than 44.2	44.2 – 48.7	48.8 – 53.4	53.5 or more
155	Less than 45.6	45.6 – 50.4	50.5 – 55.2	55.3 or more
157.5	Less than 47.1	47.1 – 52.0	52.1 – 57.0	57.1 or more
160	Less than 48.6	48.6 – 53.7	53.8 – 58.8	58.9 or more
162.5	Less than 50.2	50.2 – 55.4	55.5 – 60.6	60.7 or more
165	Less than 51.7	51.7 – 57.1	57.2 – 62.5	62.6 or more
167.5	Less than 53.3	53.3 – 58.8	58.9 – 64.4	64.5 or more
170	Less than 54.9	54.9 – 60.6	60.7 – 66.4	66.5 or more
172.5	Less than 56.5	56.5 – 62.4	62.5 – 68.3	68.4 or more
175	Less than 58.2	58.2 – 64.2	64.3 – 70.3	70.4 or more
177.5	Less than 59.9	59.9 – 66.1	66.2 – 72.4	72.5 or more
180	Less than 61.6	61.6 – 67.9	68.0 – 74.4	74.5 or more
182.5	Less than 63.3	63.3 – 69.8	69.9 – 76.5	76.6 or more
185	Less than 65.0	65.0 – 71.8	71.9 – 78.6	78.7 or more
187.5	Less than 66.8	66.8 – 73.7	73.8 – 80.8	80.9 or more
190	Less than 68.6	68.6 – 75.7	75.8 – 82.9	83.0 or more
192.5	Less than 70.4	70.4 – 77.7	77.8 – 85.1	85.2 or more
Group	**0**	**1**	**2**	**3**

Please refer to the chart on the left and follow these instructions:

1. Find your height on the left-hand column of the chart.
2. Go across that row and circle the range that your weight falls into.
3. Look to the bottom of the chart to find out what group number (0, 1, 2, or 3) your circled weight range falls into.

Write the Group Number (0, 1, 2, or 3) here: ☐

Write sum of questions A-E (from page 1) ☐

Lastly, calculate the sum of these 2 numbers. This is your SCREENING SCORE: ☐

Question F2

DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

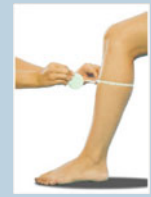
Measure the circumference of your LEFT calf by following the instructions below:

Loop a tape measure all the way around your calf to measure its size.

Record the measurement in cm: _____

If less than 31cm, enter "0" in the box to the right.

If 31cm or greater, enter "3" in the box to the right. ☐



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Write the sum of questions A-E (from page 1) here: ☐

Lastly, calculate the sum of these 2 numbers. This is your SCREENING SCORE: ☐

Screening Score (14 points maximum)

12–14 points:	Normal nutritional status	
8–11 points:	At risk of malnutrition	
0–7 points:	Malnourished	**Copy your SCREENING SCORE:** ☐

If you score between 0-11, please take this form to a healthcare professional for consultation.

Fig. 2 Self assessment part 2

Stomatitis/Mucositis (Based on Peterson et al. 2015)

The terms oral mucositis and stomatitis are often used interchangeably, but they do not reflect identical processes.

"Mucositis" describes inflammation of mucosa resulting from chemotherapeutic agents or ionizing radiation. It typically manifests as erythema or ulcerations and may be exacerbated by local factors, such as secondary infections and trauma. "Stomatitis" refers more generally to any inflammatory condition of oral tissues and should be used for oral complaints related to other causes than the above, such as targeted therapies.

Oral mucositis of grade 3 or 4 is prevalent in patients receiving radiation to the oral cavity with an incidence up to 85% and is the prime limiting factor of chemoradiation for advanced head and neck carcinoma. Patients should have preventative dental treatment before irradiation. The oral pain associated with the lesions frequently leads to the need for enteral nutritional support with or without use of a feeding tube or gastrostomy, as well as use of intensive pain therapy.

Preventive measures help to reduce the severity of stomatitis.

Sources of trauma should be eliminated, and hot (temperature or spicy) foods and drinks should be avoided. Effective oral hygiene is crucial; it is important that patients be appropriately educated about oral complications before treatment Plain water mouthwashes can usually be used; this approach is typically well tolerated by patients and may promote patient adherence to basic mouth care practices.

With targeted agents, saline-containing mouthwashes should be used instead of plain water because of the microbial burden that is considered to intensify formation of oral injury in this population. In case of use of everolimus, there are data suggesting that a corticosteroid-containing mouthwash may be very effective (Rugo et al. 2017).

The ESMO panel recommends the following measures, relevant to some elderly patients:

1. 1.30 min of oral cryotherapy be used to prevent oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy.
2. The panel recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).

Nutrition Issues in Elderly Patients (Based on Arends et al. 2017)

The prevalence of malnutrition is variable among older patients, with the highest incidences (more than 30% severe malnutrition) among those who are hospitalized and in nursing homes (Leij-Halfwerk 2019). Malnutrition can lead to osteopenia/osteoporosis, immunological deficiencies, iron, vitamin B12 or folate-related anemia, sarcopenia, and other issues.

Malnutrition has a negative impact on clinical outcome and mortality in cancer patients, with adverse consequences including impaired quality of life, higher rates of complications and worse postoperative outcomes, longer duration of hospitalization, and poorer anticancer treatment tolerance due to increased toxicity, poorer compliance, and decreased response. Severity of malnutrition is an independent predictor of shorter survival (Aapro et al. 2014).

The self-administered Mini Nutritional Assessment (Fig. 3) is suggested as an assessment tool in older patients, and the importance of nutrition is highlighted by the G-8 screening tool which comprises of several nutritional questions and is predictive of outcome at 3 years (Bellera et al. 2012).

There is a lack of high-quality randomized clinical trial-based evidence of effectiveness of nutritional therapy. While the negative impact of cancer-related malnutrition and cachexia is striking, the results on the effects of nutrition on patients' overall prognosis are weak or inconsistent (Rauh et al. 2018). Nutritional care and therapy in cancer patients encompass dietician-aided dietary counseling (aimed at improving patients' spontaneous food intake), oral supplementation

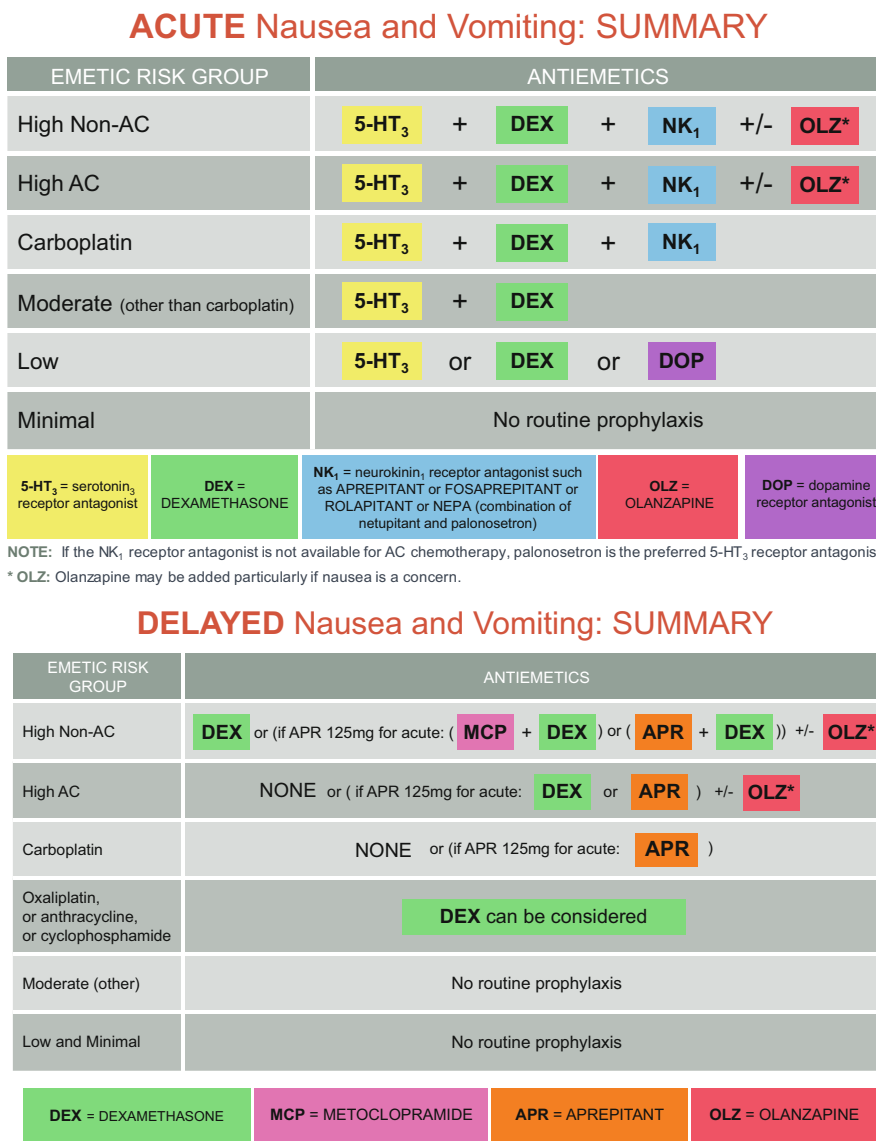

Fig. 3 Summary MASCC/ESMO guidelines

with industry-prepared oral nutritional supplements, enteral nutrition, and parenteral nutrition.

In patients with malnutrition or risk of malnutrition, the use of dietary restrictions is not recommended and considered even dangerous. Theoretical arguments that nutrients would primarily benefit the tumor lack scientific background and thus should not lead to interruption, decrease, or cessation of nutritional intervention in cancer patients. Energy intake should be initially aimed to be from 20 to 25 to 35 kcal/kg body weight, choosing the higher range for ambulatory, younger, underweight, and male patients, while choosing the lower range for bedridden, older, obese, and female patients. During follow-up, energy provisions need to be adapted according to the nutritional status and the metabolic condition. Protein intake should be above 1 and aiming for 1.2–1.5 g/kg body weight per day.

Cross-References

- ▶ Digestive Organ Aging and Cancer
- ▶ Integrating Geriatric Oncology into Clinical Pathways and Guidelines

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Exercise and the Older Cancer Survivor 57

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Abstract

Increased survival coupled with an increase in new diagnoses of cancer among elderly adults makes geriatric cancer patients the largest population of cancer survivors in the United States. Cancer and its treatment can lead to a myriad of adverse events (physical or cognitive impairment, psychological distress, and other symptoms) and negatively impact quality of life in older cancer patients and survivors. Physical activity recommendations vary across the cancer continuum and remain an important area of research in this population. Exercise interventions have been shown to be effective in treating both the physical and psychological declines associated with cancer and its treatment, with a potential to improve cancer-related outcomes. Despite the current evidence of benefits, exercise is still underutilized due to lack of awareness and knowledge among health care providers and older cancer patients. For older cancer patients and survivors to maintain or improve their physical function and possibly reduce the cancer-related toxicities, oncology clinicians must be prepared to discuss the short- and long-term benefits of exercise. Exercise professionals should identify risks and contraindications that may affect exercise safety and tolerance and create individualized exercise prescriptions to meet the unique needs of this population. More exercise intervention studies in various settings, including the community and hospital, are needed to gain widespread acceptance. This chapter summarizes geriatric cancer-related toxicities and psychological distress and how exercise mediates these side effects. Exercise guidelines and how oncologists and exercise professionals can provide the appropriate supportive care needed in this population are also described.

Keywords

Cachexia · Cognitive impairment · Fatigue · Geriatric cancer · Physical activity

Introduction

In 2016, approximately 15.5 million cancer survivors representing 4.8% of the population in the United States need oncologic survivorship care (National Cancer Institute 2016). With increasing rates of early detection and novel more-effective treatment options, oncologic outcomes stemming from cancer treatments have substantially improved (Cancer Facts & Figures 2012). For example, a recent SEER database study demonstrated significant improvements in survival for patients with breast, prostate, colorectal, lung, and liver cancer between the years of 2005 and 2009 as compared to 1990–1994 (Zeng et al. 2015). Consequently, many Americans diagnosed with these diseases are living beyond the once designated life expectancy of 5 years, and a large proportion of these survivors will live into old age. This increased survival, along with an increase in new diagnoses of cancer among elderly adults, makes geriatric cancer patients the largest proportion of the population of cancer survivors in the United States (Berger et al. 2006). In fact, by the year 2024, there will be nearly 19 million cancer survivors in the United States, and 63% or more of these survivors will be age 65 and older (DeSantis et al. 2014; Parry et al. 2011). These elderly cancer survivors constitute a population with a myriad of unique needs that will require changes in the US healthcare system in the coming decades to treat them efficiently and effectively.

Biologically, cancer and aging share a number of common underlying physiologic characteristics. For example, older adults and cancer survivors exhibit chronic inflammation, inadequate DNA repair, and shortened telomere length. Cancer and its treatments stimulate an accelerated aging process characterized by early onset frailty and multiple co-morbidities typically seen in adults over the age of 60 described as an oncologic aging phenotype. Moreover, this oncologic aging phenotype is also seen in young adult survivors of childhood cancers who demonstrate prefrailty and frailty,

with rates similar to survivors 65 years of age and older (Ness et al. 2013). While significant improvements have been made in the toxicity profiles associated with cancer treatments, treatments continue to be associated with a variety of both short- and long-term toxicities that impair physical and psychological function. These toxicities negatively affect a patient's ability to tolerate and adhere to life-saving cancer treatments, maintain independent living and perform activities of daily living (ADL), and maintain a conventional standard of living (Mustian et al. 2012). Older adults are especially susceptible to these acute, chronic, and late toxicities as a result of the cancer itself and/or treatments for cancer. Acute toxicities are those which develop before or during treatment, but have a short duration (days, weeks, or months); chronic toxicities may continue for months or years; and late toxicities develop months or years after treatments are complete. All three types of toxicities at any stage of the cancer trajectory have significant adverse effects on cancer survivors, especially when they are older.

Some of the most commonly reported toxicities stemming from cancer and its treatments are loss of physical function, sarcopenia, cachexia, bone loss, cancer-related fatigue, cognitive impairment, and distress (Mustian et al. 2011, 2012; Peppone et al. 2010). These are also among the toxicities which have the greatest negative effects on elderly cancer survivors.

Physiological Toxicities

Aging is associated with physical and functional decline. This is further exacerbated by the presence of a cancer diagnosis and cancer treatments, leading to poorer function and physical decrements (Sprod et al. 2012a, 2015; Mohile et al. 2011; Mustian et al. 2006a, 2007, 2009a, b; Bellizzi et al. 2008a, b; Mohile et al. 2009a; Bylow et al. 2008). Being able to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs) is essential for the older adult with cancer to function independently (Sprod et al. 2012a, 2015; Mohile et al. 2011; Mustian et al. 2006a, 2007, 2009a, b; Bellizzi et al. 2008a, b; Mohile et al. 2009a; Bylow et al. 2008). In a systematic review examining factors affecting treatment decision-making, the ability to maintain independence is important to older adults when deciding treatments (Chouliara et al. 2004; Ciambrone 2006; Puts et al. 2015; Sinding and Wiernikowski 2009). Older adults constituted a significant proportion (48.5%) of those reporting these concerns (Burg et al. 2015). In the general geriatric population, functional decline is associated with future disability and mortality (Cesari et al. 2008; Reuben et al. 1992). In the older cancer population, impairment in physical function is also associated with increased toxicity related to chemotherapy and mortality (Hurria et al. 2011; Freyer et al. 2005). Specifically, chemotherapy and radiation treatments can lead to reductions in cardiac and pulmonary function (DeVita et al. 2005; Hofman et al. 2007; Morrow 2007). For example, chemotherapeutic agents such as anthracyclines, taxanes, and/or trastuzumab, which are commonly used for treatment of breast cancer, can lead to acute or chronic cardiac dysfunction in patients, which may or may not be reversible. The side effects may warrant dose reduction or drug discontinuation that may ultimately lead to poorer survival (Allen 1992; DeVita et al. 2006). These cardiac toxicities can develop during treatment or years after treatment is complete and may persist for years (Yeh 2006; Sardaro et al. 2012). Other commonly used chemotherapeutic agents such as methotrexate and bleomycin may cause pulmonary toxicities (Willenbacher et al. 1998; Jacka and Chan 1995; Lateef et al. 2005; Cannon 1997). Similarly, radiation can also give rise to cardiac and pulmonary late effects (Carver et al. 2013). In the American Cancer Society Study for Cancer Survivors-II, a national cross-sectional survey of cancer survivors posttreatment, 38.2% of survivors reported unmet physical activity needs.

Muscle dysfunction is a prevalent occurrence in the oncology setting, and cancer and its related treatments lead to impaired muscle function through atrophy and loss of strength (Tisdale 2002, 2003). The sarcopenia and malaise experienced by cancer patients may impair their ability to perform activities of daily living and remain independent during and following treatment (Mohile et al. 2009b, 2011; Reuben et al. 1992). Cancer cachexia can be defined as a significant reduction in body weight resulting primarily from

loss of skeletal muscle and adipose tissue. Cachexia leads to a reduction in cancer treatment tolerance, quality of life, and increased mortality (Fearon Kenneth et al. 2012). In fact, emergent evidence suggest that muscle wasting (Martin et al. 2013) and weight loss (Utech et al. 2012) are effective predictors of mortality in cancer patients. Cancer cachexia is a multifactorial syndrome that cannot be fully reversed by conventional nutritional interventions and eventually leads to progressive functional impairment (Fearon et al. 2013). Although research is not conclusive on the efficacy of exercise on cachexia (Argiles et al. 2012), it has demonstrated the ability of exercise (specifically resistance training) to increase skeletal muscle mass in cancer patients and survivors (Fong et al. 2012; Strasser et al. 2013; Lønbro et al. 2013).

A large percentage of patients who are diagnosed with cancer experience cancer-treatment-induced bone loss (Chen et al. 2005). In some cases, patients receive treatment for cancer more than triple for the average bone lose seen with normal aging (Confavreux et al. 2007). This reduction in bone mineral density is accompanied by a 1.3–5-fold increase in fracture rate when compared to individuals not undergoing treatment (Chen et al. 2009). Female patients treated with chemotherapy, oophorectomy, and aromatase inhibitors often experience a decrease in the production of endogenous estrogens and develop premature menopause that may lead to reduced bone mineral density which increases the risk of fracture (Bruning et al. 1990; Shuster et al. 2008; Howell et al. 2005). Increasing evidence demonstrates that weight-bearing aerobic and resistance exercise may benefit bone metabolism(Lester et al. 2009) and maintain bone mineral density (Irwin et al. 2009a), and the two combined could offer a valuable intervention for moderating bone loss among cancer patients(Milne et al. 2008).

Patient-Reported Toxicities

Cancer patients and survivors commonly experience poor sleep quality and it is several times more prevalent in this population than in the general population (Savard and Morin 2001; Palesh et al. 2010). Sleep disturbance is reported by 30–50% of patients with cancer, and a history of cancer increases the likelihood of patients reporting persistent symptoms (Savard and Morin 2001; Irwin 2013; Savard et al. 2011; Theobald 2004; Mao et al. 2007). The prevalence varies by age, gender, cancer type, cancer treatment, and duration. In older cancer survivors, the prevalence of sleep disturbance was reported to be between 19% and 25%. On the other hand, in a cross-sectional study that included a convenience sample of older adults receiving active cancer treatments, the prevalence was approximately 60% (Cheng and Lee 2011). Depression (Pirl and Roth 1999), pain (Chang et al. 2000), anxiety, fatigue, and distress are also commonly reported by a large majority of cancer patients and survivors, either occurring on its own or as a symptom cluster (Stark et al. 2002). Similarly, the prevalence of these symptoms is thought to be higher in the cancer population compared to the general population. In a study looking at older cancer survivors, the prevalence of pain, fatigue, and mood disturbance were 49%, 63%, and 87%, respectively (Cheng and Lee 2011). Up to 31% of these patients reported co-occurrence of all four symptoms. Another study exploring symptom burden in older adults with cancer receiving radiation also demonstrated high prevalence of these symptoms prior to treatment: pain (35%), fatigue (69%), distress (44%), and mood disturbance (47%). The differing prevalence across studies likely reflects the heterogeneous population as well as timing and methods of assessment (Mustian et al. 2011). The mixed depression/anxiety phenotype occurs in two-thirds of patients with cancer who are depressed and has been associated with more severe depressive symptoms, with less improvement after treatment, worse quality of life, poorer adherence to treatment, slower recovery, greater suicide risk, and higher cost-utilization (Brintzenhofe-Szoc et al. 2009).

Cancer-related fatigue (CRF) is a dose-limiting toxicity and one of the most commonly reported symptoms by patients on active treatments as well as cancer survivors (Cornelison et al. 2012). It is described as “persistent, subjective sense of

tiredness related to cancer and cancer treatment that interferes with usual functioning" (Mock et al. 2000). The prevalence is reported to be as high as 95% and varies by cancer subtypes and treatments; nearly half report their condition as severe (Hofman et al. 2004). It is more common, more severe, and more persistent in those who undergo more than one treatment type (Mustian et al. 2006a, 2007, 2009c; Morrow 2007). In a study of patients with advanced cancer, older patients had a higher prevalence of fatigue compared to younger patients (W-H et al. 2011). CRF can persists for years in otherwise healthy cancer survivors (Bower 2014). Studies involving long-term cancer survivors suggest that approximately one-quarter to one-third experience persistent fatigue for up to 10 years after cancer diagnosis (Bower et al. 2006; Servaes et al. 2007). It has been reported consistently that CRF is more severe, persistent, and incapacitating compared to fatigue caused by lack of sleep or overexertion and is not alleviated by sufficient sleep or rest (Poulson 2001; Jacobsen et al. 1999; Andrykowski et al. 1998; Cella et al. 2002). Patients often self-reported CRF as being the most distressing side effect of treatment, even more so than nausea and vomiting that affects their quality of life and the ability to perform ADL (Mustian et al. 2006a, 2007, 2009c; Morrow 2007). In older adults, fatigue is further compounded by the presence of comorbidities and age-related decline and accompanied by other symptoms, such as sleep disruption, depression, pain, anxiety, and physical inactivity (Giacalone et al. 2013). CRF negatively affects all domains of quality of life and causes psychological distress and may contribute to lower survival (Bower 2014; Mormont et al. 2000). It is multifaceted and may have physical, mental, and emotional manifestations (Mustian et al. 2006a, 2007; 2009c, Morrow 2007).

The impact of cancer therapy on cognition is becoming increasingly recognized. Up to 75% of cancer patients experience some form of cognitive impairment after a cancer diagnosis and/or during cancer treatments (e.g., chemotherapy, radiation, surgery, hormone therapy). For the majority of subjects, cognition improved with time. However, 20–35% of cancer survivors report long-term changes in cognition (Janelsins et al. 2009, 2011, 2014; Brezden et al. 2000; Ahles et al. 2002, 2010; van Dam et al. 1998; Wefel et al. 2004; Jansen et al. 2008). In addition to patient-reported cognitive decline, neuropsychological testing has also demonstrated changes in cognition associated with cancer and cancer therapy, most commonly diminished memory, executive function, attention, and concentration (Kesler et al. 2013a, b; Kohli et al. 2009). Although the majority of studies regarding cognition in cancer have been performed in younger cancer survivors, a few studies have included older subjects. A study by Ahles and colleagues found that older breast cancer patients with low cognitive reserve were most likely to experience decline in processing speed with exposure to chemotherapy, as compared to younger cancer patients or those individuals with normal cognitive reserve at baseline (Ahles et al. 2010). Hurria and colleagues evaluated older adults (aged $\geq$65) receiving adjuvant chemotherapy for breast cancer with a neuropsychological assessment battery at baseline and 6 months following treatment. In this study, 39% of patients experienced a decline in cognitive function from baseline following receipt of chemotherapy (Hurria et al. 2006). Impairment in cognition can negatively impact the mental and physical well-being of patients, causing decreased quality of life. For younger patients, this may impact their ability to effectively work and maintain an income. A study of breast cancer survivors observed that 57% of subjects reported inability to do their jobs as effectively, maintain the same job, or work at all following chemotherapy due to difficulty with memory and attention (Wefel et al. 2004; Bradley et al. 2005). For older adults, decline in cognition may impact their ability to remain independent. Often older adults live alone and need to be able to manage medications and finances in order to remain independent. Cognitive impairment can compromise the ability of an older adult to perform these tasks, thus compromising independence (Magnuson et al. 2016). Cognitive impairment and loss of independence can negatively impact quality of life. In a study of older adults with cancer, 41% reported significant psychological distress, and this was related to reduced physical function and loss of

independence (Hurria et al. 2009). Cognitive impairment can also impact a patients' compliance with cancer treatments as well as contribute to social isolation (Boykoff et al. 2009; Stilley et al. 2010; Reid-Arndt et al. 2009). These negative consequences are exacerbated when cognitive impairment co-occurs with other symptoms such as sleep disturbance, depression or anxiety, pain, fatigue, and physical inactivity.

These studies highlight the prevalence of toxicity burden in the older adult with cancer. Physical or cognitive impairment, psychological distress, and other symptoms may significantly limit therapeutic options for older adults with cancer, translating to poorer health outcomes (Mohile et al. 2009b). Further studies are needed to evaluate interventions to address symptom burden in this population. Exercise interventions are one of the most promising areas to assist the older cancer patient and survivor.

Exercise as Therapy for the Older Cancer Patient

Recent literature demonstrates that maintaining the recommended amount of physical activity (defined as bodily movement produced by contraction of skeletal muscle that increases energy expenditure above basal level) through structured exercise interventions (defined as physical activity that is planned, structured, and repetitively used for the purpose of enhancing one of the seven components of fitness or psychological fitness or health-related outcomes [i.e., cancer or cancer-treatment-related toxicities and side effects]) is an effective method for treating both the physiological and psychological decrements experienced by older cancer patients and survivors (Mustian et al. 2009a, 2012; Spence et al. 2010; Caspersen et al. 1985; Klepin et al. 2013; Buffart et al. 2015; Campo et al. 2014a). Often, a cancer diagnosis and subsequent treatment result in a reduction in physical activity levels that frequently do not return to prediagnosed levels without a structured exercise intervention (Mustian et al. 2006a; Irwin et al. 2003; Courneya and Friedenreich 1997). The decline in physical activity experienced by these patients is often exacerbated by instructions to avoid or limit activities when fatigued or experiencing other side effects related to the cancer diagnosis (Curt et al. 2000; Winningham et al. 1994).

Exercise mediates a variety of physiological and psychological toxicities including loss of muscle mass and function, fatigue, immune function, insomnia, anxiety, cognitive decline, and impaired quality of life, and these improvements may be more evident in older cancer patients and survivors (Brown et al. 2011; Irwin et al. 2009b; Gleeson et al. 2011; Tang et al. 2010; Salmon 2001). Physical activity has consistently been associated with reductions in the risk of cancer, cancer recurrence, and cancer mortality in all populations (Betof et al. 2013; Ballard-Barbash et al. 2012; Bittoni et al. 2014), but specifically in older individuals (Chao et al. 2004). Despite these published reports about the health benefits of exercise in older populations, it is estimated that up to 70% of cancer survivors do not meet the ACSM's public health recommendations (Irwin 2009). Lack of awareness and understanding among health care providers, patients, and survivors in regards to exercise recommendations and the precise methods for prescribing exercise for the effective treatment of specific cancer and treatment-related outcomes may be two primary reasons for the lack of physical activity compliance among older cancer patients and survivors.

As the rate of cancer survivorship in older populations increase a continued effort has to be made to assess ways to improve health-related quality of life and to treat specific toxicities such as cancer related fatigue and impaired physical function (Mustian et al. 2009a; Leak Bryant et al. 2015a, b). Encouraging older cancer patients and survivors to increase their physical activity may assist them in regaining and improving physical function while reducing and preventing long-term effects of cancer and its treatments.

Exercise and Biological Mechanisms Involved in the Pathophysiology of Toxicities

Exercise is a feasible and effective alternative for the treatment of several cancer-related side effects that cluster together because it can be

designed to fit the specific needs and abilities of older cancer patients and survivors (Chao et al. 2004; Campo et al. 2014b). Exercise is a treatment capable of simultaneously affecting multiple biological pathways that are involved in the etiology of cancer-related side effects. Chronic immune response activation has been suggested to be the primary modulator of biological pathways that are involved in the pathophysiology of common toxicities including hypothalamic-pituitary-adrenal axis, mitochondrial (Saligan et al. 2015), and inflammatory (Saligan et al. 2015; Illman et al. 2005) dysfunction, metabolic adaptations, and genetic and epigenetic influences (Saligan et al. 2015; Oltmanns et al. 2003). For example, inflammatory immune responses that are involved in cell differentiation, proliferation, and apoptosis are associated with several symptoms (Oltmanns et al. 2003). Adaptations that occur in response to a chronic immune response compromise protein synthesis and muscle function and result in the clustering of cognitive impairment, fatigue, pain, and depression (Sprod et al. 2012a; Saligan et al. 2015; Mueller et al. 2015; Oliveira Miranda et al. 2014). The polymorphism of certain genetic strands has also been linked to fatigue. Posttranslational modifications in genotypes are directly related to increases in fatigue in response to hormone and radiotherapy among cancer patients(Saligan et al. 2015), and the burden of this fatigue is increased in older individuals when compared to their younger counterparts(Avlund 2010). Recent research strongly suggests that exercise is an effective treatment for many of the toxicities that result from cancer and its treatments. Exercise has the ability to positively affect many of the biological pathways that cause cancer-related side effects through its impact on the inflammatory response system. It has been shown to reduce the inflammatory immune response, regulate metabolic and neuroendocrine pathways, and improve genetic and epigenetic function in individuals without cancer. Exercise is a viable treatment option because it can both directly and indirectly influence these pathways individually and as they occur in a cluster (Koelwyn et al. 2015).

Exercise Guidelines for Older Cancer Patients and Survivors

In 2014, the American College of Sports Medicine (ACSM) published exercise guidelines as well as guidelines for exercise testing and prescription for older (Ferguson 2014) individuals, cancer patients, and survivors of cancer (Ferguson 2014; Schmitz et al. 2010). Collectively, these guidelines provide evidence-based recommendations for designing safe and effective (1) fitness and functional testing protocols, (2) exercise prescriptions, and (3) exercise implementation, progression, and maintenance plans for older cancer patients and survivors. For these individuals, the ACSM guidelines recommend activities that gradually progress over time to achieving the following: (1) 150 min (moderate intensity) or 75 min (vigorous intensity) aerobic exercise per week, (2) 2–3 days/week moderate-intensity muscle-strengthening training for all major muscle groups, and (3) flexibility stretching exercise of all major muscle groups daily (Sprod et al. 2012a; Schmitz et al. 2010; Haskell et al. 2007; Jones et al. 2010). The ACSM also recommends that older cancer patients and survivors obtain information regarding their baseline levels of physical and psychological function, use caution when beginning a new exercise program, progress slowly, and enlist help from qualified professionals. The goal is to avoid inactivity and to encourage older cancer patients and survivors to return to their normal activities as quickly as possible (Schmitz et al. 2010). Physical activity guidelines are to be used as a benchmark with the understanding that any level of physical activity may result in improved health outcomes. Improvement in health outcomes has been well documented in young and older disease-free individuals and young and older individuals with several types of cancer. These include decreasing fatigue, improvements in physical function, activities of daily living, psychosocial well-being, and, ultimately, improving health-related quality of life (Mustian et al. 2004, 2006a, b, 2007, 2009a, b, c, 2011; Peppone et al. 2010; Sprod et al. 2012a, 2015; Adamsen et al. 2003; Ahmed et al. 2006; Courneya et al. 2007; Crevenna et al. 2003;

Headley et al. 2004; Holmes et al. 2005; Oldervoll et al. 2006, 2011; Porock et al. 2000; Reid-Arndt et al. 2012; Schmitz et al. 2005; Segal et al. 2003; Sprod et al. 2012b; Winters-Stone et al. 2011; Kamen et al. 2016).

Exercise Prescription for Older Cancer Patients and Survivors

Exercise testing, exercise prescription, and exercise monitoring should be done by qualified exercise professionals, especially for older cancer patients and survivors experiencing a high symptom burden and those at moderate cardiovascular risk beginning or continuing vigorous exercise and those at high cardiovascular risk commencing or continuing any level of exercise (American College of Sports Medicine 2016). Exercise prescriptions for older cancer patients and survivors should be individualized and tailored based on their health status, disease trajectory, previous and/or current treatment, symptom burden, current fitness level, past and present exercise participation, and individual preferences in order to be safe and effective (Schmitz et al. 2010; Physical Activity Guidelines Advisory Committee report 2009). The standard goal is to achieve the ACSM exercise guideline for older cancer patients as weekly 150 min of moderate-intensity or 75 min vigorous-intensity aerobic exercise and 2–3 days strength training and daily flexibility stretching exercise. Some recent resistance exercise intervention studies ranging from 12 weeks to 12 months showed that the strength-training exercise program with the intensity of 60–85% 1RM, the frequency of 1–3 times per week, and the duration of 15–30 min per session significantly improved physical function and quality of life, increased muscular strength and fitness, and reduced cancer-related fatigue in older cancer patients (Segal et al. 2003, 2009; Morey et al. 2009; Winters-Stone et al. 2012, 2015; LaStayo et al. 2011). Moderate-to-vigorously intense anaerobic resistance exercise prescriptions schedule three times per week and progressively increasing up to as few as two sets, and no more than four sets of 8–15 repetitions are effective at reducing symptoms (Ahmed et al. 2006; Courneya et al. 2007; Schmitz et al. 2005; Segal et al. 2003; Winters-Stone et al. 2011). Other studies had older cancer patients did aerobic exercise at 50–75% VO_{2peak}, three times a week and 15–45 min each session (Segal et al. 2009). The participated older cancer patients also significantly improved their muscular strength, cardiovascular fitness, social functioning, and reduced fatigue and psychological distress. Combination exercise prescriptions including both aerobic and anaerobic exercise are safe and very effective for most oncology patients and survivors (Cormie et al. 2015). Older cancer patients and survivors may get overwhelmed with the amount of exercise recommended in a day. One study suggested to increase the amount of activity during the day with short bouts of aerobic exercise (3–10 min each) to build up to 30 min a day. Rest breaks are encouraged to reduce toxicities and side effects (Sprod et al. 2012a). Patients with advanced disease or metastasis can safely perform and tolerate low intensity exercise such as walking (Adamsen et al. 2003; Crevenna et al. 2003; Headley et al. 2004; Oldervoll et al. 2006, 2011; Porock et al. 2000). Low to moderately intense mindfulness-based exercise prescriptions including Yoga and Tai Chi Chuan scheduled 1–3 times a week for 60–90 min are also highly effective in reducing symptom burden among older cancer patients and survivors (Mustian et al. 2004, 2006b, 2011; Peppone et al. 2010; Reid-Arndt et al. 2012; Sprod et al. 2012b). Additionally, those with advance disease can safely perform, tolerate, and benefit from low intensity exercise (Adamsen et al. 2003; Crevenna et al. 2003; Headley et al. 2004; Oldervoll et al. 2006, 2011; Porock et al. 2000).

Exercise Professionals

Exercise professionals working in oncology are an excellent resource for older cancer patients to obtain the appropriate supportive care needed throughout the entire cancer diagnosis and treatment process. Research has shown that participation and compliance with

exercise prescriptions during and following cancer treatment is increased when patients are advised to participate and are referred to a qualified exercise professional by their treating practitioner (Cella et al. 2002; Jones et al. 2004; Jones and Courneya 2002; Yeates et al. 2005). Furthermore, patients of all ages prefer to have their practitioners initiate the discussion about exercise and continue to provide information on exercise and appropriate exercise professionals throughout the treatment and recovery period (Yeates et al. 2005; Sprod et al. 2010). Regrettably, a high percentage of older cancer patients and survivors report not discussing exercise with their treating or primary care physician throughout their cancer diagnosis, treatment, or recovery. The exercise professional that is responsible for prescribing and facilitating the exercise protocol to an older cancer patient or survivor should be a certified exercise specialist. The minimum requirements to obtain this certification include a bachelor's degree or higher in an accredited exercise science or kinesiology program. In addition the exercise professional may also be required to be certified in cancer exercise training and in training older populations. These certifications establish that the exercise professional has obtained the minimum education required to safely and effectively prescribe and assist with exercise for older cancer patients and survivors (Schmitz et al. 2010). These certifications, which may be acquired by individuals from a range of career fields (e.g., occupational and physical therapists, nurses, exercise physiology), require specialized training in the area of cancer-specific issues as they relate to older patients or survivor as they begin or progress through an exercise program during treatment and into survivorship. The procurement of these certifications allow oncology professionals the opportunity to refer older cancer patients and survivors to an established professional who has the aptitude to the deliver the high standard of care required when prescribing and facilitating exercise for older cancer patients or survivors (Schmitz et al. 2010; American College of Sports Medicine et al. 2010; Doyle et al. 2006). Routine discussions between practitioners and older cancer patients regarding exercise along with appropriate referrals to a qualified exercise professional could significantly improve exercise participation and compliance, which may lead to improved prognosis, recovery, and numerous aspects of quality of life for older individuals (Sprod et al. 2012a, 2015; Mohile et al. 2011; Mustian et al. 2009a, b; Bellizzi et al. 2008a, b; Mohile et al. 2009a; Bylow et al. 2008; Mustian et al. 2006a, 2007).

Managing Risk and Contraindications for Exercise Professionals Working with Older Cancer Patients

It is always essential to identify an individual's level of risk and address potential contraindications (e.g., orthopedic, cardiopulmonary, oncologic) that might affect exercise safety and tolerance when beginning exercise therapy with older cancer patients or survivors (American College of Sports Medicine 2016). The Five-A Model is a diagram to aid oncology providers in assessing risk and referring their older cancer patients for exercise testing, advisement, and prescription services(Schmitz et al. 2010) (see Fig. 1). Initially it is important for oncologists to determine whether their older patients are currently engaging in an exercise program and to discuss how they can safely begin, progress through, or maintain an exercise program during and after treatment. Paramount to this discussion is the identification and resolution of potential contraindications (American College of Sports Medicine 2016). It is important for both the practitioner and patient to understand that contraindications do not mean that the older patient or survivor should be precluded from exercise entirely, but instead require specific modifications to the exercise design that include only modes of exercise that the patient may engage in safely and still achieve the desired health benefits (American College of Sports Medicine 2016). Based on their age and cancer diagnosis, most older patients will be classified as moderate to high risk as defined by the ACSM guidelines; therefore, they will be

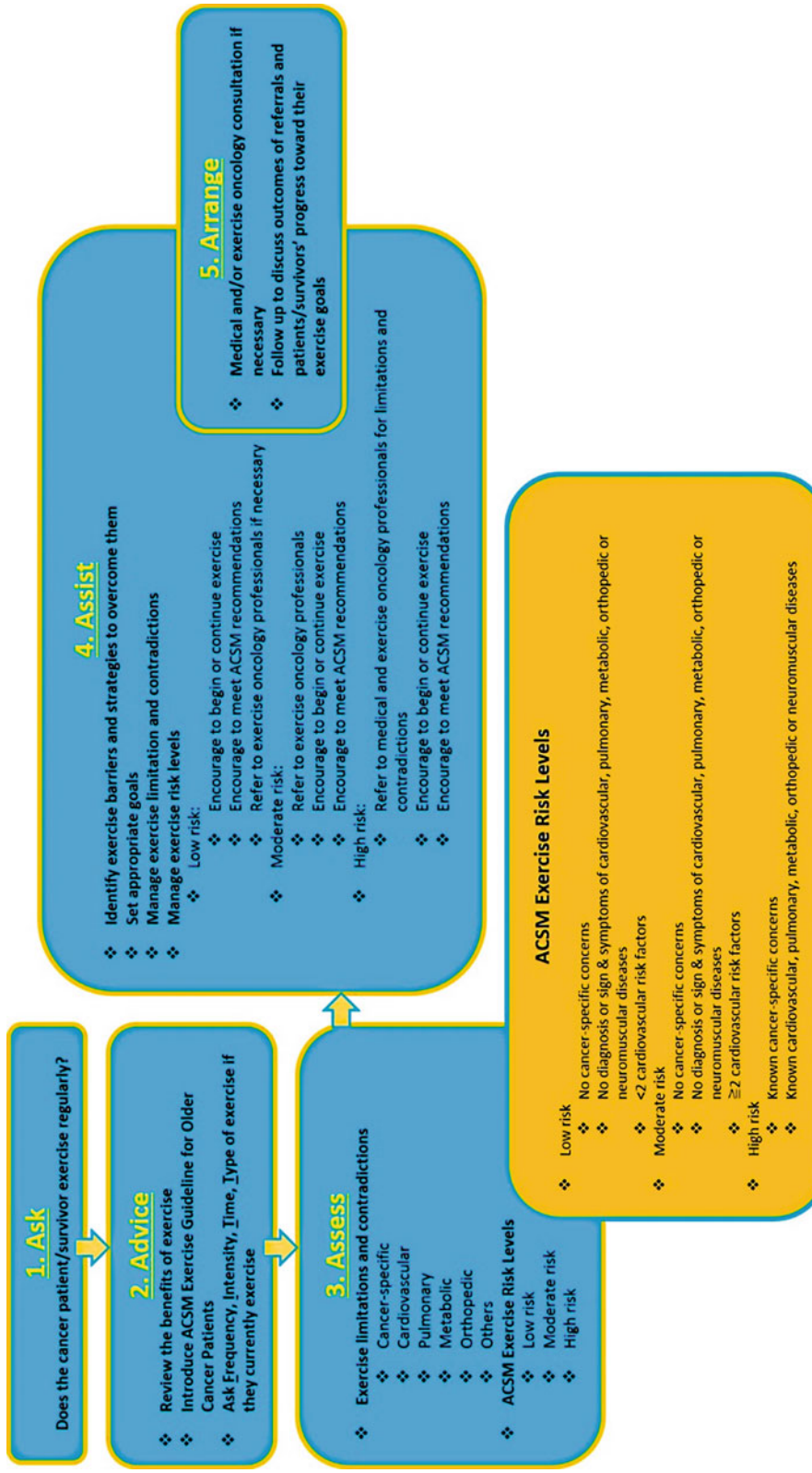

Fig. 1 The 5-A model for applied exercise oncology referral

Table 1 Exercise intervention randomized control trials among older cancer patients and survivors

Authors (year), sample size (N)	Age: Mean (Range)	Cancer Type	Intervention	Intervention Timing	Results
Segal et al. (2003), N = 155	68 (60–76)	Prostate	*Type*: Immediate vs. delayed (12 weeks) supervised resistance exercise interventions *Length of Intervention*: 12 weeks *Mode*: Supervised 9 strength-training exercises targeting to major muscle groups *Intensity*: 60–70% 1RM *Frequency*: 3×/week *Duration*: 2 sets of 8–12 reps of 9 exercises	On ADT	↑↑ Muscular fitness ↑↑ QOL ↓↓ Fatigue
Demark-Wahnefried et al. (2006), N = 182	71.5 (65–86)	Breast Prostate	*Type*: Home based diet and exercise vs. General health education *Length of Intervention*: 6 months *Mode*: Telephone counseling *Intensity*: Moderate (recommended) *Frequency*: Biweekly *Duration*: 20–30 min/session	Within 18 months of diagnosis	↑ Physical function ↑ Physical activity ↑↑ Diet quality index -No group difference was observed 6 months after the intervention
Morey et al. (2009), N = 641	73 (65–91)	Breast Colorectal Prostate	*Type*: Immediate vs. delayed (≥12 months) home-based diet and exercise interventions *Length of Intervention*: 12 months *Mode*: Telephone counseling and automated prompts *Intensity*: Strength and endurance (recommended) *Frequency*: Weeks 1–3 weekly, month 2 biweekly, month 3–12 monthly *Duration*: 15 min strength; 30 min endurance training/ session	≥5 years since diagnosis	↑↑ Physical function ↑↑ Physical activity ↑↑ QOL ↑↑ Dietary behavior ↓↓ Body weight
Segal et al. (2009), N = 121	66.3 (59–73)	Prostate	*Type*: 3 arms (resistance exercise, aerobic exercise, usual care) *Length of Intervention*: 24 weeks *Mode*: Supervised 10 strength-training exercises targeting to major muscle groups *Intensity*: Resistance (60–70% 1RM); aerobic (weeks 1–4 50–60% VO_{2peak}, weeks 5–24 70–75% VO_{2peak}) *Frequency*: 3×/week *Duration*: Started with 15 min/	RT with or without ADT	Resistance training vs. usual care ↑↑ Upper and lower muscle strength ↑↑ Aerobic fitness ↑↑ QOL ↓↓ Fatigue at both weeks 12 & 24 ↓ Body fat Aerobic training

(*continued*)

Table 1 (continued)

Authors (year), sample size (N)	Age: Mean (Range)	Cancer Type	Intervention	Intervention Timing	Results
			session then increased by 5 min every 3 weeks until it reached 45 min		vs. usual care ↑↑ Upper muscle strength ↑ Aerobic fitness ↓↓ Fatigue at week 12 but not week 24
LaStayo et al. (2011), N = 40	74 (68–80)	Breast Colorectal Lymphoma Prostate	*Type*: Resistance exercise vs. usual care *Length of Intervention*: 12 weeks *Mode*: Eccentric-induced lower extremity exercise *Intensity*: High-intensity (RPE 11-13) *Frequency*: Weekly *Duration*: 3–5 min first 2 weeks; 6–15 min weeks 3 & 4; 16–20 min weeks 5–12	8.4 ± 8 years since diagnosis	↑↑ Lower body muscle size, strength, and power ↑↑ Mobility
Winters-Stone et al. (2012), N = 106	62.3 (53–83)	Breast -early stage	*Type*: Progressive resistance + impact exercise vs. stretching *Length of Intervention*: 12 months *Mode*: Supervised and home-based *Intensity*: Progressive resistance (60–80% of 1RM) *Frequency*: 3×/week (2 supervised and 1 home-based) *Duration*: 1 h/session	≥1 year since chemotherapy or RT	↑↑ Muscular strength
Campo et al. (2014b), N = 40	72 (58–93)	Prostate	*Type*: Qigong vs. stretching *Length of Intervention*: 12 weeks *Mode*: Qigong *Intensity*: NR *Frequency*: 2×/week *Duration*: 1 h/session	5.5 years (median) from diagnosis	↓↓ Fatigue ↓↓ Distress
Cheville et al. (2013), N = 66	64.7 (51–76)	Lung Colorectal	*Type*: Incremental walking and home-based strength training vs. usual care *Length of Intervention*: 8 weeks *Mode*: 10 resistance band exercises targeting to major muscle groups and brisk walk *Intensity*: Moderate exertion after 10–15 repetitions for each resistance band exercise; brisk walk (3.5 MET) *Frequency*: Resistance band exercises: 2×/week; brisk walk: ≥4 days/week *Duration*: Individual-dependent	Stage IV	↑↑ Mobility ↑↑ Sleep quality ↓↓ Fatigue

(*continued*)

Table 1 (continued)

Authors (year), sample size (N)	Age: Mean (Range)	Cancer Type	Intervention	Intervention Timing	Results
Buffart et al. (2015), N = 100	71.7 (65–78)	Prostate	*Type*: 6 month supervised and 6 month home-based aerobic and resistance exercise vs. printed physical activity material education *Length of Intervention*: 12 months *Mode*: Aerobic: Cycling, walking or jogging; resistance: 8 exercises targeting to major muscle groups *Intensity*: Aerobic: 70–85% HRmax, RPE 11-13; resistance: 6 RM for 2–4 sets *Frequency*: 2×/week *Duration*: 150 min/week	5.5 years from diagnosis	↑↑ Global QOL ↑↑ Physical function ↑↑ Social function
Cormie et al. (2015), N = 63	69.6 (NR)	Prostate	*Type*: Aerobic and resistance exercise vs. normal care *Length of Intervention*: 3 months *Mode*: Aerobic: Treadmill walking/jogging, stationary ergometer cycling/rowing/ rowing, cross trainer machine; resistance: 8 exercises targeting to major muscle groups *Intensity*: Aerobic:70–85% HRmax; resistance: 60–85% 1RM *Frequency*: 2×/week *Duration*: 1 h/session	Within 10 days of first hormonal therapy	Preservation of lean mass ↑↑ Cardiovascular fitness ↑↑ Muscular strength ↑↑ Lower body function ↓↓ Fatigue ↑↑ Social function ↓↓ Psychological distress
Livingston et al. (2015), N = 147	65.6 (39–84)	Prostate	*Type*: Exercise vs. usual care *Length of Intervention*: 12 weeks *Mode*: Combined supervised gym exercise and home-based exercise *Intensity*: Moderate-vigorous *Frequency*: 3×/week (2 supervised and 1 home-based) *Duration*: 1 h/session	3–12 months post cancer treatment or on hormonal treatment	↑↑ Cognitive function ↓↓ Depression ↑↑ Physical activity
Martin et al. (2015), N = 160	61.3 (34–80)	Breast Prostate	*Type*: Aerobic and resistance exercise vs. control *Length of Intervention*: 8 weeks *Mode*: NR *Intensity*: Low-intensity (aerobic: 60–65% VO_{2max}, resistance: 50–65% 1RM) and high-intensity (aerobic: 75–80% VO_{2max}, resistance: 65–80% 1RM) *Frequency*: 3×/week *Duration*: 1 h/session (25 min aerobic, 25 min resistance, 10 min stretching)	≤5 years post cancer treatments	↑↑ VO_{2max} (high-intensity exercise sustained

(*continued*)

Table 1 (continued)

Authors (year), sample size (N)	Age: Mean (Range)	Cancer Type	Intervention	Intervention Timing	Results
O'Neill et al. (2015), N = 94	69.8 (62–76)	Prostate	*Type*: Diet and physical activity intervention vs. standard care *Length of Intervention*: 6 months *Mode*: Brisk walking (telephone consulting) *Intensity*: NR *Frequency*: ≥5 days/week *Duration*: ≥30 min/session	On ADT	↓↓ Body weight ↓↓ BMI ↓↓ % Body fat ↑↑ Functional capacity ↑↑ Dietary intake
Sprod et al. (2015), N = 97	67 (NR)	Breast Others	*Type*: Yoga intervention + standard care vs. standard care only *Length of Intervention*: 4 weeks *Mode*: Yoga *Intensity*: NR *Frequency*: 2×/week *Duration*: 75 min/session	2 months to 2 years post cancer treatments	↓ Fatigue ↓ Global side effect burden
Winger et al. (2014), N = 641	73.6 (68.5–78.7)	Breast Prostate Colorectal	*Type*: Immediate diet and exercise intervention (combined tailored mailed print materials and telephone prompts and counseling) vs. delayed-intervention control *Length of Intervention*: 1 year *Mode*: Resistance bands for lower extremity exercises, walking *Intensity*: NR *Frequency*: Strength exercise: Every other day; endurance exercise: Daily *Duration*: Strength exercise: ≥15 min; endurance exercise: ≥30 min	≥5 years since diagnosis	↑↑ Physical function ↑↑ **L**ower extremity function ↑↑ Mental health ↓↓ BMI
Winters-Stone et al. (2015), N = 51	70.2 (NR)	Prostate	*Type*: Progressive resistance + impact exercise vs. stretching *Length of Intervention*: 12 months *Mode*: Free weights, multijoint movements common to daily activities and resistance band *Intensity*: NR *Frequency*: 3×/week (2 supervised, 1 home-based) *Duration*: 1 h/session	On ADT	↑↑ Muscular strength ↑↑ Physical function ↓↓ Disability
Yagli and Ulger (2015), N = 20	68.7 (65–70)	Breast	*Type*: Yoga vs. exercise *Length of Intervention*: 8 weeks *Mode*: Yoga (warm up, yoga postures, relaxation); exercise (warm up and breathing exercises, physical exercises, cool down)	≥6 months since chemotherapy	Both groups: ↑↑ QOL ↓↓ Fatigue, depression and pain ↑↑ Sleep quality Yoga vs. exercise

(*continued*)

Table 1 (continued)

Authors (year), sample size (N)	Age: Mean (Range)	Cancer Type	Intervention	Intervention Timing	Results
			Intensity: NR *Frequency*: Weekly *Duration*: 1 h/session		(post-intervention): Yoga group ↓↓ Fatigue ↑↑ Sleep quality better than Exercise group
Zopf et al. (2015), N = 85	64.5 (58–70)	Prostate	*Type*: Supervised multimodal exercise vs. control *Length of Intervention*: 15 months *Mode*: Aerobic, resistance, and pelvic floor exercises *Intensity*: Moderate (3.84–4.84 MET-hour) *Frequency*: 2×/week (1 supervised and 1 home-based) *Duration*: 1 h/session	6–12 weeks after prostatectomy	↑↑ Physical fitness ↑↑ Emotional and social function ↓↓ Dyspnea, urinary, and bowel symptoms
Gilbert et al. (2016), N = 50	70.2 (58–84)	Prostate	*Type*: Supervised exercise training and dietary advice vs. usual care *Length of Intervention*: 12 weeks *Mode*: Aerobic (stationary cycles, rowing ergometers, treadmills), resistance, and balance exercises *Intensity*: Aerobic: 55–75% HR_{max}, RPE 11-13; resistance: 60% 1RM, 2–4 sets of 8–12 repetitions *Frequency*: 3×/week (2:1 supervised to home-based in weeks 1–6, 1:2 in weeks 7–12) *Duration*: 1 h/session	On ADT	↑↑ Endothelial function ↑↑ Skeletal muscle mass ↑↑ Treadmill walking time

ADT Androgen deprivation therapy, *BMI* Body mass index, *QOL* quality of life, *1RM* One repetition maximum, *RT* radiotherapy, *NR* not reported
↑- Trend towards improvement
↓- Trend towards reduction
↑↑- significant improvement
↓↓- significant decrease

required to obtain medical clearance and assessment beyond their medical team before participating in an exercise program. However, most older cancer patients will be able to safely initiate, progress through, or continue an exercise program (American College of Sports Medicine 2016).

In older cancer patients further medical assessments by surgeons, cardiologists, orthopedists, and

neurologists among others may be necessary to obtain required medical information regarding cancer-specific, cardiovascular, pulmonary, metabolic, orthopedic, neurologic, and other co-morbidities needed by exercise physiologists to safely and appropriately prescribe exercise (American College of Sports Medicine 2016). It is important that these additional medical evaluations be conducted prior to the older cancer patients engagement in baseline exercise testing which precedes the exercise design and participation (American College of Sports Medicine 2016). For the safety of the patient, it is recommended that all exercise testing, prescription, and monitoring be completed by a certified cancer exercise training professional and when needed additional medical professionals may be required during exercise for an older cancer patient and survivor (American College of Sports Medicine 2016).

Conclusion

Regular exercise during and after treatment is shown to have physical and psychological benefits(Sprod et al. 2012a; Mustian et al. 2006a, 2009a), including reduction in symptom severity. For older adults with cancer to maintain or improve their function, oncology clinicians must be equipped to discuss the short- and long-term benefits of exercise. Exercise professionals should be prepared to work with older cancer survivors and to meet the unique needs of this population. Additional studies are needed in the older adult with cancer population in a variety of settings including the community and hospital. Resources that oncology providers can share with their patients include: (1) the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention(www.cancer.org); (2) American Geriatrics Society (AGS) Healthy Aging Go4Life program (www.healthinaging.org); (3) Physical Activity Tips for Survivors at the American Society of Clinical Oncology site (www.cancer.net); and (4) National Cancer Institute Physical Activity and Cancer (www.cancer.gov) (Table 1).

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Geriatric Oncology in Tropical and Developing Countries

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Abstract

Developing countries include countries with the lowest per capita gross national income in the world. The majority of these countries are located in tropical areas where cancers and hematological malignancies are generally characterized by frequent viral and microorganism origin, specific biology, advanced stage disease, and poor outcome. Access to treatment is generally resource-limited and must be adapted to resources. In these countries the population is still young, but in the next 20 years, the burden of aging will increase with less perinatal mortality and longer life expectancy, and the number of elderly cancer patients will thus become similar to the one in high-income countries. Principles of contemporary geriatric oncology are not always enforceable to patients from these areas: this is often due to cultural differences, different comorbidities, different socioeconomic environment, and a lack of geriatricians and health professional education. This chapter reflects the present knowledge in this field and discusses specificities and potential propositions for the future.

Keywords

Tropical countries · Low-income countries · Transcultural mediation · Geriatric assessment · Global oncology

Introduction

Geriatric oncology is a relatively new area in oncology as it was conceptualized in the early 1990s (Monfardini and Yancik 1993). Since 2000, the International Society of Geriatric Oncology (SIOG) has developed education, clinical practice, and research (SIOG 2017). SIOG has also favored the participation of oncologists from all over the world. Nevertheless, the significance of the aging process in tropical and low-middle-low-income countries (TLMLICs) will increase the importance of geriatric oncology in this setting.

TLMLICs are defined basically by gross national income (GNI) per capita as classified by the World Bank (Worldbank 2016a). Countries with less $1,006 GNI per capita are classified as low-income countries and those between $1,006 and $3,975 as lower middle-income countries. Additionally the majority of these countries are located in the tropical areas where hematological malignancies and cancers present specific characteristics (Droz et al. 2015).

The objective of this chapter is to attempt to review the most important knowledge compilation on this subject.

Reference searches were performed to try and select the most informative articles. First, issues of Journal of Global Oncology and Journal of

Geriatric Oncology were reviewed: 7 and 6 informative articles were found, respectively. Then three researches were performed with the following MeSH terms: ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("patients"[MeSH Terms] OR "patients"[All Fields]) AND ("poverty"[MeSH Terms] OR "poverty"[All Fields] OR ("low"[All Fields] AND "income"[All fields]): 132 articles; ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("patients"[MeSH Terms] OR "patients"[All Fields]) AND tropical [All Fields] AND countries[All Fields]): 82 articles and ("geriatric assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "geriatric assessment"[All Fields]) AND ("poverty"[MeSH Terms] OR "poverty"[All Fields] OR ("low"[All Fields] AND "income"[All Fields]) OR "low income"[All Fields]) AND countries [All Fields]): 38 articles.

Geography and Demography

Geography of the Most Important Countries

The tropical area is located between the tropic of Cancer in the north (latitude 23° 26′ 14″° N) and the tropic of Capricorn in the south (latitude 23° 26′ 14″° S), equidistant from the equator. This includes America (a part of Mexico and all countries in Central America, all Caribbean islands, Colombia, Venezuela, Guyana, Surinam, French Guiana, Brazil, Bolivia, Peru, Ecuador), a large part of Africa (except Morocco, Algeria, Tunisia, Libya, Egypt, and South Africa), Asia (the south of India, Bangladesh, Myanmar, Thailand, Laos, Cambodia, Vietnam, extreme south of China, Malaysia and Brunei, Singapore, Indonesia, Philippines, Papua New Guinea, north of Australia), and many islands in the Pacific Ocean (Amat-Roze 2015; Wikipedia 2017).

The tropical area is the hottest and most humid part of the world. Climate is equatorial in a large part of Brazil, the shield of Guyana, coast of the Gulf of Guinea and Central Africa, Indonesia, Malaysia, Philippines, and Papua New Guinea: there is a dry season and a wet season (longer when near to the equator). The Tropical monsoon is observed in parts of the equatorial area but also in India, Bangladesh, and Southeastern Asia, generally the north of the equatorial area. It is characterized by a less pronounced dry season and large amounts of rain during the wet season, usually in the form of frequent thunderstorms. The dry tropical climate can be seen mainly in the north of equatorial area in Africa (Sahel) (Wikipedia 2017).

A great part of this space is occupied by hot deserts. The region is home to nearly 80% of the world's population, a figure likely to reach 90% by the end of the century.

Nominal GIN per capita in tropical countries is less than $12,276 in South America except Venezuela and French Guiana; it is less than $3,976 (and generally less than $1,006) in Africa apart from Botswana, Gabon, Equatorial Guinea, and South Africa; and it is less than $3,976 in Asia, except Thailand, Malaysia, and Indonesia, just like Singapore (Worldbank 2016b).

It is noteworthy that there is not a strict congruence between tropical countries and low- and lower-middle-income countries. However, the two aspects generally fit together. Therefore we will consider here low and low-middle income countries and particularly tropical countries.

Population in Tropical, Low- and Lower-Middle-Income Countries (TLLMICs)

The International Monetary Fund (IMF) (International Monetary Fund 2016) produced projections of the world population through 2050: population in the more developed countries will plateau around one billion (constant since 1950) inhabitants, while it will increase to around eight billion inhabitants in less developing countries (around five billion in 2008). An

important population increase is principally expected in Central Africa, India, and Southeastern Asia.

Health Expenditure

Health expenditure varies widely from one country to another (Worldbank 2015). Nevertheless there is a correlation between income and health expenditure: the lower the country income is, the lower the health expenditure is. Therefore countries with low health expenditure are principally located in the tropical area.

Aging in the World and Aging in TLLMICs

In 2013 the population of people aged 65 and above represents 4% of the whole population in low-income countries and 16% in high-income countries (Worldbank 2016b). Information on aging of the world population has been published by the IMF in 2015 (International Monetary Fund 2016). Projections of the world population through 2050 indicate that the population of persons over 60 increases. Nevertheless, the elderly people population will rise from 0.2 billion in 2008 to 0.4 billion in 2050 in the more developed countries, whereas it will rise, during the same period, from 0.4 billion to 1.6 billion in the less developed countries. Moreover in less developed countries, the size of the elderly population will surpass that of 12–24 age groups near 2045. However, the nonagenarian population is still marginal in less developed countries (United Nations Department of Economic and Social Affairs/Population Division 2015).

Cancer in TLLMICs

Incidence and Characteristics in the Whole Patient Population

Cancer incidence repartition is different in high-income countries when compared to low-income countries (International Agency for Research on Cancer 2012). In low-income countries, the most frequent cancers in women are the following: breast, cervix, lung, colon-rectum, esophageal, and stomach cancers; in men: lung, stomach, liver, prostate, colon-rectum, esophageal, and bladder cancers. In both sexes the mortality is higher in low-income countries than in high-income countries (Bray et al. 2015). Moreover cancers in the TLLMICs have some specific characteristics: more advanced stages and consequently increased mortality (Roue et al. 2016); particular biological features like frequency of triple negative breast cancers (Huo et al. 2009) and of BRCA1–2 mutations (Fackenthal et al. 2012); frequent microorganisms implicated in the carcinogenesis (de Martel et al. 2012; Nacher and Roue 2015).

Incidence and Characteristics in the Elderly Patient Population

Information of cancer burden in low-income countries is scarce. Nevertheless projection to 2035 of estimated number of new cancers in patients older than 65 in less developed countries (International Agency for Research on Cancer 2012) shows an increase by 2.35 in both sexes. Consequently the estimated total number of new cancer patients should increase from 3.2 million to 7.5 million. During the same period, the estimated number of cancer patients younger than 65 should increase by 1.5 (4.8 million to 7.2 million). Therefore the total number of cancer patients in the two age groups will be equal at the horizon 2035. This demonstrates that geriatric oncology is a real challenge in less developed countries. The spectrum of most frequent cancers in elderly patients is not very different from the one of younger patients: breast, cervix, lung, colon-rectum, and stomach cancers in women and lung, liver, stomach, prostate, and colon-rectum cancers in men. However breast cancer (Vanderpuye et al. 2016) and cervical cancer (Roue et al. 2012) in women are of importance. Moreover cancers in these TLLMICs have some specific characteristics: more advanced stage and consequently increased mortality (Roue et al. 2016).

Elderly Cancer Patient Health Status in TLLMICs

Awareness of the need to develop geriatrics is quite recent in western countries (around 50 years) (Morley 2004), but still not completely understood in less developed countries (Gutierrez-Robledo 2002). By 2020, it is estimated that three quarters of all deaths in less developed countries will be attributable to noncommunicable diseases such as diabetes mellitus, cardiovascular diseases, and cancers. Furthermore, older people in these countries are expected to experience more chronic disease and disability than is usual in more developed societies (Gutierrez-Robledo 2002).

Comorbidities

Causes of death are classified in three groups (Mathers et al. 2006): group I (communicable, maternal, perinatal, and nutritional conditions), group II (noncommunicable diseases), and group III (injuries). In less developed countries, 2030 projected death rate in the group II (cancer is one of these causes) is increasing due to demographic growth, increase in life expectancy, and age-related-specific mortality (Mathers and Loncar 2006).

Prevalence of diabetes is however high in western countries, but on a total of more than 340 million patients with diabetes, more than 30% live in Brazil, Africa, India, and Southeastern Asia (Scully 2012). It is noteworthy that prevalence of diabetes is particularly high in some indigenous populations as in Papua New Guinea (40%) and in many Pacific Ocean islands and, one noteworthy fact, also in US Native Americans (Yu and Zinman 2007).

Prevalence of hypertension is high in Russia but also principally in tropical Africa and at a less degree in tropical South America in men. Prevalence is lower in women (principally in tropical Africa) (WHO 2015a, b).

This information is accessible in the whole adult population, but it is difficult to assess it in the elderly patient population. Nevertheless comorbidities are chronic diseases which prevalence increases with age (WHO 2015c). They are an important domain of the aging process.

It is noteworthy that in tropical countries, sensorial impairment may be very important as stated by Allain et al. (1997): 55% of elderly have cataract which is the main cause of blindness in Zimbabwe.

Comorbidities are generally measured by the Charlson Index (Charlson et al. 1987) or CIRS-G (Linn et al. 1968).The Charlson Index is a good prognostic factor of mortality but a poor descriptive tool for comorbidities; the CISR-G is a good screening tool but too complex and time consuming. The specificity of tropical diseases like comorbidities is not included in the common comorbidity screening tools (apart AIDS in the Charlson Index), and no study has been conducted yet to evaluate their impact on health status in elderly patients and especially in elderly cancer patients.

Dependence

Dependence is extremely frequent in low-income countries (Sousa et al. 2014). The author pointed out that physical performance in elderly people in TLLMICs was lower than in western countries and was correlated with childhood social and economic adversity. These disadvantages and inequalities were cumulative lifelong. Health status decline with age is very well correlated with income level of people (WHO 2015c). It is interesting to point out the fact that dependence in the Katz Index of Independence in activities of daily living (ADL) (Katz et al. 1963) in Zimbabwe (Allain et al. 1997) is less frequent in people living in the rural area (not more than 10–15%) than those in urban area (10–35%), independently of visual impairment and comorbidities.

Cross-cultural validation of ADL has been performed and published only in some countries: Morocco, Turkey, the Netherlands (Reijneveld et al. 2007), and Brazil (Lino et al. 2008). In this later, ADL impairment increases with age. Lima-Costa et al. (2003) also demonstrated a relationship between age and dependence but

describe major impairment to bath in 20% of people, 60% to move, and 55% to move at walking distance. Instrumental ADL (IADL) (Lawton and Brody 1969) is not applicable in TLLMICs because of western country cultural conception (Collingwood et al. 2014). Patient interview is more useful to detect the most common deficiencies related to cognitive impairment in this setting.

An important aspect of functional status is the risk of fall. The Tinetti test is an appropriate tool to screen such problems (Tinetti 1986). Nevertheless with respect to TLLMICs, it is a too complex tool to use: the "timed up and go" is more appropriate (Podsiadlo and Richardson 1991). It is a relatively simple test of walking speed and risk of fall: impairment is predictive of morbidity and mortality.

Nutritional Status

Malnutrition is a major factor of frailty, morbidity, and mortality and even leads to complication of cancer surgery and medical treatments in elderly patients (Blanc-Bisson et al. 2008). Worldwide, the number of undernourished people was estimated at 852 million people in 2000–2002, most of them (815 million) living in developing countries (Muller 2005). Investigators in Bangladesh used the Mini-Nutritional Assessment (MNA) (Guigoz et al. 2002) to screen malnutrition in more than 600 elderly patients in rural area. MNA was actually performed in two-thirds of patients. Twenty-six percent and 62% percent of people screened by MNA had severe malnutrition and were at risk of malnutrition, respectively. Prognostic factors of malnutrition were infection, gastrointestinal disorders, depression, cognitive impairment, female gender, illiteracy, and low incomes.

Cognitive and Thymic Impairments

Depression is a frequent problem in TLLMICs. In Nigeria, Sokoya et al. (Sokoya and Baiyewu 2003) showed that the rate of geriatric depression in primary care was 7.4%. Severe depression was only 1.5%. Very low income and subjective report of poor health were significantly associated with depression in the cohort.

In India prevalence of depression was measured to 14% (Rajkumar et al. 2009) and prognostic factors of severe depression were suffering from hunger, malnutrition, diabetes, transient ischemic attack, past head injury, disability, and loneliness. A comparative study of anxiety in different countries part of the 10/66 Dementia Research Group study (Prince 2000) shows that anxiety was more frequent and intense in South America than in China and India (Prina et al. 2011b). Urban centers had higher estimates of anxiety than their rural counterpart. Age, gender, socioeconomic status, comorbid physical illnesses, and disability were all associated with a diagnosis of anxiety.

The prevalence of co-occurring anxiety and depression ranged between around 1% and 4% across sites (Prina et al. 2011a) but was depending on dementia screening tool (Stewart et al. 2016): geriatric screening tools are generally not feasible; other alternative may be better. In a recent study, Palmer et al. (2014), using the Diagnostic and Statistical Manual of Mental Disorders criteria (DMS-IV), found in rural Bangladesh a prevalence of questionable dementia of 11.5% and definite dementia 3.6%. These are similar to prevalence in high-income countries. The same observation was made in Tanzania (Longdon et al. 2013): the age-standardized prevalence of dementia (DMS-IV) was 6.4%, but that one was 21.6% using the 10/66 Dementia tool (Paddick et al. 2013); education was a significant predictor of "10/66 dementia," but not of DSM-IV dementia. The authors concluded that despite its possible flaws, the DSM-IV criteria represent an international standard for dementia diagnosis. The 10/66 diagnostic criteria may be more appropriate when identification of early and mild cognitive impairment is required. The HIV Dementia Scale (HDS) and International HIV Dementia Scale (IHDS) are brief tools that have been developed to screen for and aid diagnosis of HIV-associated dementia; they have been evaluated: both scales were low in accuracy (Haddow et al. 2013). Thus the choice

of screening tools is not yet well established and requires further evaluation.

Nonetheless depression and dementia are important health issues in elderly patients in low TLLMICs.

Socioeconomic Status

In the USA also, education level and socioeconomic status have a major impact on the last years of life (Liao et al. 1999). The same is observed in the UK (Grundy and Sloggett 2003). Apart from the importance of socioeconomic status on healthcare provision, they have an impact on different aspects of elderly patient health status. Low income is a risk factor of dementia and depression (Prina et al. 2011a). Similarly in Bangladesh, poorer household and poverty increase the incidence and mortality due to chronic diseases (Khan et al. 2015).

Geriatric Assessment Tools

The Comprehensive Geriatric Assessment (CGA) is the gold standard not only for evaluating elderly health status but also to propose geriatric interventions (Extermann et al. 2005; Decoster et al. 2015) which require a time-consuming multidisciplinary management. The different health domains in elderly patients could be screened through different tools, to perform a diagnostic procedure. Such tools were described in details (Burhenn et al. 2016; Puts et al. 2012). The majority of these health status screening tools could be performed by trained nurses. The most important domains are functional status, comorbidities and polypharmacy, nutritional status, cognitive and thymic functions, geriatric syndromes, and socioeconomic status. It is important to choose tools with a sufficient clinical signification, and applicable in TLLMICs: it is likely that it should be based on very standardized and simple screening tools and clinical exams.

Short screening tools have been studied in TLLMICs, like the Campbell Assessment of Needs (CANE) which was validated in Brazil, but the clinical usefulness is questionable (Sousa et al. 2009b). EASY-Care is also a screening of elderly patient needs (Craig et al. 2015). It is principally based on ADL and IADL. It was validated in some cross-cultural studies: in Lesotho, Tonga, Iran, and Colombia as well as in the UK (Philip et al. 2014). A study in TLLMICs demonstrated the internally consistency of the scale which is increased by the exclusion of two items: unable to use telephone and manage finances (Jotheeswaran et al. 2016). Clearly geriatric assessment tools in TLLMICs require further studies.

Geriatric Series Published in TLLMICs

Different prospective evaluations of health status performed in different TLLMICs give an overview of elderly health. In Brazil, Lima-Costa et al. (2003) observed in a cohort of about 30,000 people over 60: 45% with poor health status, 15% with a performance status (PS) 3 and 9% PS 4. Comorbidities were multiple: 44% elevated blood pressure, 37% rheumatisms, 19% cardiovascular diseases, 10% diabetes, lung diseases 10%, 7% chronic renal failure, and 1% cancer. Sixty-nine percent of patients had at least one comorbid condition. Interestingly, Zunzunegi et al. studied frailty in women and men in Latin America and Caribbean countries: women showed poorer health outcomes as compared with men for all health indicators and in all cities (Zunzunegui et al. 2009). In the 10/66 study (Sousa et al. 2009a), dependence was linked to dementia, depression, comorbidities, and eyesight troubles. Surprisingly the prevalence of disability in Tanzania looked quite low: 6.2% moderate and 3.7% severe. Independent predictors were age, female gender, memory, and neurological problems (Dewhurst et al. 2012). This prevalence is lower than in high-income countries; the authors hypothesized that this may reflect increased mortality from disabling diseases in low-income countries.

Predictors of disability and mortality were studied in Cuba, Dominican Republic, Venezuela, Mexico, Peru, India, and China within a 10/66 study. Weight loss, underactivity, slow walking speed, and cognitive impairment predicted both

outcomes, whereas malnutrition predicted only mortality and sensory impairment only dependence. Exhaustion predicted neither outcome (Jotheeswaran et al. 2015).

It is pointed out that some domains of health status are not assessable in non-western populations as it has been assessed in Canada (Puts et al. 2011) and Thailand (Jitapunkul et al. 1994). Tools wording are rarely understood in cultures other than western culture: in Hospital Anxiety and Depression Scale (HADS), the questions "I feel tense or wound-up" or "I get a sort of frightened feeling like butterflies in the stomach," had different meanings for participants from different countries (Puts et al. 2011). In Thailand, because of misinterpretation of behavioral and intellectual disability, ADL tool use leads to 99% of subjects being scored as disabled (Jitapunkul et al. 1994).

Geriatric Oncology Series Published in TLLMICs

Few studies have been published on health status evaluation in elderly cancer patients in TLLMICs. Aggaval et al. reviewed the perspectives of cancer in elderly patients in middle-income countries (Aggarwal et al. 2015). They concluded that the burden of cancer in elderly will increase exponentially, and it is a major public health objective to develop geriatric oncology. Nevertheless they pointed out the importance of the cost and the lack of insurance coverage to support such expensive treatments.

An important study was performed in China (even though this country is not strictly a country part of the TLLMICs) (Kanesvaran et al. 2014). A CGA was performed in 800 elderly cancer patients from the Beijing area and treated in tertiary centers. Mean age was 72 (extremes 65–94); 60% were men; only 11% patients had no caregiver; they generally live in their family and the majority received a pension; it is not stated whether some patients had major poverty; around 37% patients had professional activity; 65% had exercise; around 70% of patients were independent in ADL and 40% had no impairment in IADL; and some forms of malnutrition occurred in 24% of patients. Fifty-five percent of patients had three or more comorbidities as assessed by the Older American Resources Service (OARS) Comorbidity Scale; polypharmacy is noted in 38% of them. More importantly 45% of patients take traditional Chinese medicine: these patients have more comorbidities than those who do not take traditional medicine. This interacts also with patient decision-making process.

France introduced the G8 mandatory screening tool in the management of elderly cancer patients (Soubeyran et al. 2014). Within the framework of Geriatric Oncology Coordination Units of the French National Cancer Institute (INCa), a retrospective study and a prospective study were performed in the French Guiana. The retrospective study reviewed the clinical files of 71 cancer patients over 70 treated in the Cayenne hospital, French Guiana, in 2010–2012 (Droz et al. 2012). The population is that of an equatorial country which benefit from a European country health organization. Oncogeriatric evaluation was achievable but was far from being routinely used. Selection of frailty screening tools was difficult. However, specific problems emerged: cultural differences, low income, illegal immigrants, comorbidities, specific tropical diseases, and the incidence of HIV, HTLV1, and hepatitis viral infections (Droz et al. 2012). Two prospective cohorts were analyzed from 01/09/2015 to 30/04/2016: one in the main public hospital in Cayenne (Joachim et al. 2016) and one in Saint-Laurent du Maroni Hospital (Droz 2016 abstract S6). In the Cayenne Hospital, 130 patients >70 were followed for cancer in the outpatient clinic; 60 patients (46%) had a G8 screening of which 57 were abnormal (Joachim 2016 poster 105). The small number of G8 procedures was due to organizational problems, but there were also difficulties in obtaining all G8 items: loss of appetite was biased by the treatment; weight loss during the last 3 months was difficult to measure in these patients who don't follow their weight; number of medications did not take in account traditional medicine intakes; and "feeling of their health status" was biased by cultural perception of health, of disease, and of cancer, by belief and by comparison to their previous heath status. In Saint-Laurent

du Maroni, 23 new cancer patients were older than 70 years (Droz 2016). There were 14 French, 7 Surinamese, and 2 Haitian patients. Language was Sranantongo 10, French 7, Creole 4, and Hmong 2 patients, respectively. Ten patients benefited from the National Health Security, 7 of Emergency Medical Assistance, and 5 of Universal Medical Coverage, and one had no medical coverage. G8 screening tool value was 0 to 16 and only 6 pts. had a value >14. Assessment in health status groups was based on ADL, Cumulative Illness Score Rating-Geriatrics (CISR-G), and malnutrition (weight loss) (Droz et al. 2014). There were fit 4, vulnerable 9, frail 7, and too sick 3 patients. The item "self-rated health" was difficult to assess in 15 pts., due to a lack of understanding and wording (rated 0.5: "don't know"). Correlation between G8 and components of Health Status was poor.

These studies focus on the difficulty in both screening frailty in elderly cancer patients and evaluating their health status for practical problems but also for the use of poorly adapted screening tools, partly due to cultural features.

Nevertheless most of elderly patients from TLLMICs suffer from two or more concurrent diseases. Hussain (Hussain and Sullivan 2012) in Bangladesh found that only 8% of elderly patients with cancer have no other illnesses, 37% have one or two other illnesses, and 55% actually have three or more comorbidities. According to a World Bank report (Worldbank 2015), the health expenditure per capita in Bangladesh is $18.43, whereas according to WHO guidelines it should be a minimum of $44.4. Major limits to the management of elderly cancer patients in TLLMICs are available expenditure and also physician awareness in geriatrics and end-of-life care.

Diagnostics in Elderly Patients

Delay to Cancer Diagnostics in TLLMICs

Aggarwal et al. collected information on the duration of symptoms prior to seeking medical attention in cancer patients according to age (Aggarwal et al. 2015). Delay in patients aged 65–69 years was >12 months in 43% and 38% in men and women, respectively, and in patients aged 75–79 years, it was 41.5% and 34% in men and women, respectively.

The Reasons to Explain Cancer Diagnostic Delay

Cultural factors are important. In Nigeria, sociodemographic factors and reasons associated with delay in breast cancer presentation were ignorance of the nature of illness, belief in spiritual healing, fear of mastectomy and belief in herbal treatment (Ibrahim and Oludara 2012). Nevertheless, the availability of laboratories (and particularly laboratories of pathology) is of importance: a recent survey of laboratories in Kampala, Uganda, demonstrated that only 0.3% of laboratories (3/954) met international quality standards (Schroeder and Amukele 2014). Conversely, density of accredited laboratories in South Africa, Namibia, and Botswana was similar to that of western countries. There is a direct proportionality between density of accredited laboratories and health expenditure per capita. The solution to solve these inequities, particularly for pathology laboratories is to establish collaboration and partnership with laboratories in the western and high-income countries just as they do in Lilongwe (Malawi) (Gopal et al. 2013).

Health Status Evaluation

Health status evaluation of elderly cancer patients is generally based on a three step procedure. The first step is the use of a screening tool: different tools are available like the G8 (Soubeyran et al. 2014) which is recommended by the EORTC Geriatric Oncology Task Force, the INCa, the European Association of Urology (Cornford et al. 2016; Mottet et al. 2016), and the SIOG (Droz et al. 2014). Other tools are also available: the Groningen Frailty Index (Drubbel et al. 2013), the PPT (Terret et al. 2010), and VES-13 (Soubeyran et al. 2014) .The objective of such screening tools is to determine whether a more advanced geriatric evaluation would be

necessary. The use of such tools in TLLMICs is likely difficult, as it has been previously described in various articles. This is often linked to cultural differences between western countries where these tools were developed and TLLMICs. It is unlikely that a universal screening tool may be developed for these countries for the great cultural heterogeneity.

The third and final step is CGA and is the standard of care. It is not only about a series of screening tools but, more importantly, a complete clinical exam, laboratory and imaging additional exams, and finally a comprehensive synthesis of health problems and decision-making for geriatric intervention planning (Decoster et al. 2015). However, CGA is time consuming, requires the intervention of multiple professionals, and is consequently very expensive. It is therefore unlikely to develop such procedures in TLLMICs.

There is nevertheless a second step in the geriatric evaluation procedure: what is sometime called "simplified geriatric evaluation." To date the interest of such procedure is still questionable (Puts et al. 2012, 2014). Still, this has been developed with the pragmatically objective of screening the most important needs of elderly cancer patients (Overcash et al. 2006). Recently it has been used to tailor treatment of elderly prostate cancer patients (Droz et al. 2014). Generally the most important factors of disability are dependence (ADL, IADL), comorbidities (Cumulative Illness Rating Score-Geriatrics – CIRS-G) (Linn et al. 1968), malnutrition (Mini-Nutritional Assessment – MNA) (Guigoz et al. 2002), and cognitive impairment (mini-COG™) (Borson et al. 2003) and Mini-mental Status Evaluation (MMSE) (Folstein et al. 1975). The limits of these tools in TLLMICs have been discussed previously. Table 1 reviews the different tools, experiences in TLLMICs, and possible modified tools.

Therapeutic Tools

Therapeutic tools are not really specific to elderly patients, but it is important to point out the major facts on their availability and use in TLLMICs.

Palliative Treatments

Palliative treatments of cancer are a priority in TLLMICs because many patients are diagnosed at a late stage. Thus quality of life is the most important objective with a priority for pain control and end-stage disease management. Guidelines on pain management in elderly patients have been published and are commonly used (Urban et al. 2010; Malec and Shega 2015; Tracy and Sean 2013). Treatment of pain is nonetheless far from optimal in TLLMICs. As an example, consumption of opioid analgesics in sub-Saharan Africa is low, and at least 88% of cancer deaths with moderate to severe pain are untreated. Access to essential drugs for pain relief is limited by legal and regulatory restrictions, cultural misperceptions about pain, inadequate training of healthcare providers, drug access difficulties, weak health systems, and concerns about diversion, addiction, and misuse (O'Brien et al. 2013). Efforts are made by national governments and local and international organizations to improve access to pain treatment.

Radiotherapy is however a curative treatment but also one of the most active and cost-effective treatments in advanced cancer: it ensures very effective palliation in most advanced diseases (Barton et al. 2006). Less than 25% of cancer patients in tropical Africa have access to radiotherapy.

Surgery

Surgery remains the best curative treatment and also the treatment with the best cost-efficiency (Kingham et al. 2013). A complete situation analysis of surgical services was published by the World Bank group (Gelband et al. 2015). There are four step platforms for surgery: cancer community health center is only able to refer patients; first-level centers (district) can perform biopsies and deliver only simple oral treatments; second-level centers (regional) can perform the majority of exams, surgical procedures, and medical treatments; and finally, third-level centers (tertiary) are able to perform specialized surgery, intensive

Table 1 Possible useful tools to evaluate elderly cancer patient health status in TLLMICs

Domain	Tool	Practice in TLLMICs[a]	Possible substitution[a]
Activities of daily living 1	ADL	Cross-cultural validation	ADL feasible
Activities of daily living 2	IADL	Not adapted for cultural reasons	Interview
Comorbidities	Charlson Index CIRS-G	Not adapted: prognostic tool Time consuming, too complicated	Clinical exam++; BAP; diabetes screening; heart exam, EKG, Echo? creatinine clearance
Functional symptoms	Interview		# ADL and comorbidities
Medications	Number	Traditional medicine	Interview
Cognitive functions	MMS CSID CANE	Cross-validation India, Brazil Cross-validation 10/66 study Cross-validated	In other cultures: interview
Depression	GDS	Not always cross-validated	GDS or more efficient: interview
Nutritional status	MNA	<2/3 evaluable Too complicated	BMI; albumin: lymphocytes;
PS	ECOG PS	Cultural influence	Can be used
Fall risk	Tinetti test		Monopodal station; "timed up and go"
Visual exam	OPH clinics	Cataract 55%	Visual acuity test: 2 fingers at distance
Audition	Audiometry	Impossible	Interview
Caregiver	Interview	Cultural influence	Interview
Social support	Interview	Health organization of TLLMICs	Interview
Income	Interview	Income level of TLLMICs	Interview
Cultural evaluation	Not done	Mandatory	Transcultural mediation if needed

Legends: *TLLMICs* tropical and low-middle-low-income countries, *ADL* activities of daily living (Katz et al. 1963), *IADL* Instrumental ADL (Lawton and Brody 1969), Charlson Index (Charlson et al. 1987), *CIRS-G* Cumulative Illness Rating System – Geriatrics (Linn et al. 1968), *BAP* blood arterial pressure, *MMS* Minimal Mental State (Folstein et al. 1975), *CSID* Community Screening Instrument of Dementia (Prince et al. 2009), *CANE* Campbell Assessment of Needs (Sousa et al. 2009b), *GDS* Geriatric Depression Scale (Yesavage 1988), *MNA* Mini-Nutritional Assessment (Guigoz et al. 2002), *BMI* Body Mass Index, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, Tinetti test (Tinetti 1986), *OPH* ophthalmologic

[a]References in the text

postoperative cares, and radiotherapy; they have also teaching activities. Treating elderly patients by surgery requires specific skills: guidelines were proposed by the SIOG (Audisio et al. 2004). Careful preoperative evaluation of elderly patients is required and is based on PS, ADL, IADL, and comorbidities (Audisio et al. 2008). It is also mandatory to prevent postoperative confusion in frail patients.

Radiotherapy

As mentioned previously, radiotherapy is an important treatment with curative intent (Barton et al. 2006). In high-income countries, half of cancer patients will require radiotherapy during their disease. Many countries in TLLMICs have limited access to radiotherapy facilities and even 22 countries in Asia and Africa don't have any service of radiotherapy at all. In Africa it is estimated that only 20% of the needs are covered. This is a major lack of means in these countries. If radiotherapy facilities are available, treatment in elderly patients should follow the SIOG recommendations (Kunkler et al. 2014).

Medical Treatments

Access to medical treatments is highly variable in TLLMICs (Kingham et al. 2013; Vanderpuye et al. 2015). The major problem is the cost. The following drugs are generally available:

doxorubicin, cisplatin, fluorouracil, capecitabine, folinic acid, steroids, dactinomycin, vincristine, vinblastine, methotrexate, etoposide, hydroxyurea, melphalan, cytarabine, mercaptopurine, L-asparaginase, daunorubicin, and thioguanine to perform the treatment of an important number of cancers and hematologic malignancies. Nevertheless even though access to irinotecan, oxaliplatin, carboplatin, gemcitabine, taxanes, and antiemetics is possible, it is the only available with out-of-pocket payment. Other new and important drugs, as trastuzumab, rituximab, and G-CSF, are rarely available (Kingham et al. 2013). Metronomic chemotherapy – the chronic administration of chemotherapy at low, minimally toxic doses on a frequent schedule of administration, with no prolonged drug-free breaks – has recently emerged as a potential strategy to control advanced or refractory cancer and represents an alternative for cancer patients living in developing countries. This low-cost, well-tolerated, and easy-to-access strategy is an attractive therapeutic option in resource-limited countries (Andre et al. 2013).

However, medical treatments in elderly cancer patients may require specific management and rigorous precautions of administration: the SIOG produced guidelines and reviews in this setting (Biganzoli et al. 2012, 2016; Aapro 2011). Moreover supportive cares are essential and should follow adapted guidelines (Stepney 2016). Unfortunately a large amount of supportive care drugs are not available in TLLMICs.

Difficulties often occur when administrating medical treatments to elderly patients, especially due to renal function decrease (Duncan et al. 2001). Drug interaction is another limitation for elderly patients often receive polypharmacy (Salwe et al. 2016). The frequency may be as high as 50% of elderly patients and 75% of elderly cancer patients.

The incidence of HIV infection in TLLMICs is higher than in high-income countries. Its estimated prevalence in sub-Saharan Africa is estimated to 5% (Shao and Williamson 2012); it is therefore important to consider potential drug interactions between antiretroviral therapy and anticancer drugs (Spano et al. 2016).

Perspectives of Management Optimization

To Develop Interventions That Are Highly Effective, Cost-Effective, and Resource-Level Appropriate

To date there is no specificity in geriatric oncology in TLLMICs. Cancer management is based on principals focused on the development of appropriate and ethical cost-effective interventions (Ngoma 2015). The example of an efficient project is the Breast Health Global Initiative (BHGI) (Anderson 2003; Anderson and Distelhorst 2008; Anderson et al. 2008; Anderson and Jakesz 2008; Anderson and Tsu 2008). The recommendation proposes decision trees for global management, adapted to resources, and with a significant impact on outcomes. Thus, management is focused to screen, diagnose, and treatment of early breast cancer at an early stage, the consequence being to decrease diagnosis at late stage and decrease mortality and global cost. The BHGI model should be applied to the most frequent and curable cancers like breast, cervix, colon-rectum, and head and neck cancers. Another important objective is to promote joint ventures between oncologists from the northern/western countries and southern countries, to develop appropriate decision trees, and to favor skill training through grants from various governmental and nongovernmental institutions (Ngoma 2015). Finally the implementation of tertiary centers ("excellence centers") is important. There are different possibilities of organization, depending on the local prior health organization; these centers should not only be reference centers for treatment but also reference centers for teaching and for implementing of a national network of secondary centers dedicated to routine treatments. These centers should

collaborate to clinical and translational research (Rehman et al. 2016; Adewole et al. 2014). It is a major challenge which main objectives would be efficiency and equity.

To Develop Geriatric Oncology in This Setting

Considering the burden of elderly cancer patients in TLLMICs in the future, such kind of project could be implemented in geriatric oncology. This would involve:

- Geriatric oncology units in "excellence centers"
- Training of either oncologists or internist in geriatrics
- Resource-adapted guidelines based on the SIOG guidelines (Biganzoli et al. 2012; Papamichael et al. 2015; Armstrong et al. 2016; Morrison et al. 2015; Stauder et al. 2016; Pallis et al. 2010)

SIOG would have a key role in this setting. On the one hand, it is important to adapt the ten priorities defined in 2011 (Extermann et al. 2011) to the case of TLLMICs. On the other hand, it is a priority to propose guidelines for health status evaluation which should be adapted to TLLMICs populations on resources and cultures. It is not possible yet to know whether it would be possible to develop a unique model or to tailor models to different area defined by their resources, cultures, or any other characteristic.

It Is Important to Include Information and Transcultural Mediation in These Objectives

SIOG considered the cross-cultural aspect of management (Surbone et al. 2007). Still, the SIOG approach is based on a western view of diseases. In many TLLMICs, the cultural understanding of the body, life, health, disease (illness), cancer, and death is different and may lead to a failure of the conventional approach of elderly patients (Droz et al. 2016; Joachim et al. 2016). The non-western world approaches are widely different from one country to another and from one ethnic group to another within the same country. As an example in the French Guiana, the ethnic group "noirs Maroons" is characterized by a social organization based on the clan, the transmission being matrilinear; a strong relationship between humans, ancestries, spirits, and nature; and alliances between humans, spirits, and duties toward ancestors through strict rites. Good health refers to strength; illness is a disorder which is often due to a spell. Diagnosis is divinatory and requires a medicine man; treatments are based on plants and baths. Death is never natural, but it is due to a spell, a spirit, or an ancestor. A postmortem examination aims to answer the question: Is the defunct worthy to be an ancestor (Vernon 1980, 1993)? The use of such tools in TLLMICs is likely difficult as it has been previously described in various articles. Usually, the doctor and the patient make two discourses that don't take account of each other. The doctor has the universal knowledge and particularly that of the disease. The patient narrative helps him to give sense to something which aggresses himself. This is not universal, but singular, and still it does not exclude understanding of the disease nor therapeutic alliance (Larchanché and Bouznah 2015). Several studies in TLLMICs pointed out the demand of information adapted to the patient culture and their resort to traditional procedures and treatments (Zekri and Karim 2016; Dorio et al. 2016; Berger-Gonzalez et al. 2016; Kanesvaran et al. 2014). These cultural approaches are particularly important in the practical implementation of programs of early diagnosis, cancer screening, and cancer prevention which are the potentially most active process to decrease the cancer burden in TLLMICs (Sitas et al. 2008; Gelband et al. 2015).

Conclusion

Throughout the next 20 years, elderly cancer patients will represent more than half of the whole cancer patient population and the half will live in TLLMICs. The knowledge on cancers and hematological malignancies in TLLMICs enhances rapidly and especially knowledge on the biology of these malignancies. Conversely the characteristics of aging in the TLLMICs populations are still scarce. Furthermore, geriatric evaluation techniques in high-income countries are not necessarily relevant in this setting. It is therefore important to make efforts to develop geriatric oncology in this part of the world. The most important aspects will be:

- Development of adapted screening tools of frailty
- Establishment of a decision-making process to suit resources and cultures and based on very standardized and simple screening tools and clinical exam
- Training of health professionals (MD and other medical health professionals)
- Production of scientific knowledge both in clinical and basic research

This requires cooperation between northern/western institutions and south institutions, a global worldwide willingness to give elderly cancer patients in TLLMICs access to adapted and active cares based on efficiency and equity.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Frailty in Cancer Patients
- ▶ Geriatric Screening in Cancer Patients
- ▶ Integrating Geriatric Oncology in Public Health Planning
- ▶ Integrating Geriatric Oncology into Clinical Pathways and Guidelines
- ▶ Normal and Abnormal Aging (General Perspective for the Oncologist)
- ▶ Organizing the Clinical Integration of Geriatrics and Oncology
- ▶ Pain Management in Older Cancer Patients
- ▶ Population Trends in Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management
- ▶ Principles of Cancer Surgery in Older Adults
- ▶ Principles of Cancer Targeted Therapy in Older Adults
- ▶ Principles of Chemotherapy in Older Adults
- ▶ Principles of Radiation Therapy in Older Adults
- ▶ Research Methods: Epidemiologic Research in Geriatric Oncology
- ▶ Research Methods: Quality of Life and Patient-Reported Outcome Research in Geriatric Oncology
- ▶ Research Methods: Translational Research in Geriatric Oncology
- ▶ Research Methods: Using Big Data in Geriatric Oncology
- ▶ The Older Cancer Patient: Religious and Spiritual Dimensions

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Integrating Geriatric Oncology into Clinical Pathways and Guidelines

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Contents

Abstract

Cancer is a disease of the elderly, and more research is needed to improve geriatric oncology care. The complexity of older cancer patients requires clinicians to consider a declining organs' function and competing comorbidities to balance pros and cons of every treatment choice within the context of estimated life expectancy.

A comprehensive geriatric assessment (CGA) is helpful and mandatory to establish an appropriate care plan as research demonstrated it can detect issues that would remain otherwise neglected and improve the care of older cancer patients. Predictive tools for chemotherapy toxicity may also help complete the assessment for patients eligible for anticancer therapy. Nevertheless, CGA may be time-consuming, and several screening tools have been developed and validated to identify potential candidates for a full assessment.

Due to the underrepresentation of older patients in clinical trials and the shortage of studies specifically addressing this population, a solid evidence base for the management of cancer in this setting is currently lacking. However, less robust levels of evidence may be

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used to inform treatment decisions. Therefore, the guidelines available can provide clinicians with the tools to pilot the care of older adults with cancer, yet more specific research in the field is awaited.

Keywords
Geriatric oncology · Clinical pathways · Guidelines · CGA

Introduction

Cancer Burden in the Elderly

Age is the most important risk factor for cancer. Sixty percent of the incidence of cancer and 70 percent of its mortality occur in patients aged 65 years and older (Ries et al. 2003). By 2030, in the United States, new cancer cases in older patients aged over 65 are expected to increase by 67 percent compared to 11 percent in younger adults (Smith et al. 2009). In Western countries up to 30 percent of the population will be aged 65 or older by 2050, and individuals aged 80 and overrepresent its fastest growing part; worldwide one in six people will be aged over 65 (WHO 2002). Geriatric oncology accounts for a relevant part of the everyday practice for the medical oncologist and is expected to be increasingly important. More research in geriatric oncology is needed in order to improve cancer prevention, its early detection and specific therapies addressing elderly patients, since a solid amount of evidence in the field is still lacking. Developing an appropriate management approach for vulnerable patients is key for oncology care (Thompson and Dale 2015). The American Geriatrics Society's guidelines propose the following: 1) assessing patient preferences, 2) interpreting the available evidence, 3) estimating prognosis, 4) considering treatment feasibility, and 5) optimizing therapies and care plans (American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity 2012). Applying these recommendations to oncology is crucial for optimizing the care of older adults with cancer.

Complexity of Older Cancer Patients

Chronological age alone cannot fully depict the complex care an older cancer patient requires, including special attention to treatment toxicities, quality of life, estimated life expectancy, age-related organ function decline, and competing medical comorbidities.

Aging correlates with a loss of physiologic reserve in critical organs' function, and older individuals are at risk of decompensation upon exposure to stresses such as surgery or chemotherapy. Table 1 enlists some of the specific challenges in elderly cancer patients and their clinical implications. Nevertheless, chronological age may not correlate with functional status due to the heterogeneity of older cancer patients. Older patients are as willing to try anticancer therapies such as chemotherapy as their younger counterparts but less keen on enduring severe treatment-related adverse events (Yellen et al. 1994), and quality of life always needs to be considered in the decision-making process (Sanoff et al. 2007). Prior to treatment initiation, an evaluation is helpful for assessment of the many domains that can affect cancer care in older adults including comorbidities; polypharmacy; functional, nutrition, and cognitive status; social support; and psychological status. Predictive tools including tools to determine expected life expectancy are available online to support decision-making with regard to cancer care in this patient population (ePrognosis n.d.; Walter and Covinsky 2001).

Comprehensive Geriatric Assessment

There is a continuum ranging from functional independence to frailty (Hamerman 1999), with some older patients without any significant limitations and minimal or no reduction in functional reserve, with others who are more vulnerable and suffer from decreased functional reserve. The oncologist is faced with the task of differentiating between the fit older individual who is likely to benefit from and tolerate standard therapy and the frail elderly patient who is prone to experience treatment-related side effects and requires

Table 1 Specific challenges in elderly cancer patients and clinical implications (Sawhney et al. 2005; Sehl et al. 2005; Peterson et al. 2016; Rolland et al. 2009)

Organ system	Aging-related changes	Implications
Liver	Hepatic volume decline Hepatic blood flow decline	Decreased drug metabolism Decreased drug elimination Increased treatment toxicities
Kidney	Decreased glomerular filtration rate	Volume depletion Decreased drug elimination Increased treatment toxicities
Muscles	Sarcopenia	Decreased mobility Impaired functional status Increased risk of falls
Bone marrow	Decreased bone marrow reserve	Increased treatment toxicities
Bone	Osteopenia and osteoporosis	Increased risk of fractures Decrease mobility Impaired functional status
Central nervous system	Neurons loss Reduced brain blood flow	Impaired cognition and dementia Increase risk of falls Increased susceptibility to benzodiazepines
Gastrointestinal	Poor motility Decreased acid production	Poor drug absorption
Cardiovascular	Decrease ventricular compliance Diastolic dysfunction Increased wall thickening	Increase risk with cardiotoxic drugs Higher risk of arrhythmias
Lungs	Decreased lung compliance Decreased sensitivity of the respiratory center Decreased mucociliary function	Decreased pulmonary capacity Higher risk of pulmonary infections Limitation on options for lung surgery/ radiation

different treatment options. Moreover, some apparently fit patients are found to have deficiencies that would have become evident after treatment initiation upon thorough evaluation. A comprehensive geriatric assessment (CGA) evaluating all the factors that may potentially influence the treatment outcomes is particularly useful.

A CGA can predict treatment complications and survival (Ramjaun et al. 2013), aid in therapeutic decision-making (Kenis et al. 2013), detect subtle problems at baseline which are not recognized by routine consultation (Extermann et al. 2004), and improve mental health and pain control (Rao et al. 2005). Despite the recommendations by the National Comprehensive Cancer Network (NCCN) (VanderWalde et al. 2016) and the International Society of Geriatric Oncology (SIOG) guidelines (Extermann et al. 2005), its routine use is limited, likely due to time constraints and challenges of implementation into a busy oncology practice. Hence, screening tools have been developed that can identify patients who will benefit from an extensive CGA (Decoster et al. 2015) such as the abbreviated CGA (Overcash et al. 2005), the Vulnerable Elders Survey-13 (VES-13) (Saliba et al. 2001), the G8 tool (Bellera et al. 2012), the modified G8 (Petit-Moneger et al. 2016), and the Flemish version of the Triage Risk Screening Tool (fTRST) (Braes et al. 2009).

The domains tested by CGA and some useful instruments to evaluate them are enlisted in Table 2. Compared to their counterparts without a history of cancer, older cancer patients have been found to have a statistically significant higher prevalence of limitations in activities of daily living (ADLs) (31.9% versus 26.9%), limitations in instrumental activities of daily living (IADLs) (49.5% versus 42.3%), geriatric syndromes (60.8% versus 53.9%), low self-rated health (27.4% versus 20.9%), a score above 3 on the VES-13 (45.8% versus 39.5%), and satisfying criteria for frailty (79.6% versus 73.4%) (Mohile et al. 2009). Functional disability is common in elderly cancer patients, with 17 percent of them

Table 2 CGA domains and available tools

Domain	Tools	Importance in oncology
Demographic data and social status	History regarding living situation, marital status, educational level, safety of environment, financial resources Caregiver burden	Support in the community
Comorbidity	Charlson comorbidity index (Charlson et al. 1994) CIRS-G	High score correlates with decreased OS and increased chemotherapy toxicity
Functional status	ADLs (Katz index) IADLs (Lawton scale) Visual and/or hearing impairment (glasses, hearing aids) Mobility difficulty (requiring help or use of walking aid) Timed get up and go Hand grip strength ECOG/Karnofsky PS Self-reported no. of falls	Poor functional status correlates with survival, quality of life, treatment toxicity
Cognition	Mini-mental state examination Clock-drawing test Montreal cognitive assessment	Poor cognitive function is a predictor of poor survival. May affect decision-making capacity
Depression	Geriatric depression scale Hospital anxiety and depression scale Presence of depression (as geriatric syndrome) Distress thermometer	Poor quality of life and compliance to treatment
Nutrition	Body mass index (BMI) Weight loss (unintentional loss in 3 or 6 months) Mini nutritional assessment	Increased morbidity and mortality with low BMI
Fatigue	Mob-T	Poor symptom control and compliance to treatment
Polypharmacy	Beers criteria STOPP and START criteria	Risk of drug interactions with chemotherapy
Geriatric syndromes	Dementia Delirium Incontinence (fecal and/or urinary) Osteoporosis or spontaneous fractures Neglect or abuse Failure to thrive Constipation Polypharmacy Pressure ulcers Sarcopenia	

Abbreviations: ADL, activity of daily living; CIRS-G, Cumulative Illness Rating Scale-Geriatrics; ECOG, Eastern Cooperative Oncology Group; GA, geriatric assessment; IADL, instrumental activity of daily living; MOB-T, Mobility -Tiredness Test; PS, performance status; START, Screening Tool to Alert Doctors to Right Treatment; STOPP, Screening Tool of Older Person's Prescriptions

reporting limitations for ADLs and 58 percent for IADLs (Serraino et al. 2001), with impact survival, quality of life, and rates of chemotherapy toxicity (Maione et al. 2005; Extermann et al. 2012; Hurria et al. 2011). Studies have shown that performance status scores as determined by care providers underestimate the degree of functional impairment in older patients (Repetto et al. 2002; Jolly et al. 2015), while the use of validated scales provides a more precise evaluation (Hoppe et al. 2013). The history of falls in an important item (Sattar et al. 2016) and their prior occurrence are consistent predictors of subsequent functional disability among older patients.

Comorbidities and cognitive function are an independent CGA domains and are considered independent prognostic markers (Extermann et al. 1998) (Charlson et al. 1987) (Miller et al. 1992; Williams et al. 2016) (Neale et al. 2001). Comorbidities impact life expectancy and treatment outcomes and correlate with poorer survival (Satariano and Ragland 1994; Asmis et al. 2008; Hines et al. 2009). Cognitive function has direct influence on the decision regarding both cancer diagnosis and treatment with regard to capacity and compliance (Gupta and Lamont 2004; Wolfson et al. 2001; Gorin et al. 2005). As such it should always be evaluated at baseline prior to any cancer treatment and ensure the compliance to the therapeutic recommendations and capacity to make treatment decisions. Nutritional status is also crucial, since weight loss and low body mass index (BMI) increase mortality for older adults (Newman et al. 2001) and impact on survival, performance status, and chemotherapy tolerance (Dewys et al. 1980). Nutritional issues are heterogeneous and may include weight loss during anticancer therapy, malnutrition during advanced disease, and obesity during survivorship (Presley et al. 2016).

A regular and comprehensive review of all medications should be performed in order to remove any unnecessary or potentially inappropriate medications and to assess potential drug interactions (Lichtman and Villani 2000; Vestal 1997). Among elderly cancer patients, medication errors and use of potentially inappropriate medication are more frequent (Coleman et al. 2005; Nightingale et al. 2015). One example is the high sensitivity of older adults to benzodiazepines, that increase the risk of falls and cognitive impairment (Schroeck et al. 2016). This class of drugs should be avoided in favor of alternative medications and approaches (Hurria et al. 2014a). There are also a number of potentially dangerous interactions of some medications with chemotherapy (e.g., warfarin and capecitabine).

Psychological distress is experienced by one third of elderly cancer patients and frequently implicates depression (Kua 2005), especially in the context of inadequate social support, higher risk of functional decline, and increased utilization of healthcare resources (Penninx et al. 1998). Social support should always be evaluated in conjunction with treatment planning (Stuck et al. 1993; Cohen 2002). Also, it should be considered whether the patient is a caregiver for someone else or if there is anybody available to take on such role (Klepin et al. 2015). Caregivers may be exposed to stress and depression, to neglect their own health (Germain et al. 2016) (Navaie-Waliser et al. 2002). Cultural, social, psychological, and behavioral variables should be considered when evaluating the individual situation (Baider and Surbone 2014).

A number of interventions can address the issues detected in each domain of CGA (Mohile et al. 2015), including physiotherapy and occupational therapy, caregiver involvement, reducing polypharmacy, social work and home safety assessment, counseling, oral care, and nutrition consult. CGA should also be repeated throughout the continuum of cancer care, since the needs may be different in different times and settings.

Lack of External Validity of the Current Evidence

A solid amount of evidence is needed in support of the optimal management in this specific patient population. However, older patients are underrepresented in clinical trials (Hutchins et al. 1999; Lewis et al. 2003). Strict trial eligibility criteria, competing comorbidities, and logistic barriers limit enrolment of older patients (Trimble et al. 1994; Kemeny et al. 2003; Yee et al. 2003). As a result 11 percent of elderly cancer patients are excluded from clinical trials a priori on the basis of their age (Javid et al. 2012) despite evidence showing that treatment tolerance in clinical trials is similar across various age groups (Javid et al. 2012; Giovanazzi-Bannon et al. 1994; LoConte et al. 2010; Townsley et al. 2005). An additional factor hindering accrual of older patients on clinical trials is physicians' fear of toxicity, resulting in clinical trial options being discussed less frequently with elderly patients (Javid et al. 2012; Foster et al. 2010). Other potential barriers to trial enrolment of older patients include lack of

autonomy over treatment choice (Townsley et al. 2006), concerns about potential adverse events, relatives opposing participation (Javid et al. 2012), different literacy rates (Townsley et al. 2006), ambiguities in the trust in physicians (Jenkins et al. 2013), and perception of the efficacy of a trial (Jenkins et al. 2013). Nonetheless, altruism remains a powerful incentive to facilitate participation of older patients in clinical trials (Jenkins et al. 2013).

The underrepresentation of older individuals in clinical trials supporting the current available guidelines limits their applicability in the elderly population (Battisti et al. 2015). Therefore, eligibility criteria should be less restrictive to allow for enrollment of real-world patients. Furthermore, research specifically addressing older people are needed and have been proved to be feasible (Cunningham et al. 2013; Muss et al. 2009). Such trials might also inform treatment options for younger patients who are not fit for more intensive treatment. Novel study approaches and methodologies, for example, mandating certain percentages of older subjects on registration studies that would resemble the proportion of elderly patients in the real-world population, can certainly advance this field and improve the evidence base to guide the management of older cancer patients (Hurria et al. 2014b; Hurria et al. 2015). The assessment of vulnerable older patients is the ideal setting to test patient-reported outcomes. There is a consistently high risk of underreporting of subjective toxicities by physicians, even when these data are prospectively collected within randomized studies (Di Maio et al. 2015). Therefore, the incorporation of patient-related outcomes into clinical trials is strongly encouraged.

Integration of Geriatric Oncology into Clinical Pathways

Geriatricians developed and validated CGA as a holistic approach to assess older patients in 1999 (Reuben et al. 1999; Cohen et al. 2002). Following a first attempt to adapt the CGA for use in oncology (Monfardini et al. 1996), its efficacy was prospectively assessed in a large population of elderly cancer patients at the end of last century (Repetto et al. 2002; Repetto and Balducci 2002). During the early 2000s, its importance was validated in routine oncology practice (Monfardini and Balducci 1999; Extermann and Hurria 2007). Some landmark studies demonstrated that CGA domains are associated with poor tolerance to cancer therapies, that they can predict mortality and influence treatment decisions, thus potentially leading to further tailoring care and improving older patients' quality of life (Clough-Gorr et al. 2010; Decoster et al. 2013; Freyer et al. 2005; Pottel et al. 2014). During the last decade, research has focused on the optimization of CGA in routine multidisciplinary cancer care (Sattar et al. 2014), on the most optimal screening tool to detect patients requiring a CGA (Kenis et al. 2013; Soubeyran et al. 2014), and on the proposal and validation of new tools for use within the assessment (Ketelaars et al. 2013; Lycke et al. 2014).

New models have been recently developed and validated to predict chemotherapy toxicity based upon geriatric assessment items. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score has been designed by Extermann et al. to anticipate the risk of chemotherapy-related hematologic and non-hematologic toxicity in older adults (Extermann et al. 2012). It takes into account the specific chemotherapy regimens to be used as well as clinical and laboratory values including blood pressure, creatinine, albumin, hemoglobin, lactate dehydrogenase and liver function tests, and assessment of functional, mental, and nutritional status including ECOG Performance Status, Mini-Mental Health Status (MMS), and Mini Nutritional Assessment (MNA). Hurria et al. developed the Cancer and Aging Research Group (CARG) model in order to predict which patients are at increased risk of developing severe or fatal toxicity from chemotherapy (Hurria et al. 2011; Hurria et al. 2016). It is based upon a number of parameters accounting for age, type of cancer, the proposed chemotherapy regimen, renal and hematologic function, hearing, and activity levels (ability to take medications, physical activity, social support), and it has been shown to be superior to

the Karnofsky Performance Status. Finally, European investigator showed that advanced disease, a low MNA score, and a long Timed Get Up And Go test are associated with a higher risk of early death (within 6 months) after initiation of first-line chemotherapy (Soubeyran et al. 2012).

A recent analysis demonstrated that a web-based symptom reporting system for adults aged 26 to 91 undergoing chemotherapy resulted in better health-related quality of life, fewer emergency room admissions, fewer hospitalizations, a longer duration of palliative chemotherapy, and a superior quality-adjusted survival (Basch et al. 2016). CGA can also be conducted in an outpatient setting also using a self-reported format, and this approach has been reported as highly reliable and may be more feasible in a busy oncology practice (Ingram et al. 2002). Along with the mailing of a questionnaire, such an approach may save a substantial portion of clinic time. Nevertheless, the use of patient self-assessment tools may be time-consuming and challenging for patients with cognitive impairment. In addition, elderly cancer patients are more likely to perceive symptoms as inevitable and as a consequence of cancer and their treatment; therefore, underreporting can still be an issue in this setting. Hence, patient self-assessment is feasible in the geriatric cancer population, yet further research is needed to allow for its wide spread adoption.

Models of Care in Geriatric Oncology

The proportion of older cancer adults is increasing, and this required more collaborative training in geriatric principles and cancer care. Nevertheless, there are insufficient geriatricians and even less geriatric oncologists to address the unique needs of this population of patients. It has been documented that in North America there are 0.5–1.5 geriatricians per 10,000 adults aged 65 and older (Hsu 2016). Therefore, these low figures make it more difficult for oncologists to refer patients for appropriate geriatric management, and they often have to act as geriatricians themselves despite having received limited training in the principles of older adults' care (Maggiore et al. 2016). The use of appropriate geriatric oncology guidelines can be helpful in such a difficult setting (Hurria et al. 2014a). Three different models of geriatric oncology care have been tested and established in different environments, as shown in Table 3: the consultative model, the shared care model, and the comprehensive care model (Magnuson et al. 2014).

In the consultative model, the oncologist refers older cancer patients to a geriatric oncology/geriatric team in order to request a geriatric assessment and consequent recommendations and to inform treatment recommendations. The geriatrician performs a CGA in a multidisciplinary setting. The advantages include the specific geriatric oncology/geriatric expertise of the team that provide guidance based on a variety of different competencies. On the other hand, this model requires a referral from a physician, and it more frequently implies a one-time visit without any possibility of longitudinal follow-up, and the interventions are often left to the treating team. Moreover, as the visits are usually long, the number of patients per clinic session may be limited. Moreover, frequently patients have to attend multiple clinical appointments, and this may be challenging for older adults. In addition, some institutions do not have a full-time geriatrician or geriatrics service.

According to the shared care model, the oncologist will refer the patient for a geriatric assessment and subsequent interventions or treatment recommendations. A CGA is performed by a geriatrician or a geriatric oncologist, and its results as well as the care plan are reviewed within an interdisciplinary meeting. Then, the geriatric oncology team collaborates with the treating oncologist and provides concurrent care across the disease trajectory. The advantages of this model include a collaborative care through the course of the disease, a geriatric expertise, and the possibility to implement interventions and recommendations over time. Nevertheless, visits may not be centralized, and patients might require extra consultations, and again this model requires a referral from a physician. Both the shared care and the consultative model require routine and strong communication

Table 3 Models of care in geriatric oncology

Model of care	Pathway	Advantages	Challenges
Consultative	• Oncologist refers patient • Reasons: CGA and intervention recommendations, treatment recommendations • CGA performed by geriatrician and multidisciplinary team	• Geriatric/geriatric oncology expertise • Recommendations from a multidisciplinary team	• Physician buy-in need to refer • One time visit • No longitudinal follow-up • Interventions often left to treating team • Long visits: Limit no. of patients per clinic session • Multiple visits and physicians for patients • Need to maintain good communication in the team
Shared care	• Oncologist refers patient • Reasons: CGA and intervention recommendations, treatment recommendations • CGA performed by geriatrician/ geriatric oncologist and multidisciplinary team • Interdisciplinary meeting to review the results and care plan • Geriatric oncology team collaborates with treating oncologist and provides concurrent care across the disease trajectory	• Collaborative care through disease trajectory • Geriatric/geriatric oncology expertise • Interventions and multidisciplinary recommendations can be implemented over time	• Physician buy-in need to refer • Visits may not be centralized • Shortage of geriatricians • Extra visits for the patient
Comprehensive	• Geriatric oncologist is the treating oncologist throughout the patient's disease trajectory • No need for additional referrals. • GA performed • Results and recommendations are reviewed with the patient • Referrals to the multidisciplinary team	• Geriatric oncology expertise throughout the treatment trajectory • Convenience: One-stop shopping (geriatrics and oncology)	• Shortage of geriatric oncologists • Complex patient population (limited no. of patients can be seen)

Abbreviation: CGA, comprehensive geriatric assessment

between the oncology and geriatric team, which may be a challenge.

In the comprehensive care model, the geriatric oncologist is the patient's treating oncologist throughout the disease trajectory. No referral is needed since this is a one-stop shop and the full care is provided by the geriatric oncologist. CGA results and the subsequent recommendations are reviewed with the patient, and referrals may be made to the multidisciplinary team accordingly. The advantages include the benefit of a continuous geriatric oncology expertise and the convenience of combining geriatrics and oncology qualifications. However, there is a shortage of geriatric oncologists, and the number of patients that can be seen may be limited due to the complexity of this population. Therefore, oncologists should be enabled to become familiar with geriatric assessment and be able to perform it following appropriate screening to identify patients requiring a more intense geriatric evaluation. A slightly different version of the comprehensive model has been developed in some centers which involves a combined geriatric oncology clinic where patients are seen by the oncologist and immediately afterward by the geriatrician or up front by a geriatric

oncologist. In these clinics the patients can be offered additional services such as physical therapy, nutrition, and psychiatry based on deficiencies identified in the assessment.

Currently the most relevant challenges across these different models include limitation of resources in terms of space, personnel, and funding. The need for buy in and champions willing to endorse such an activity and the fact that the demand may be greater than the capacity of a geriatric oncology service, due to the demographic changes are the most important challenges. As a geriatric oncology, multidisciplinary team usually involve different professionals including geriatricians and/or geriatric oncologists, nurses, social workers, pharmacists, psychiatrists, physician assistants, nutritionists, rehabilitation services, case managers, and visiting nurses. Certainly a business, financial model, and institutional resources are needed, along with more education and more research in the field. However, the biggest challenge involves choosing the right model for the right setting.

For example, in a community clinic, separate geriatrics and oncology practices may exist, possibly within a hospital-affiliated system. Therefore, the primary care doctor or the geriatrician usually consults the oncologist when a cancer is suspected or diagnosed. Patients may be already known to geriatricians, thus facilitating the use of CGA before the treatment plans. Furthermore, common electronic records may facilitate a shared care model. However, lack of communication between the two disciplines in a timely manner may be an issue and affect the decision-making process. In a setting where oncologists are familiar with geriatrics principles and geriatricians and geriatric oncologists are not available, they can directly refer patients to relevant services and professionals based on a CGA performed by themselves.

In an academic medical center, the relationship may be determined by the size of the geriatrics and oncology departments, and referrals may be made either by the geriatricians or by the oncologist according to patients' entry into the hospital system. Such an environment promotes clinical collaboration and research, although time constraints and lack of understanding between the two areas may have an impact on shared goals.

In a comprehensive cancer center, oncologists usually are the patients' primary care physicians during cancer care and a geriatric consultation may occur at any time. Screening tools can help determine which patients are at risk of increased toxicity and guide appropriate geriatrics referrals. However, the high volume of elderly cancer patients may overwhelm the capacity of a geriatrics service.

The NCCN Senior Adult Oncology guidelines (Hurria et al. 2014a) try to give the tools to the oncologists and provide guidance for the identification of patients requiring more of a multidisciplinary approach. SIOG has issued guidelines about geriatric assessment and screening tools that can provide clinicians further guidance (Decoster et al. 2015; Wildiers et al. 2014): The SIOG panel recommended the use of screening tools for busy oncology practice while emphasizing that these assessments should not replace a full geriatric assessment. In addition, there are several disease-specific guidelines issued by the SIOG regarding the management of older patients with number of cancers (Body et al. 2016; Stauder et al. 2016; Biganzoli et al. 2012; Biganzoli et al. 2016; Ghignone et al. 2016; Biganzoli et al. 2015; Morrison et al. 2015; Droz et al. 2014; Pallis et al. 2014; Papamichael et al. 2015; Aapro et al. 2011; Bellmunt et al. 2009; Launay-Vacher et al. 2007). Implementation of these guidelines in each specific disease setting would further advance and improve the care of the older population.

Survivorship Care of Elderly Cancer Patients

A cancer survivor is defined as any person diagnosed with cancer, from the time of initial diagnosis until the end of life (National Coalition for Cancer Survivorship 2016). Two thirds of all cancer survivors will be aged over 65 by 2020 (Parry et al. 2011), and they will increase to 11 million of people in the United States due to demographic changes and increased survival of older patients after cancer diagnosis. Fatigue, physical

limitations, cognitive impairment, osteoporosis, and chemotherapy-related peripheral neuropathy are cited among the clinically significant long-term outcomes of cancer in this population (Rowland and Bellizzi 2014). As the number of survivors continues to increase, guidelines specifically addressing this topic have been developed by the NCCN (Denlinger et al. 2016).

Survivorship care plans should be incorporated into clinical care and include treatment summaries, surveillance plans, and tailored lifestyle information. The older patient's needs should be assessed in the survivorship care planning process, and some of them may need a CGA in order to define those needs. Based on this, an interprofessional team can develop a plan that is individualized for each patient. It should address needs regarding exercise, nutrition, polypharmacy, comorbidities, and social support. Survivorship guidelines should always be applied to older cancer patient, who should be able to access patient-centered, non-fragmented care.

The use of survivorship care plans in elderly cancer patients may improve the quality of care and health outcomes, but the most appropriate model of care for older adults during survivorship is still debated. Models including shared care, primary care physician only, or cancer-specific survivorship clinics have been proposed. The shared care model involves different professionals whose role may vary over time based on the specific needs of each patient (Cohen 2009); nevertheless, its impact on the management of complex older patients is currently uncertain. There is considerable need for more research to understand pros and cons of survivorship care plans, as their format, timing, and outcomes are still uncertain (Mohile et al. 2016).

Unique considerations about survivorship care plans for older cancer patients include comorbidities, polypharmacy, and the heterogeneity of this population identified through the different domains for the CGA. Fatigue and weight gain may be addressed by all clinicians and prompt an appropriate referral to physical/occupational therapists for energy conservation and function maintenance as well as nutritional services (Morgan and Tarbi 2016).

Long-term effects of chemotherapy are of paramount importance for older cancer survivors. For example, peripheral neuropathy is a debilitating toxicity associated with various chemotherapy regimens, including taxanes and platinum compounds. Taxanes have been documented to cause grade 2 to 4 neuropathy rates ranging from 15% to 23% based on different drugs, schedules, and durations of treatment (Schneider et al. 2015). This side effect which may be permanent is particularly relevant to older adults as it can severely interfere with function and result in increased risk for falls. In addition, effective therapies are lacking for its treatment and prevention (Hershman et al. 2014). Elderly patients with a history of complication from diabetes, receiving paclitaxel, and those treated with a platinum agent have an increased risk or neuropathy (Hershman et al. 2016). A variety of comorbid conditions including hypothyroidism, vasculitis, infections (herpes varicella zoster and HIV), and some medications treating hypertension and hypercholesterolemia, which are more prevalent in the older population, can increase the likelihood of developing peripheral neuropathy. Monitoring of these symptoms and interventions by the rehabilitation team may help improve the management of this long-term treatment related outcome.

Anthracyclines are effective and commonly used chemotherapy agents for both solid and hematological malignancies, but they are known to cause short- and long-term cardiotoxicity, including potentially fatal congestive heart failure (CHF) (Ewer and Lenihan 2008). Older adults with a diagnosis of hypertension or diabetes and a limited cardiac reserve may be at particular risk for these long-term complications of anticancer therapy (Barrett-Lee et al. 2009), and their life expectancy is still sufficient for potential long-term toxic effects to become apparent (Aapro et al. 2011). Doxorubicin has been associated with a 29% increase in risk of CHF in a retrospective series of older patients treated for diffuse large B-cell lymphoma (Hershman et al. 2008). In

elderly breast cancer survivors, the incidence of CHF 10 years after completion of adjuvant chemotherapy has been found to be 38% (Pinder et al. 2007). Regarding breast cancer, the risk of cardiac dysfunction may be exacerbated by the sequential use of trastuzumab after anthracyclines, as this is a known side effect of such monoclonal antibody (Denegri et al. 2016). In case of aggressive lymphomas, options are more limited than in breast cancer; the use of epirubicin rather than doxorubicin, different treatment schedules, liposomal formulations, and non-anthracycline-based regimens may be possible useful approach in this population, along with a closer cardiac function monitoring. As such cardiac monitoring as part of survivorship care should be considered specifically in older patients who received these treatment regimens.

Finally, such plans should consider the specific cultural context and the beliefs, desires, and wishes of this population. The engagement of family, friends, and caregivers is relevant, as some older adults may want to include them as part of the survivorship care process. Also, the way information is delivered is important, as some of them might prefer having a paper copy of their plan rather than going paperless.

Many older adults present a myriad of health issues, and healthcare is often provided by a fragmented group of professionals. Therefore, it is important that survivorship care is well coordinated, comprehensive, and focused on the patient's goals and preferences. Prompt communication between different members of the multidisciplinary team and especially between different specialists is key, while the primary care physician or the geriatrician should coordinate and facilitate the overarching care plan. Older cancer patients should always be at the center of all interprofessional teams, and clinicians must consider that their needs may change over time and that adjustments may need to be made accordingly. Health professionals including medical oncologists, radiation oncologists, surgeons, primary care physicians, registered and advanced practice nurses, physician assistants, psychosocial support professionals, pharmacists, dieticians, rehabilitation specialists, palliative care clinicians, and research coordinators are considered integral part of the survivorship care team, along with any other specialists possibly involved in the care of other medical conditions. Additional members might include patient navigators, nurse aides, home health and home care aides, and patient advocates. Finally, caregivers, who hold the responsibility of the care of older adults at home, have also a crucial role within the team. Each of them contributes uniquely with a broad range of skills, knowledge, and expertise and should communicate clearly, educate one another, and develop clear expectations and accountability in order to deliver and promote coordinated, patient-centered care. Across the continuum from acute cancer treatment to survivorship, the team leader may change based on the patient's conditions and needs.

Integration of Geriatric Oncology into Disease-Specific Guidelines

The underrepresentation of elderly patients in clinical trials and their exclusion from studies due to variety of reasons undermine the applicability of disease-specific guidelines for the care of an older patient (Battisti et al. 2015). Trials' subjects are a selected group of healthy and fit patients whose characteristics do not necessarily reflect those of the senior adults that an oncologist meets everyday in clinic. Due to the lack of evidence to guide therapy in this patient population, significant heterogeneity exists between key opinion leaders regarding the appropriate care, which adds additional challenge to the development of guidelines. Few studies addressing the management of cancer in older adults are available and therefore included into guidelines. When such evidence is lacking, the incorporation of less robust data, including retrospective series, meta-analyses, single-institution studies, and phase II trials, may provide some more guidance for the oncologist.

Assessing whether the expected benefits of treatment are superior to the risks in a population

with a reduced life expectancy and decreased functional reserve and tolerance to stress may be challenging. Moreover, the biology of cancer and its responsiveness to therapy are different in older adults compared to their younger counterparts (Balducci 2006). In addition, elderly patients have decreased tolerance to anticancer treatments and view the benefits of therapy differently. On the other hand, age alone should not preclude patients from receiving effective treatment potentially improving their survival and quality of life (Extermann 2004). Addressing these clinical questions is challenging via guidelines, and therefore most provide the practitioner an overview of the appropriate areas that need to be evaluated, deficiencies that should be addressed and issues that must be discussed with the patient during the continuum of cancer care. In this sense, the NCCN Older Adult Oncology guidelines (VanderWalde et al. 2016) discuss more of the assessment and treatment decision algorithm in older patients rather than specific therapeutic recommendations. For example, they provide guidance on assessing the ability to make decisions and point out specific considerations for using anticancer therapies in the elderly; they also highlight the relevance of estimating life expectancy in this setting and of the assessment of the domains of CGA. These are not specific treatment guidelines, but rather more general tools to allow the oncologist to better evaluate and manage older patients, regardless of their cancer.

In summary, specific problems related to aging formed the basis for the development of the NCCN Older Adult Oncology guidelines in order to suggest to clinicians the adequate mindset and tools and ensure an appropriate evaluation and management of older cancer patients in an individualized manner. Properly selected patients can receive effective and safe cancer therapy, whereas treatments that may potentially affect their quality of life without any significant benefit in survival should be avoided. As oncologists we are tasked with determining the best mechanism to incorporate the available assessment tools and supportive care measures, to ensure appropriate evaluation of the older cancer patient and delivery of a treatment plan that would result in the optimal outcome. Additional research is needed in this field to better inform our approach to this growing patient population.

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Decision Making and Safety Issues in Older Cancer Patients

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Margot Gosney

Contents

Abstract

More older people will present with cancer and require either curative or palliative treatment in the future. A major fact that influences all treatment is the decision making that occurs prior to treatment and safety considerations that need to be highlighted. As more older individuals with cognitive impairment, multicomorbidity, and polypharmacy are treated, a balance between improved morbidity and mortality must be made against safety issues particularly when addressing treatment in the very frail elderly individual.

Keywords

Comorbidity · Safety · Decision making · Cognitive impairment · Screening · Comprehensive assessment · Quality of life · Functional status

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Introduction

The older patient with or without cancer starts their cancer decision journey by making choices about primary, secondary, and tertiary screening. For those individuals proven to have cancer, the final decision will be about place of death. It would be difficult to discuss decision making and safety issues without considering the patients' decision, the healthcare provider's decision making, and the effect of family and carers on all decisions made by both patients and healthcare providers.

All decision making needs to consider safety issues as not all older patients have the capacity to make decisions and communicate them due to cognitive or communication issues.

Screening/Prevention

Prevention has been classified into three distinct types: primary prevention aims to prevent the onset of a disease while secondary prevention aims to halt progression of a disease after it has been established. If a disease can be identified early when a patient is asymptomatic, the administration of prompt and appropriate treatment may be given which will stop the disease (Donaldson 2000). In tertiary prevention, the aim is to rehabilitate the patient who already has an established disease in an attempt to minimize residual complications or disabilities. All three are relevant to older people especially as the incidence and prevalence of cancer is increased with aging. Decision making by the patient, doctor, and other healthcare providers will influence all screening either directly or indirectly.

If 80% of all cancers are potentially preventable, the focus even for older people must be on primary and secondary prevention. Unfortunately, it is well documented that older subjects are less likely to decide to participate in screening and cancer detection. This may be due to a variety of factors which include inadequate knowledge about cancer (Young and Severson 2005; Arnold-Reed et al. 2008), a lower educational level than in younger counterparts (Sessa et al. 2008), the older individual's perception of susceptibility to cancer (Shokar et al. 2008), and fear of cancer (Domati et al. 2008). Many older individuals have difficulty differentiating between the normal changes of aging and those symptoms which may be indicative of cancer. Ethnicity (Shokar et al. 2007), fatalism (Farmer et al. 2007), and the fear of the cancer treatment have all been implicated in the older patients behavior. Although most screening is for tumors related to women, e.g., breast and cervix, men are less likely than women to participate in screening.

The general involvement of healthcare providers undoubtedly influences the behavior of older people. An illustration of this is that many healthcare practitioners are more keen to examine the breasts of an older woman than to teach the older woman to self-examine (King et al. 1993). This may be partly due to nurses not believing that teaching breast health is part of their role (Turnbull and Roberts 2004). When breast screening groups of older women, those with a low income and African-American ethnicity are less likely to be screened (Young and Severson 2005; Farmer et al. 2007; Buki et al. 2007) · The negative effect of disability on screening (Schootman and Jeffe 2003; Liu and Clark 2008; Kiefe et al. 1998) and male rather than female radiographers (Fitzpatrick et al. 2008) is predictable.

Colorectal cancer screening which affects both genders uses fecal occult blood testing. Personal factors such as "forgot to undertake the screening" and "did not notice the test in my mailbox" are known (van Rijn et al. 2008). However, the effects of physician recommendation (Sessa et al. 2008) and instruction design (Feufel et al. 2010) are factors that are easily adjusted and can increase compliance. Any negative decision making that stops or reduces screening needs to be challenged especially in older people.

Screening colonoscopy can increase life expectancy but is not entirely without risk, and safety in the most frail individuals must be weighed up. Although patient preferences (Lin et al. 2006) should be considered, the procedure can be safe and worthwhile (Syn et al. 2005) and not avoided in older otherwise fit individuals.

Older patients are less likely to be involved in colorectal cancer screening than younger individuals. When older patients received either a scripted controlled message briefly describing the role of colorectal cancer screening methods, and efficacy, or information about mortality risk reduction in either relative terms or in absolute terms it did not affect the individual's preferences for screening. However, those individuals who received the information about the efficacy of screening rated the information higher than those who received either relative risk reduction or absolute risk reduction (Wolf and Schorling 2000) . Older people therefore should have information about screening targeted to give efficacy data.

A positive screening fecal occult blood test (FOBT) should result in further investigations. Some studies have found that only 41% of patients with positive FOBT undergo a full colon examination within 12 months of the positive test. This is not associated with comorbidity and may therefore reflect that either inappropriate patients were screened in whom further investigations would not be appropriate which is less likely or that the patients subsequently declined further input. This has obvious ethical and financial consequences (Garman et al. 2006). Older patients should only be screened if further investigations or definitive treatment are appropriate and will be accepted. This decision needs to be based on extreme comorbidity but never age alone.

In a study of patients aged 67 years or older who received a diagnosis of colorectal cancer, there was a predictable decreased life expectancy in those with comorbidity. While this may reduce the rigor with which clinicians encourage such patients to undertake screening it highlights that patient informed choice is equally important in such situations (Gross et al. 2006). It is therefore gratifying to see that colorectal screening utilization in some studies is not impacted by the Charlson score of comorbidity (Fisher et al. 2007), thus reassuring us that clinical decision making still outweighs some arbitrary scores.

Decision making by clinicians is influenced by the patient in front of them. An older depressed patient is less likely to receive colorectal cancer screening recommendations than those who are younger and not depressed. Comorbidity and marital status, i.e., those who are younger and married have potentially greater social support and may therefore be more compliant with screening (Sewitch et al. 2007). Such influences are important as a doctor's recommendation has a greater influence on the uptake of the colorectal cancer screening (OR 3.86), than awareness of screening (OR 3.32), higher education level (OR 2.02), or perceived cancer susceptibility (OR 1.76) (Shokar et al. 2008). Therefore, for older people where other factors often impact on decision making, it is important for the physician to recommend such screening if the patient is robust enough for further investigations or treatment.

The benefits of prostate cancer screening are debatable, and this will therefore be discussed no further.

Lung cancer screening trials which have used low dose computed tomography (LDCT) have included present or ex-smokers (Goulart and Ramsey 2013; Pastorino et al. 2003) up to the age of 74 years, and this gives increasing benefits over the routine use of screening (Pastorino et al. 2003). Older people should therefore have equal access if they fulfill screening criteria.

A systematic review of screening intention data for over 2000 women (including data up to August 2016) showed that women who used breast cancer screening patient decision aids (BCS-PtDAs) were significantly more likely not to undergo screening mammography. This was particularly evident in women aged 38–50, and it also had a nonsignificant effect on the intentions of women between the ages of 69 and 89 years to discontinue screening. This further illustrates that while decision aids may influence the behavior of younger women it has less effect on older women (Ivlev et al. 2017). A UK study was undertaken to identify why individuals do not engage with information provided via leaflets prior to organized screening programs. The study focused on breast, cervical, and bowel screening programs. They showed that information engagement was higher for White British participants compared with other ethnic groups when considering breast or bowel screening information. However, this was not consistent for older participants. The higher

rational decision-making scores being associated with reading more of the screening leaflets which again encourages the use of such leaflets in older people although it will not exclusively influence all screening decisions in this group (Ghanouni et al. 2017).

The influence of women on men's screening behavior is still poorly understood. Populations of African descent where incidence and mortality from prostate cancer is high need to be informed about screening in order to make a decision about participation. African-American women's knowledge was low although those women aged over 51 years had a higher knowledge as did those with a family history of prostate cancer. Further information should therefore be focused on informing women not only about the benefits of their own screening but the role of screening for husbands or partners (Eastland 2017).

Ethnicity influences decision-making preferences as does marital status. In a predominantly Spanish speaking Hispanic population, the majority of individuals preferred a collaborative role in healthcare decisions about participation in colorectal cancer screening programs. Those individuals who were married or living with a partner were more likely to prefer an active or collaborative role than their unmarried counterparts. Those individuals who spoke Spanish at home were more likely to prefer a passive rather than active role. Therefore, an individual's preference for decision making is key to decisions about involvement in various screening programs (Molokwu et al. 2017).

While screening is clearly important, the factors that determine an older person's participation are complex and multiple. The healthcare provider is a major influence in the older person's decisions-making behavior and therefore ageist attitudes must be avoided. Information must be delivered in an easy to understand form.

Assessment

Patients, carers, and healthcare providers should not make decisions about cancer treatment until the patient has been fully assessed. The comprehensive geriatric assessment (CGA) is well validated and identifies frailty and its appropriate treatment (Kim et al. 2011). CGA identifies the health economics of cancer care (Ellis et al. 2011), discharge destination, and life expectancy.

Some measures of frailty are undoubtedly reversible with appropriate input and may help the clinician to make appropriate decisions about when to treat or not treat the underlying cancer.

The CGA is used in various forms and can utilize postal or computer-based self-administered questionnaires even in very elderly groups (Kalsi et al. 2014; McCleary et al. 2013). It is important that functional status, mood, cognition, and instrumental activities of daily living are documented in whatever form. Although a mini geriatric assessment has concordance with a full CGA, it does lack sensitivity when assessing the effect of comorbidity and nutritional status.

The key usefulness of a geriatric assessment is how it affects decision making and safety issues. To improve safety, the CGA should be used to predict treatment related toxicity (Versteeg et al. 2014; Hamaker et al. 2012; Baitar et al. 2014). In surgical management, it should be used to focus efforts to optimize patients (Ramesh et al. 2005; Puts and Alibhai 2015), which increases the choices available to patients and cancer specialists. Optimization also improves patient safety irrespective of whether the patient declines or accepts treatment. Although the CGA alone should not be used to make a final therapeutic decision, it can contribute (Chaibi et al. 2011) particularly when identifying survival and therefore allows more frank discussions about relative benefits and risks of decisions made (Kuo et al. 2004; Walter et al. 2001).

Hospital readmission impacts on the safety of older patients; it increases delirium and hospital associated infection and such readmissions can be predicted by CGA (Chiang et al. 2015).

With retrospective data, it is difficult to determine whether comorbidities should affect surgical treatment of cancer. For some individuals, overall decision making and safety will appropriately reduce the amount of surgical treatment after a comprehensive assessment (Parks et al. 2015).

Although there has been much progress in ensuring that older patients are diagnosed early, this is influenced by decision making at all levels. The older person themselves may delay seeking medical advice with the resultant tumor being at a more advanced stage. Once again patient ignorance, atypical presentation, general frailty, or cognitive issues may have influenced decision making regarding early presentation.

Some 30 years ago, there was a clear relationship between age of patient and stage of the cancer at diagnosis (Goodwin et al. 1986; Mor et al. 1985) and treatment received (Bergman et al. 1991; Markman et al. 1993; Silliman et al. 1989). This however is diminishing, probably as a result of better information for patients and clinicians. Better education of geriatricians about cancer management and oncologists about normal aging will further improve this (Kalsi et al. 2013). There is, however, a group that are increasing in number, i.e., patients with cognitive impairment for whom decision making and safety issues are more pertinent. This will be discussed further under cognition.

Management

Prior to much of the advocacy work undertaken in the late 1990s, many older people with cancer were receiving less definitive treatment than younger patients. Although this has now improved mainly due to the decision making of clinicians, the evidence base for these decisions should still be cautiously considered. Patients over the age of 75 years are grossly underrepresented in clinical trials not only in absolute numbers but also in proportion to the incidence and prevalence of different tumors. There is a clear linear relationship that shows participation in cancer trials being inversely related to age (Shokar et al. 2008). The decision making of patients which results in further underrepresentation of certain ethnic groups and women needs further exploration as this finding is not exclusive to the US or the UK (Yonemori et al. 2010; Townsley et al. 2006). Exploration of this negative decision making has identified "anxiety about entering a clinical trial," "not being interested," "no time," or "too sick" as reasons given by older patients for not wishing to be included in clinical trials (Puts et al. 2009).

The ACTION trial which sought to provide evidence on the effects of chemotherapy in women aged over 70 years only recruited four patients in 10 months despite being a well-designed randomized controlled trial. Clinicians were unable to convince older patients to accept randomization, and the trial was terminated early (Leonard et al. 2011).

Outside clinical trials, safety issues about cancer treatments are still expressed by older individuals. Some older patients believe that cancer treatment is worse than the disease itself, although some older individuals do experience less emotional distress than their younger counterparts.

Some older women assume a more passive role in treatment decision making. In breast cancer, older women considered that stage of disease, likelihood of cure, and treatment options are less important than self-care issues. These individuals may need additional support if treatment is being offered and subsequently accepted.

Decision making is affected by how patients receive the cancer diagnosis. Although the relatives of older patients with cancer often wish that the diagnosis is not disclosed (Ozdogan et al. 2004), patients want to be informed even in extreme old age (94 years) (Ajaj et al. 2001).

Any management decision making by patients can be considered in three areas: the actual, the preferred, and the perceived role. Although individual patient preferences regarding the information given to support decision making is difficult to assess, the clinician should attempt to determine what the patient really wants and needs. Patient education should always be tailored to the individual cancer patient (Posma et al. 2009). Older cancer patients predominantly prefer to receive less information about both their illness and its potential treatment and are more likely to assume a less active role in treatment decisions (Pinquart and Duberstein 2004). The clinician and family members must not use this to reduce the involvement of the patient in the decision-making process, but deliver information in a more appropriate way.

During the early 1980s authors became interested in assessing a patients preferred level of participation in decision making. It soon became obvious that preferred and actual levels of patient participation were different and while we have come some way to ensuring that these are more closely matched it is now important that not only actual participation but perceived involvement in decision making is to be understood to increase satisfaction particularly among older adults (Tariman et al. 2010).

Older patients in contrast to younger ones have more difficulty in processing information and then remembering it following consultation. Information given to older people must be reinforced and delivered in a way that increases patient participation in decision making (Posma et al. 2009). Indeed when patients were asked their views regarding healthcare, they rated safety, expertise, performance, and attitude of physicians and nurses as the most important issues in cancer care (Wessels et al. 2009) . Puts et al. found in a systematic review of 38 studies that the important factors for the older person when accepting treatment were convenience and success rate of the treatment; understanding the necessity of treatment; trust in the physician; and when directly following the physicians recommendation. In contrast, those factors considered important when declining treatment included: concerns about discomfort of the treatment, fear of side effects, and transportation difficulties (Puts et al. 2015).

Communication must be tailored to improve the patients understanding of the risk and benefit information and how this affects decision making. Presenting absolute risks, i.e., using frequencies, rather than presenting relative risks, is important for patients. Clinicians must identify how treatment changes risks from preexisting baseline levels. The use of pictures is mandatory in some clinical situations (Fagerlin et al. 2011).

The role of relatives in decisions to limit treatment is fraught with difficulty. One third of relatives act against the known or presume wishes of patients, and this occurs predominantly when relatives hold views that contradict known patient preferences (Hauke et al. 2011).

The initial stages of cancer treatment are very focused on the underlying medical condition. For those older patients with complex health and social care needs, decision-making processes are more haphazard and can result in less effective and workable treatment plans particularly when clinicians have targeted deadlines to deliver care (Bridges et al.2015).

Information is critical for the older patient to ensure optimal care. In a group of 133 patients with cancer who had a mean age of 79.6 years, all patients wanted full information. About 74.2% wanted to participate in decisions about their care although 87.2% would designate a family member to serve as a surrogate in life-threatening situations and of these 15% had already designated a surrogate. When comparing this group with cancer to an age-matched control group without cancer different themes emerged. Those patients with cancer wanted more information particularly in life-threatening situations. Those patients who had children, a higher mini mental state examination (MMSE) score, being of a younger age, without cancer, or being cancer free were all factors independently associated with patients wanting their informed consent to be obtained for all interventions. While a higher MMSE, being younger and without cancer or being cancer free is somewhat predictable, having children may not be (Paillaud et al. 2017).

Comorbidity affects treatment decisions and mortality. Some of the observed differences in breast cancer specific mortality may be due to less extensive treatment as well as other factors. It is therefore important that comorbidity is recorded and acted upon (Berglund et al. 2012). Comorbidity may decrease the likelihood of cancer screening recommendations although conversely some patients with comorbidity with increased preventative services have earlier cancer screening resulting in earlier stage of diagnosis (Gonzalez et al. 2001) although this is not consistent across all studies.

During multidisciplinary cancer team meetings, comorbidity undoubtedly affects treatment decisions. When information about comorbidity is lacking, the MDT delays making recommendations and may become more conservative. While this may

be appropriate, there is little evidence about how comorbidity is considered or impacts on decisions in busy MDT's (Stairmand et al. 2015).

Chemotherapy Safety

There is conflicting data about the willingness of older patients to accept potentially toxic chemotherapy. Yellen et al. (Yellen et al. 1994) assessed patient's willingness to potentially accept toxic chemotherapy to improve survival by the use of various structured scenarios. They found almost equal numbers of young and older patients willing to choose chemotherapy in different scenarios although the older patients when choosing a more toxic regime over a less toxic alternative required a greater survival advantage before being willing to have such a therapy. This has decision making and safety implications.

Older people are less likely to enter clinical trials, thereby reducing the knowledge base particularly around chemotherapy. Older people have altered pharmacokinetics and pharmacodynamics and for some chemotherapeutic agents this will pose particular issues. Some clinicians will decide to reduce the drug dosage, its frequency, or the number of cycles administered. This is not universally supported by evidence and though it may improve tolerance if it results in lower response rates with worsening survival this is neither scientifically nor morally justifiable. Repetto in 2003 considered that age was a risk factor for neutropenia as a complication of chemotherapy and advocated the use of colony stimulating factors in older patients (Repetto 2003). Such factors and other support mechanisms are now mainstay therapies for all ages.

The risks and benefits of using erythropoietin to combat anemia needs to be fully considered (Massa et al. 2006; Bohlius et al.2009), and decision making about concomitant medication and potential drug interactions should be considered by the clinician treating the older cancer patient (Lord et al. 2010; Riechelmann and Del Giglio 2009; van Leeuwen et al. 2010).

Published narratives help us to understand some of the difficult decision making around adjuvant chemotherapy for those requiring it for both curative and palliative intent. Adjuvant chemotherapy is likely to benefit patients only with a life expectancy greater than 5 years and mortality benefits become less pronounced with increasing age. The older patient wants chemotherapy as long as the side effects do not reduce the quality of life or the ability to function independently. The specific barriers that the older person experiences such as sensory and memory problems and poorer health literacy (Johnson 2012) must be considered by healthcare professionals.

Cancer Trials

If older people are to enter into clinical trials, appropriate adaptations will have to be made to ensure that patients are not disadvantaged. This will include choosing therapies that have a low underlying potential for drug–drug interactions assessments of bone marrow reserves, and central and peripheral nerve function to avoid treatment related adverse effects. For those with hepatic and/or renal dysfunction, necessary drug dose adjustments can be made for those agents where pharmacokinetics are affected (Aapro et al. 2005).

While many older people when asked are willing to consider participation in cancer clinical trials, however, older patients do not appear to actively seek clinical trials and even smaller numbers are informed of the availability of clinical trials (Townsley et al. 2006).

When older people are recruited to clinical trials, retention is important and may be affected by the need to have additional tests or interviews although most patients enjoy such participation (Puts et al. 2009).

End-of-Life Care

Advanced care planning is very important before individuals become unable to make decisions for themselves. When considering the quality of life assessment of individuals aged 70 years or over and their desire for specific interventions four particular scenarios (a current health state, mild to moderate stroke, incurable brain cancer, and

severe dementia) were studied. The individuals identified a surrogate who was then asked to predict the older individual's responses. The surrogate and the older individual had significant differences in their quality of life ratings. The surrogate over estimating the quality of life of the older adult compared to the older adults self-assessment. The difference in these ratings then predicted the desire for life-sustaining interventions in hypothetical situations. The greater discrepancy in the quality of life ratings, the more likely the surrogate was to over-estimate the older adults desire to be treated. This indicates that many family members find it difficult to make decisions for their loved ones and this can result in over treatment of the older individual compared to their desires (Bravo et al. 2017a).

To understand public preferences for care toward the end-of-life a large cross-sectional study of the general public in the UK and the USA sought to identify decision making when a patient had deteriorating capacity. There were no significant differences between the UK and the USA but the preference for measures to sustain life at all costs peaked for the scenario where the patient had short-term memory loss. As the neurological condition deteriorated, respondents selecting "measures to help me die peacefully" increased from 3.9% to 37%. The predictors of who would choose "measures to help me die peacefully" at any stage were a previous personal experience of the chosen scenario or increasing age. The latter finding increasing across the decades. The negative predictors of choosing "measures to help me die peacefully" were living with children or being of black race/ethnicity. A significant number chose preservation of life at all costs even in those with end stage dementia. This may affect decision making for those patients with coexisting cancer and dementia (Clarke et al. 2017) and others have reported similar findings (Bravo et al. 2017b) .

Surgery

The older cancer patient who is about to consider surgery needs adequate risk assessments, as complications in hospital are associated with increased death during that period of hospitalization (Marrelli et al. 2000). The risk assessment is undertaken in order to fully explain the relative benefits and risks of undertaking such surgery (Marrelli et al. 2000; Ramesh et al. 2006; Donati et al. 2004; Monk et al. 2005; Khuri et al. 2005; Manku et al. 2003; Seymour 2008). Better predictions can be made by the use of preoperative cardiopulmonary exercise testing (Lai et al. 2013) and cardiovascular interventions such as perioperative beta blockade (Bangalore et al. 2008). Pulmonary complications can be reduced by preoperative intensive inspiratory muscle training which improves pulmonary safety after surgery (Dronkers et al. 2008). Postoperative delirium is predicted by increased blood pressure fluctuations rather than absolute or relative hypotension during surgery (Hirsch et al. 2015). The older cancer patient would therefore be best treated using evidence-based recommendations such as those developed by SIOG (Audisio et al. 2004).

Quality of life is affected by a number of issues including physical activity that are important to patients. Therefore, any surgery that results in reduced physical activity can impact on the patients' quality of life (Santa Mina et al. 2010).

The most appropriate treatment for operable breast cancer is surgery. Only those patients with reduced life expectancy or significant comorbidity should be treated with primary endocrine therapy. Guidelines make it clear that age should not be a factor in this decision. In a 2017 study, a discrete choice experiment was used to determine which key variables impacted on treatment decisions. Overall age, comorbidity, cognition, functional status, and cancer size were all independently significantly associated with treatment preference. However, only comorbidity, cognition, and cancer size correlated with a preference for primary endocrine therapy. Therefore, while age did not influence the use of primary endocrine therapy it was a factor when healthcare professionals were making decisions for an elderly population (Morgan et al. 2017). In a similar study of 106 surgical, 37 radiation, and 31 medical oncologists who provided treatment for older women with breast cancer a variety of scenarios were presented. Altering the age from 84 to 76 increased the recommendation

for breast conserving surgery plus radiotherapy (73 vs. 56% P = 0.001). Adjuvant chemotherapy for an otherwise healthy older women with triple negative breast cancer was considered by 83% of the participants. Appropriately, performance status influenced specialist treatment recommendations but perhaps inappropriately also patient age did as well (Hamelinck et al. 2017).

Patient choice between surgery and primary endocrine therapy for early breast cancer was most influenced by the impact, safety, and efficacy of treatment with patients expressing least interest about cosmetic outcomes after surgery. The patients on the whole preferred information to be provided verbally by doctors and nurses supported by booklets and had little interest in technology-based sources of information (Burton et al. 2017).

Qualitative data also can be used to explore the experience of decision making in older women with invasive breast cancer. Intrapersonal and interpersonal communications challenges (emotional distress, patient provider communication, "making it personal," access to information) are important. If inter professional models of care can be utilized, they may minimize existing barriers to information provision and empower patients to make decisions consistent with their individual wishes (Campbell-Enns et al. 2017).

Radiotherapy

For men with newly diagnosed non-metastatic prostate cancer, black men were significantly more likely to receive radiation therapy and significantly less likely to receive radical prostatectomy. Irrespective of the treatment received, black men received aggressive therapy at rates approaching those of the white men (Rose et al. 2007). Age did not appear to influence such therapy.

When studying the needs of older women with early stage breast cancer who require decision making about radiation therapy, participants viewed benefits and side effects to be the most important factors and more than 96% of participants indicated that they were the main decision maker before receiving radiation therapy (Wang et al. 2017).

Healthcare Professionals Treatment Decision Making

A number of individuals are involved in treatment decision making, and it is vital that ageist attitudes do not creep into this process.

Practicing US medical oncologist's were randomly assigned one of two scenarios with identical vignettes apart from the age of the patient. Intensive therapy was significantly less likely to be recommended for the older than for the younger individual despite the remaining features being identical. This occurred irrespective of the stage of the tumor. While the oncologist did identify that patient age was an influence on treatment choice, they were more likely to cite that it was the performance status rather than the age that determined their treatment decisions (Foster et al. 2010).

There is some evidence that primary care providers in the US are perceived to contribute in the older person's decision making. Such engagement is associated with higher decision satisfaction when compared with lower engagement with primary care providers. However, this involvement did not improve a patient's appraisal of their own individual decision making (Wallner et al. 2016).

Qualitative studies including physicians, patients, and relatives before the treatment of colorectal or pancreatic cancer identifies the complexity of some decision making. Authors encouraged the role of primary care physicians and recommended dividing decision making into more sessions. This may be both beneficial in the decision- making process but also helps emphasize the patient's own responsibility in decisions. This, however, may delay treatment and this was not emphasized by the authors (Geessink et al. 2017).

Cognition

With increasing survival of older patients with a variety of comorbidities, cancer is increasingly likely to be diagnosed in those with cognitive

impairment. Unfortunately, much of the data that relates cognition to diagnosis, treatment, and outcomes is anecdotal and complicated by other comorbidities. Van Deudekom reported that only two of 31 articles reported a cognitive test when assessing outcomes from the treatment of head and neck cancer. Nevertheless, cognitive impairment was associated with adverse outcomes. Of greater concern is that none of the included studies addressed frailty or objectively measured physical capacity using well-documented grip-strength, balance test, or indeed gait speed (van Deudekom et al. 2017). The use of the CGA to support clinical decision making and personalized care plans of the older person with cognitive impairment is essential (Pilotto et al. 2017).

Much further work is required to ensure that older patients have safe, effective treatment that is evidence based. Comorbidity including moderate cognitive impairment should not stop palliative cancer treatment. Overall, what is lacking in this group of individuals is the evidence base. Clinicians must endeavor to recruit such patients to add to our knowledge base.

Cross-References

- Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- Comorbidity in Aging and Cancer
- Digestive Symptoms Control and Nutrition Issues in Older Cancer Patients
- Drug Interactions in Aging and Cancer
- Frailty in Cancer Patients
- Geriatric Interventions in Oncology
- Geriatric Screening in Cancer Patients
- Normal and Abnormal Aging (General Perspective for the Oncologist)
- Pharmacology of Aging and Cancer
- Principles of Cancer Surgery in Older Adults
- Principles of Chemotherapy in Older Adults
- Principles of Radiation Therapy in Older Adults

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Improving Communications with Older Cancer Patients

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Abstract

Currently, older adults (age 65 and older) represent about 62% of cancer survivors and by 2040, it is anticipated that 73% will be 65 years or older. The changing demographics of the older cancer population reflect, in part, a growing multicultural, multilingual, and immigrant population. Effective communication is an essential cornerstone of cancer care and influences patient and family experiences and outcomes across the care continuum, from screening and adherence to prevention, to decision-making, adaptation and acceptance of illness and treatment regimens, to resolution of symptoms and rate of recovery, just to name a few. Also, effective communication impacts interest and participation in clinical trials and research and is necessary as clinical trials increase in their complexity in study designs (e.g., multistage adaptive designs) and precision and genomic considerations. Fundamental to effective communication for an increasingly older diverse cancer population, including many whom are socially isolated or marginalized, is attention to culture and literacy and intersectional perspectives to advance health equity. This chapter highlights techniques and skills to improve communication with older patients within the oncology setting, and emphasizes the value of recognizing and appreciating cross-cultural similarities and differences for strengthening acceptable therapeutic care, support, and education. The importance of warm, empathic, and clear interactions also is reinforced to aid in a patient's healing, well-being, and quality of life. Finally, the **REAL** (**r**elatable, **e**ngaging, **a**ctionable, and **l**iteracy-friendly) framework is presented as a useful approach and tool for delivering cancer information that resonates with the everyday lives of patients and their families.

Keywords

Communication · Health literacy · Culture · Language · Patient-centered Care

Introduction

"Talking and listening to patients" is performed more often than any other single medical procedure (Fallowfield and Jenkins 1999). Patients rely upon effective communication to gain critical information about health promotion/disease prevention, treatment and care coordination, cure (when possible), and palliative/hospice care (when cure is not possible). Effective communication is crucial as patients cope with their diagnosis, understand what it means, and figure out how to best navigate a course of treatment (Prip et al. 2017). Three core functions of effective communication are the demonstration of empathic behavior, promotion of information processing, and facilitating decision-making (Van Vliet et al. 2015). Further, a therapeutic relationship requires a commitment to recognizing, appreciating, and negotiating patients' ethno-cultural beliefs and values and responding appropriately to varying learning styles and preferences (Green et al. 2002; Surbone 2006a, 2008; Surbone et al. 2007). At the heart of effective communication is a provider-patient relationship that is deeply rooted in culturally caring, sensitive, and clear communications.

Consider the following scenario:

What might be the most effective way to communicate with an elderly Hispanic patient (71 years) who presents at a cancer clinic as part of follow-up

from a free screening program for colorectal cancer? As background, Mr. Lopez recently arrived from Puerto Rico (relocated due to a hurricane), speaks only Spanish, has completed 8 years of schooling, worked for 25 years as an agricultural/farmworker, and currently lives with his daughter in a rural setting in Southeast Florida (about 3 h from the cancer clinic). He has secured a part-time job at a local strawberry farm. He is a grandfather of six children and the patriarch of his family (his wife died 2 years ago), and he derives great enjoyment from his family. Upon his arrival Florida, at the urging of his daughter, he took part in a free health screening (including colorectal cancer screening) and was navigated to a nearby clinic by a bilingual community outreach worker for follow-up care due to an abnormal fecal immunochemical test (FIT). While unfamiliar with the health care system, he trusts the community worker who helped navigate him to colonoscopy due to an abnormal FIT.

. . . What is Mr. Lopez's understanding of what "abnormal" means? What might a colonoscopy mean to him and to his family? How will he successfully negotiate the health care system (resources, transportation, finances, language, etc.) in order to complete a colonoscopy? What can make this a successful encounter with the gastroenterologist? If the colonoscopy shows cancer and he requires follow-up care and treatment, what treatment options are available? What might the demands of cancer care and treatment mean to his everyday life? What can be done to promote effective communication with the oncologist and treatment team at the cancer center? How can information be provided in understandable, language-appropriate, and acceptable terms and be consistent with his values, beliefs, and obligatory sense of family responsibility that has recently changed due to situational factors?

Such questions remind providers of the importance of effective communication in cancer care and the need to recognize the numerous factors including culture and literacy that can influence the patient-provider relationship and outcomes.

Demographic Shifts in Health Care

While the overall growth in population from 2010 to 2050 is projected to slow down, a large shift is expected toward the oldest age groups, both globally and in the USA. According to a 2015 aging report commissioned by the National Institute on Aging produced by the US Census Bureau, 8.5% of people worldwide (617 million) are aged 65 and over today (He et al. 2016). He and colleagues (2016) reported that projections over the next three decades for America's 65-and-over population will nearly double – from 48 million to 88 million by 2050. Moreover, it is estimated that 62% of all cancer survivors are older adults, and this number may even reach 73% by 2040 (Bluethmann et al. 2016).

Nearly 59 million immigrants have arrived in the USA over the past 50 years, mostly from Latin America and Asia. This accounts for a near-record 14% of the country's population being foreign-born compared with just 5% in 1965, with the majority of the US population's increasing growth over the upcoming decades being related to new Asian and Hispanic immigration (He et al. 2016). In particular, the changing demographic shift associated with an increasing number of racial/ethnic minorities, foreign-born, and new immigrants represent important subpopulations of older adults that are at risk to encounter disparities and potentially suboptimal care. The persistence of health disparities is especially striking among older adults and racial/ethnic minorities and requires comprehensive, highly competent, and strategic approaches to ameliorate such injustices (Williams 2007). The populations shifts bring to light the central imperative that all people should have equal access to high-quality cancer care, treatments, and cutting-edge cancer clinical trials. Inextricably linked with culturally effective communications for a growing and diverse older vulnerable population is making *health equity* part of a larger social justice mandate (Alcaraz et al. 2017; Surbone and Halpern 2016). As such, insights into a patient's worldview are an instrumental step toward effective communication.

Culture, Worldview, and Effective Communication

Communication is contextual and providers need to have knowledge of the concept of culture and its impact on their relationships with patients. As Surbone (2008) relates, each clinical interaction should be viewed as an exercise in cultural effectiveness that aims for understanding,

transparency, and truth-telling. Further, Kagawa-Singer et al. (2014, 2016) describes culture as a socially constructed set of dynamic and ecologically based interrelated elements that function together as a living, adapting system. A cultural group shares an "identity" that shapes norms, values, goals, expectations, perceptions, and behaviors. In short, culture informs health and human behavior, allows people to see the world through their life experiences and gives meaning to their everyday lives.

Kleinman (1978), an anthropologist and psychiatrist, offers additional insights into understanding how culture, religion, ethnic beliefs, and practices influence healthcare-seeking behaviors, since health care systems are both social and cultural in nature. He relates that clinical realities are often culturally constituted and vary cross-culturally across the domains of health care (communication, spirituality, death/dying, etc.). They often are heavily rooted in a patient's explanatory model. *But what is a patient's explanatory model?* Quite simply, it represents a person's notions and ideas about health and disease. For example, Mathews et al. (1994) reported that many Black women who presented late with advanced breast cancer disease came to terms with their illness by drawing on a model of health that emphasized balance in the blood, popular notions about cancer, and biomedical conceptions about breast disease and treatments. Too often, providers felt that women did not use screening services and delayed treatment because they lacked knowledge, were too poor to access care, or were excessively fatalistic. Trying to eradicate "fatalism" by giving them materials obviated the need to understand their beliefs and values within a wider sociocultural context. Hence, the potential positive or supportive aspects of cancer "fatalism" beliefs are not well-appreciated when providers do not consider the fuller social context. Another example by Braun et al. (2014) relate that some Hawaiians believe that good health means a balance among one's responsibilities to the group, the land, and the spiritual world. Or as Venkatasalu (2017) recounts in her examination of older British South Asians' views on dying at acute hospitals, many patients felt that dying in a hospital versus home evokes feelings of guilt among family members and represent missed family responsibilities. As such, these varying perspectives illustrate how important it is to have a biomedical lens that considers a "patient's worldview" in a clinical interaction. These perspectives remind providers to delve into what patients and family members believe and experience both when healthy and when ill. For example, broader questions about health and illness might be: *What does good health look like for you? How are health decisions made in your family and who makes treatment decisions in the family? What role do home remedies play in your recovery? What roles do vs. does faith or religion play in your life and medical decision-making? What is the role of family, church, and/or community toward good health or toward a good death? Where or what do you turn to for support in times of poor health?*

Improving patient-provider communication includes gaining an appreciation and awareness of how culture and worldview influence patients' expressions of their clinical condition. This, in turn, helps to illuminate an understanding of patients' beliefs about their health and illness. It also helps to ascribe personal and social meaning attached to an illness (cancer) as well as expectations about what will happen, what will be done, and the expected therapeutic goals. Incorporating and/or adapting the following questions into patient discussions may provide helpful insights about patients' everyday lives and help understand patients' cultural meaning of health and illness (Kleinman et al. 1978; Kleinman 1980) (See Table 1). Depending on the clinical situation, the wording and ordering of questions may vary.

Culturally effective health care providers demonstrate a number of humanistic and empathic characteristics as summarized by Meleis (1999). First, they value diversity. They are not drained by the constant attempt to understand and interpret meaning and symbols but rather are highly energized by these variations in human behavior. Second, they show expert assessment and communication skills that expertly decipher and deconstruct different and similar patterns of responses that move conversations toward what matters most (as noted in Table 1). Third, they are

Table 1 Examples of questions to elicit patients' meaning of health and illness

Key point	Question(s)
"Comparison between patient and doctor explanatory models should center on the crucial points requiring patient education, clear clinical explanation, or frank negotiation" (Kleinman et al. 1978, p. 257)	• *What do you think caused your problem?* • *Why do you think it started and when did it?* • *What does your sickness/problem do to you? How does it work?* • *How severe is your sickness? Do you think it will last a long/short time?* • *What kind of treatment do you think you should get?* • *What are the most important results you hope to get from treatment?* • *What are the biggest problems your illness has caused for you?* • *What do you fear most about this problem/illness?*

aware of the diversity and complexity of communication patterns and how language and communication are important to the "trustworthiness of the relationship." They recognize that marginalization and noninclusivity increase health risks for patients and their family members, and that the expertise of insiders in the culture or social network enhances therapeutic relationship and outcomes. Finally, they acknowledge and appreciate similarities *and* differences across multicultural groups and do not stand for inequities and injustices. Damaskos et al. (2018) relate that providers have a deep obligation toward the practice of cultural humility, self-reflection, and patient-centered care. As a result of the delivery of culturally competent care and effective communication, providers too can gain a deep personal sense of privilege, honor, and professional fulfillment (Surbone 2008).

Impact of Effective Patient-Provider Communications

Patients and their family caregivers commonly express the need for improved communication with their providers (Puts et al. 2017). Effective communication has been shown to influence rates of emotional and physiological health, patient recovery, pain control, adherence to treatment regimens, improved psychological functioning, decision-making about treatment options, consequences of treatment (or no treatment) and facilitates supportive and psychoeducational care (Cousin et al. 2012; Gilligan et al. 2018; Karnakis et al. 2016; Prip et al. 2017). It is linked to increased rates of cancer screening (Carcaise-Edinboro and Bradley 2008; Underhill and Kiviniemi 2012), acceptance of recommended treatment including chemotherapy (Puts et al. 2015, 2017), end-of-life preparation (Wentlandt et al. 2012), and patient satisfaction and overall enhanced quality of life (Baker et al. 2016; Ernstmann et al. 2017). Furthermore, it has been observed that many older cancer patients experience worse patient-provider communication than their younger counterparts (Shelton et al. 2013). Such differences in the quality of various facets of patient-provider communication (e.g., respecting, listening, explaining, and time spent with the patient) have been noted based upon race/ethnicity (White-Means and Osmani 2017). These reports further underscore the importance of developing strong patient-provider relationships through culturally competent communication.

The importance of culturally effective communication has been further reinforced by the 2017 release of the American Society of Clinical Oncology Consensus Guidelines for Patient-Clinician Communication (Gilligan et al. 2017). This document summarizes best practices for cancer clinicians and offers primary guidance and strategies for implementation across a number of clinical domains (e.g., treatment selection, end-of-life, etc.). These guidelines include a number of recommendations to enhance communications and can be reviewed at: http://ascopubs.org/doi/full/10.1200/JCO.2017.75.2311. Moreover, the Accreditation Council on Graduate Medical Education (http://www.acgme.org/) and the American Board of Medical Specialties (http://www.abms.org/) identify interpersonal communication skills as a clinical competency (ACGME Home 2018). Taken together, these professional guidances help

in shaping competency standards for current oncology providers and the next generation of oncology practitioners, an important measure towards improving effective communication with older cancer patients.

Factors That Influence Culturally Effective Communication

What providers communicate – or believe that they are communicating – and what a patient (or a family) hears is not always identical. As such, culturally effective communication involves getting to know patients as individuals – beyond their diagnosis and medical history – and assessing their goals, information needs, priorities, wishes, and values. It requires a keen awareness of the factors that play a role in communication patterns and recognizing that effective communication is an important part of the healing and the therapeutic aspects of cancer care. Among identified influencing factors of communication are the sheer physical aspects of cancer itself (e.g., pain, suffering, physical changes, disfigurement, etc.), and the multiple psychosocial and emotional aspects and responses to cancer as a potentially life-threatening disease (e.g., anxiety, confusion, uncertainties, depression, changes in familial roles and dynamics, etc.) (Baile and Aaron 2005; Finkelstein et al. 2017; Surbone 2006b, 2008). Furthermore, for many older cancer patients, due to the complexity of health or other multiple comorbid problems and polypharmacy, they may interact more frequently with oncology team members (Armstrong and Holland 2004; Baile and Aaron 2005; Finkelstein et al. 2017; Liang et al. 2006). Such multiple health concerns coupled with cancer concerns and fears can make patients feel quite overwhelmed and ultimately result in feelings of increased vulnerability and loss of control (power shifts) (Sattar et al. 2014). Moreover, the metaphorical value that is often placed on a cancer diagnosis (which might be negative in some instances) plays a crucial role in patient-provider communications and is notably important in many cultures and contexts (Surbone 2006b). To enrich interpersonal interactions, Cain et al. (2018) emphasizes the need for personalization of care and understanding and consideration of patients' "individual circumstances and life histories."

Importantly, there are factors that detrimentally influence effective communications including ageism, classism, discrimination, racism, prejudice, social stigmatization, lack of understanding of the impact of historical trauma, stereotyping, and negative depictions of the elderly (Surbone 2008). These very real risks may reflect providers' and researchers' biases (explicit vs. implicit) and intrinsically call for ongoing self-awareness and reflection (Banaji and Greenwald 2016; Braun et al. 2014; Cain et al. 2018; Herrera et al. 2010). To further broaden providers' cultural relevance and competence and transdisciplinary expertise, specialized and education and training is needed as well as a commitment to mentoring others to develop and share cultural expertise across all sectors of cancer care. This latter point reinforces a strategic need for targeted workforce development via continuing education to raise cross-cultural communication skills and knowledge to advance health equity efforts (Alcaraz et al. 2017).

Intersectionality

Given the proliferation of marked demographic and social change in our society, there are many population subgroups characterized by multiple factors or socio-behavioral identities – *intersectionality* – wherein individuals may be racial-ethnic minorities, older, and self-identify as sexual and gender minorities, for example. These overlapping social identities (intersectionality) represent multiple concurrent (co-occurring) experiences and conditions that coexist and interact to produce complex context that may hinder communications, self-care, or effective care delivery (Evans et al. 2017). Among some older populations such as Blacks/African Americans, historical transgressions in health care may perpetuate mistrust and foster critical biases and failed communications, particularly when conveying complex or new topics such as precision medicine, genomics, or biobanking research (Kraft et al. 2018).

Acculturation

There is increasing cultural diversity of the American older adult population growing beyond the predominant European-centric culture, with exponential growth of the older populations segments from other racial/ethnic groups (Brettell 2007). Level of acculturation to USA culture has also been found to influence health care communication and access to cancer care (Andreeva et al. 2007; John et al. 2005; Katz et al. 2017; Lee et al. 2014; Monroe et al. 2003; Nasseri and Moulton 2011; Nguyen et al. 2014). For example, Latinas diagnosed with breast cancer with low levels of acculturation have been found to experience decreased likelihood of high-quality communication with their medical oncologists and surgeons (Katz et al. 2017). Furthermore, acculturation has been associated with willingness or lack thereof to undergo cancer screenings among diverse groups, including Vietnamese Americans (Nguyen et al. 2014). On the other hand, length of time in the USA (more than 20 years compared to less than 10 years) has been positively associated with likelihood of completing breast, colorectal, and cervical cancer screenings among Vietnamese, Chinese, and Korean Americans (Lee et al. 2014).

In addition, immigration to the USA has been associated with incidence of some cancers; the direction of this association depends upon country of origin and length of time in the USA (Andreeva et al. 2007; John et al. 2005; Monroe et al. 2003; Nasseri and Moulton 2011). Thus, an essential aspect of patient-provider communication is learning about their patient's backgrounds and experiences to fully understand their explanatory models of health and illness within the context of their lived experiences.

Even within the Black/African American population there are potential subgroup differences in worldview about disease etiology and management when comparing African Americans (born in the USA) with immigrant Blacks from the Caribbean, for example (Gwede et al. 2010, 2011). In addition, a combination of religious, spiritual perspectives, and historical experiences with segregation and discrimination also have molded the unique cultural and life perspectives of African Americans that ultimately shape communications and interactions with the health care system (Katz et al. 2017; Penner et al. 2016). Furthermore, one of the contributions of the family reunification amendment (Maddali 2016) has been increased diversity due to immigration of older adults (parents) joining their children in the USA (Brettell 2007). The influx of older immigrants, especially from Asia, Africa, Caribbean, Latin and South America (rather than Europe), has brought into play many new diverse cultures and deepened worldviews.

Communications, interactions, and rooted beliefs about health and disease converge deeply in the context of cancer care (Katz et al. 2017; Lillie et al. 2014; Hawley et al. 2008). Furthermore, the demographic diversity of the older American population includes growth driven by the aging population of Native American, Hawaiian, and Alaskan Natives, as well as immigrant Asians, Hispanic/Latinos, and immigrant Blacks from the Caribbean, Latin America, South America, Europe, and Africa. Along with their rich cultures and communications styles, immigrant populations may take longer to assimilate to the mainstream ways of the USA, and thus, may experience difficulties when seeking health care not only because of language or communication differences (in many cases), but also due to differing perspectives on cancer, and help-seeking. For example, in the arena of cancer screening and early detection, some individuals may not value the goals of these test methods for finding cancer early depending on their experiences. Some new immigrants may not even have heard of the word *cancer.* Also, some may believe that most cancer types cannot be detected early or that early treatment can enhance the chance for cure (Gwede et al. 2011).

Regardless of their prognosis, older oncology patients (and if patients desire, or if, they completely lack the ability to engage) their family caregivers should be involved in the decision-making process. Patients should be given honest and timely information about their diagnosis, prognosis, as well as the risks and benefits of various treatment options to make a well-informed decision. For patients with a terminal

illness, providers should be aware that what constitutes a "good death" in one culture may not necessarily carry over to other cultures. In addition, shifts in beliefs about end-of-life can occur based upon increased acculturation (Mori et al. 2017). As such, the growing need for clear communication in light of the increasing cultural and linguistic diversity in patient populations is a central imperative. In the next section, a number of *essentials of communication* are presented to enhance positive interactions for therapeutic benefit among older cancer patients.

Essentials of Communications to Promote Effective Patient-Provider Relationship

There is insufficient space in this chapter to fully discuss all the potential differences in communication style among all the cultures and geographic regions of the world. Since communication norms vary both between and within cultures, it is important to not stereotype patients based upon their background characteristics, including age. While there may be some cultural differences in communication style, most cancer patients, regardless of age, greatly appreciate providers who listen to them and demonstrate respect, warmth, empathy, and inclusivity (and potentially, their family) in decisions about their care. The following suggestions may seem rather straightforward but serve as important reminders especially in light of a technology-driven environment. These include: *introducing yourself, setting an agenda for the visit collaboratively with the patient, sitting down, facing the patient, making consistent eye contact, using active listening skills, asking open-ended questions, demonstrating respect, warmth, empathy, and interest in each patient, assessing patient goals, priorities, and values, and addressing psychosocial needs of patients and caregivers*, among others (Baile and Aaron 2005; Delgado-Guay et al. 2013; Gilligan et al. 2017). Table 2 outlines several basic communication skills. Descriptions of these skills are highlighted in the literature (Baile and Aaron 2005; Delgado-Guay et al. 2013; Gilligan et al. 2017), which are excellent reference resources.

Creating a Patient-Centric Environment for Learning

Throughout this chapter, suggestions for promoting effective and clear communication are closely tied to enhancing providers' interpersonal skills. As van Vliet et al. (2015) point out, aging is associated with a number of cognitive, physical, and social changes (memory, hearing, visual, social networks, etc.). These changes often (in) directly affect the way older people may process, assimilate, and use information to make decisions. Thus, it is important to be aware of such factors that might get in the way of effective communication. Table 3 outlines a number of techniques to facilitate effective communication and mitigate hidden traps in communication.

Preferred Methods of Learning and Communication Technologies

Preferred Methods

Preferred methods of communication should be considered when communicating – regardless of whether one is coordinating care or providing consultation or education. Although this may change in subsequent decades, many older cancer patients age 65 and older still report that they prefer making medical appointments through phone calls (as opposed to through email, websites, or text message) and many still like receiving educational health information in person or in paper format (as opposed to website or other electronic means) (Saied et al. 2014). Relatedly, in one study, older lung cancer patients reported preferring education provided verbally or in written format compared to online or in class format (Jewitt et al. 2016). On the other hand, it is estimated that 67% of US adults 65 and older now use the internet (Anderson and Perrin 2017) – and this number has increased by 400% since 2000 (Smith 2014; Anderson and

Table 2 Essential interpersonal skills and methods to promote effective communication

Essential interpersonal skill/ method	Helpful tip/information	Example	Sources
Introduce yourself Introduce self and your specialty/area of clinical care and role in patient's care	This introduction can be brief but is important in laying the foundation for developing a strong patient-provider relationship and to get to know what is important to the patient. This sets the stage for a warm trusting relationship	"Hello, Mrs. Green. My name is Dr. Williams. I am a medical oncologist. I provide treatment to patients with breast cancer, including chemotherapy and immunotherapy. I see that you have brought some important people with you today. Would you like to introduce them to me?" "Please tell me about your day so far"	Gilligan et al. 2017
Setting a collaborative agenda At the start of the visit, ask the patient what topics they would like to discuss	This fosters an inclusive environment in which the patient and their family are engaged in a collaborative process of treatment decision-making and healing with the treatment team	"There are number of topics to cover during our time together today, however, I want to check-in to see what your top 3 questions/concerns are so that we can be sure to discuss those"	Gilligan et al. 2017
Sit down, facing the patient/ family, and making consistent eye contact	This helps to create a trusting and positive patient/family-provider relationship and further solidifies the stage for co-learning to occur. This also demonstrates interest in a patient's unique experience by being fully attuned to his/her needs. It also helps to pace/slow down the interaction according to cues that can be readily picked up	Sitting on a chair/stool at eye level with the patient shows engagement. If is absolutely necessary to use a computer, tell the patient that you are going to do so, but that you are still attending to him/her. For example, "Forgive me for turning away from you for just a moment. I am going to pull up your recent scans so that we can look at them together. However, I am still listening."	Hillen et al. 2015; Gilligan et al. 2017
Demonstrate respect, warmth, empathy, and interest	Smile! These simple gesture communications volumes about caring. Demonstrate respect through multiple behaviors, including treating patients as individuals, engaging them in conversations about their experiences and treatment decision-making, and making statements about what you admire about them. Respond with empathy when patients and their caregivers express emotions	"Hello, Mrs. Green (shaking hands, smiling warmly at patient, and making eye contact), it is so good to see you. How have you been doing? How was your grandson's wedding? I know you were really looking forward to it!"	Delgado-Guay et al. 2013; Gilligan et al. 2017; Hillen et al. 2015
Use active listening skills Active listening skills demonstrate to patients that providers are not only listening but actually *hearing* their patients. These skills are largely demonstrated through	Consider facial expressions, head nodding, and body language, asking open-ended questions, and listening to patients' responses to questions during interactions and what they convey	An example of summarizing what a patient has said through active listening. "What I hear you saying, Mr. Smith, is that urine leakage has been an especially troubling problem lately and you are wondering what might be done	Delgado-Guay et al. 2013; Gilligan et al. 2017

(*continued*)

Table 2 (continued)

Essential interpersonal skill/ method	Helpful tip/information	Example	Sources
nonverbal behaviors or gestures		to help improve your symptoms. Is that correct?"	
Assess goals, priorities, and values Engaging patients in conversations about their goals, priorities, and values assists in providing patient-centered care	Multiple conversations about goals and priorities are essential throughout treatment, especially when changes to the care plan are necessary or when therapy transitions from curative intent to end-of-life care	"As we begin to make treatment decisions, I always like to get a sense of what is important for each patient. For example, some patients are concerned about pain control and have that as a primary focus. Others are more concerned about length of life over quality of life. What would you say are your primary goals and priorities?. . .[after a patient has shared goals/priorities]. . . thank you for sharing those with me. I'm glad that we had this conversation. And just to let you know, I may bring this up at various points during your treatment to see if any of your goals/priorities have changed. Please feel free to bring it up with me too."	Balducci and Dolan 2016; Gilligan et al. 2017
Address psychosocial needs of patients and caregivers throughout course of treatment Depression, anxiety, and social support should be assessed throughout the treatment trajectory	Offer to refer patients and caregivers to psychosocial services in a nonjudgmental manner	At start of treatment: "Many patients experience a lot of different emotions and feelings after a cancer diagnosis. It is normal to feel a range of emotions including sadness or anxiety. We have a number of different and helpful services along the way, including counseling. Our team includes social workers, counselors, psychologists, psychiatrists, and members of the clergy. I am happy to refer you to services if you are interested." During treatment: "Coping with cancer is often rough. How have you been doing emotionally?"	Gilligan et al. 2017

Perrin 2017). Yet, many older adults report being less comfortable in using the internet compared to younger adults, having difficulties logging in, reading text on the screen, or understanding the numerous interfaces and levels of a website (Saied et al. 2014; Smith 2014; Price-Haywood et al. 2017). Further, many older adults compared to their younger counterparts report having less access to the internet and lower rates of daily internet use (Saied et al. 2014).

In the age of heightened technology, a number of strategies have been found to be effective in

Table 3 Techniques to facilitate effective communication

Technique	Helpful tip/information	Sources
Schedule adequate time with patients	This allows time to fully establish a relationship and to assess any unique learning needs. It allows patients to ask questions to promote an exchange of information and promotes shared understanding of important information, even when providing patients with extensive written information. It sets the stage for a warm empathic relationship	Puts et al. 2017
Consider the unique/ special needs of older cancer patients	Recognize and assess any patient unique needs that might affect communication needs/ preferences, such as hearing loss, visual impairment, or problems with cognition and memory. Provide cancer information using a variety of alternative formats, if needed. This might include visuals, teaching cards, or simple drawings. Engage family members of the patient's representative/support person	Loh et al. 2017; Mohile et al. 2011; National Eye Institute 2018; National Institute on Deafness and Other Communication Disorders 2017; Meade 2018; Edwards et al. 2018
Cognition	Having metastatic cancer, having a higher level of comorbidity, prior stroke, and taking warfarin have been associated with cognitive issues	
Vision	Vision impairment is common among older adults. In addition, rates are projected to rise in the coming years as the US population ages	
Hearing	Affecting about one in four individuals aged 65–74 and half of individuals 75 and older, significant or disabling hearing loss is common among older adults in the general population	
Promote information recall	Provide information is small chunks, pause, and assess patient and caregiver understanding It is essential for providers to consider that when receiving bad news, it may be especially difficult for patients and their caregivers to attend to, absorb, and retain information shared during the visit	Delgado-Guay et al. 2013; Gilligan et al. 2017
Incorporate teach-back method	After delivering health information, ask patients to summarize what was said in their own words. Then, either affirm what the patient said (if accurate) or edit/correct (if inaccurate) For example, say "I know that I just presented a lot of information about treatment for lung cancer. In your own words, can you tell me about the treatment options I shared?" When patients demonstrate misinformation or misconceptions, providers should respond tactfully and gently correct the patient or caregiver, without blaming or seeming condescending. For example, a provider might respond with a sentence starting "I may not have explained it well. Please let me try to explain it again." and then provide the information using different lay terminology	Badaczewski et al. 2017

promoting information recall among older cancer patients when using online information and adding illustrations such as graphs and icons as opposed to text only (Bol et al. 2015a). Also, online health information, for both younger and older cancer patients, has been found to be more beneficial when the information is provided in a conversational-style narration (Bol et al. 2015b). This may point to the promise of embodied conversational agents (ECAs) to supplement provider interactions (Bickmore et al. 2016). Also, the efficacy of remote symptom monitoring/reporting via technologies (e.g., tablets) may be helpful tools for oncology providers to monitor their cancer patients from home after surgery or treatment (Maguire et al. 2015; Maguire et al. 2017). Thus, questions about patients' preferred methods of learning, current internet access and usage, and whether they like using the internet and electronic tools to obtain information about their health, treatment, and care are especially helpful to ask during initial assessments.

Mobile Technologies

Regarding ownership of cell phones, many Americans (95%) own some type of a cell phone and can send and receive text messages (Pew Research Center 2018), thus, opening new doors for health communications. Since Pew's first survey of smartphone ownership in 2011, US rates have climbed to 77%, up from about 35% (Mobile Fact Sheet [Internet] 2018). While rates of cellphone and smartphone ownership among *older* US adults are lower than the national rates, they are steadily increasing. Indeed, 80% of US adults age 65 and older now own a cellphone and 42% own a smartphone (Anderson and Perrin 2017).

Likewise, smartphone ownership has climbed in many developing countries with a 37% increase in smartphone adoption since 2015 (up 21% since 2013) (Rainie and Perrin 2017). The use of text messaging and/or tablet-based education and/or telemedicine offers novel and promising ways to communicate health information, provide screening reminders, and/or report and manage symptoms, irrespective of distance, as examples. These approaches may be especially appealing to older adults in rural and geographically remote areas, particularly when patients are instructed in their usage. Yet, even in countries with advanced economies, a digital divide exists between more educated and less educated people as well as among the young and the old (Rainie and Perrin 2017). Thus, reducing the digital divide requires finding ways to improve greater access to reliable, easy-to-understand, and language-appropriate information and resources, as well as implementing telemedicine/telehealth systems that increase data integration and boost IT infrastructure among multiple health care systems.

Language and Health Literacy

Language

According to the 2011 American Community Survey conducted by the US Census Bureau, nearly 15% of individuals aged 60 years and older speak a language other than English at home (Ryan 2013). Among this group, less than half report speaking English "very well" (39% among primarily Spanish speakers and 45% among individuals who speak a language other than Spanish or English at home) (Ryan 2013). Furthermore, rates of English-speaking ability are associated with multiple sociodemographic factors, including race/ethnicity, foreign born status, education, socioeconomic status, and insurance status (Ryan 2013). As such, documentation of preferred language for communicating and reading are important aspects of patient intake forms.

Trained professional interpreters should be sought to facilitate high-quality and impartial communication and improve patient satisfaction as opposed to use of nonprofessional interpreters, including family members (especially children) and other staff members (Juckett and Unger 2014). In cases where professional interpretation services were not utilized for discussions with cancer patients with limited English proficiency at end-of-life, worse quality of communication about goals for care as well as end-of-life care

was reported (Silva et al. 2016). A plethora of reliable language-specific cancer educational resources are available from the American Cancer Society and the National Cancer Institute websites in various languages such as English, Spanish, Korean, Bengali, French, Haitian Creole, Hindi, Arabic, Portuguese, and Vietnamese, among others (American Cancer Society n.d, n.d; National Cancer Institute 2016).

Health Literacy

Health literacy is defined as "the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions" (Kindig et al. 2004). Health literacy skills are needed to help people find health information, engage in interactions, navigate the health system, understand screening and treatment options, interpret charts and tables, and decide what to do with the information. For example, using a map to find the location of the clinic, knowing the importance of cancer screenings and their frequency, reading a medication insert label and recognizing drug actions and interactions or understanding risks of a new experimental treatment (Kindig et al. 2004). Yet, too often, communications are steeped in difficult and unfamiliar terminology and words that are often "over the heads of many patients," and misaligned with patients' cultural backgrounds, beliefs, or views (Meade 2018). As such, the importance of **health literacy** cannot be understated.

A number of factors are associated with being at risk for low health literacy, including age, educational attainment, socioeconomic status, geographic location, and race/ethnicity. In particular, older individuals with lower educational attainment (less than high school), non-native speakers, and those with fewer financial resources are more likely to be at risk for limited health literacy (Kutner et al. 2006). However, it is important not to simply assume that individuals who fit these characteristics have low health literacy. Many individuals, who are educated, middle or of high socioeconomic status may also be at risk for low health literacy, once they "enter the culture of health care."

Patients with limited health literacy may find it difficult to sort and sift through the plethora of medical terminology commonly used in health care settings. As such, the topic has received considerable attention in the Healthy People (2020) imperative that relates the importance of health communications and health IT that advance effective health care and health equity, see http://www.healthypeople.gov/2020/topicsobjectives2020/ for more information. Moreover, with the growing emphasis and emerging role of precision medicine and personalized treatments in oncology, there are even more increasing demands on older adults to become engaged in complex conversations and decisions about their care. For example, patients might ask: *What are the benefits of my tissue to this study? What are the pro/cons of donating a sample of my tumor for research? What can I do to manage and cope with this debilitating fatigue that I have with my meds (*e.g.*, Tyrosine Kinase Inhibitors [TKIs])? What are the chances that this clinical trial will really extend my life?; What will my quality of life be like during and following radiation treatment? or How can I manage the pain associated with my metastatic breast cancer?* This calls for patient-centered communication that encourages older cancer patients to share their questions and information needs. Paasche-Orlow and Wolf (2007) suggest that health literacy be viewed as a "risk factor to be managed in clinical care."

Health Literacy Universal Precautions

Simplified language and clear communication with all patients as opposed to medical jargon is suggested to improve understanding, satisfaction, and positive health outcomes. This includes the use of plain language, that is, concise, well-organized, and direct ways to express an idea (General Services Administration). The Agency for Healthcare Quality and Research (AHRQ) coined the term *Health Literacy Universal Precautions*, whereby improving health literacy is *universal* for all patients regardless of their level of health literacy (AHRQ 2017). Thus, promoting understanding is not just for those who are at risk

for low health literacy but for *all* patients and their family members. Furthermore, numeracy is another important component of health literacy and involves skills that help patients make sense out of numbers, tables, graphs, and probabilities (Jacobs et al. 2016; Schapira et al. 2014). This aspect of literacy is also crucial in comprehending medication schedules, chemotherapy treatment regimens, food labels, genetic risks, and following the myriad aspects of clinical trials including randomization, probabilities of risk or treatment effects, etc.

Assessing Health Literacy

The literature identifies numerous ways to assess health literacy via word recognition lists, health literacy comprehension tools, or through informal methods (e.g., patient states they have low reading skills, or report that they do not like to read, or like having others read for them). One approach is to gauge health literacy through brief single item measures that can be incorporated into the patient's assessment intake form. For example, the single item literacy screener (SILS) asks "How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?" with response options of 1-Never, 2-Rarely, 3-Sometimes, 4-Often, and 5-Always (Morris et al. 2006). Scores greater than 2 are considered positive, indicating some level of difficulty with reading printed health related material. For a comprehensive listing of available health literacy tools, go to the *Health Literacy Toolshed*, an online database of health literacy measures compiled by the National Library of Medicine (2015).

Deconstructing Information to Improve Communication

A key challenge in health care is to take very specialized, technical, and advanced knowledge and break it down into parcels of information that match older adult's specific and unique language, cognitive, physiological, and social needs, and learning preferences in ways that are understandable and that involve their social, caring network (Sparks and Nussbaum 2008). Striving for a health literacy mindset is essential in today's health care climate and involves deconstructing (or simply breaking down) complex information into manageable and relatable bytes. Regardless of a patient's educational level, most people want and need simple and clear information (Doak et al. 1996). For example, consider how to introduce patients and family members to the topic of precision medicine that requires donation of a biospecimen. This means explaining new concepts and words such as genomics, biospecimens, biobank, annotation, etc. It necessitates clear, patient friendly, and familiar language that aids comprehension, promotes receptivity of information for decision-making, and opens the door to better understanding about a new field of cancer. For example, when explaining the term "biospecimen," it might mean defining it as material from the human body, such as urine blood, spit, nail, or tissue from biopsies or surgeries. When discussing the term "biobank," the analogy of a library collection of books could be used to explain how biospecimens similarly are stored, logged, and catalogued (Meade et al. 2015).

Creating a Literacy Friendly Environment

Another consideration for improving communications for older cancer patients is creating a literacy friendly environment as "*first impressions make a difference*." This means taking time to assess common health care system's communication features such as the phone system, patient portal, webpages, and even ease of navigation of the cancer clinic and facility (e.g., signage). Every interaction has the potential to contribute to or detract from a patient's experience such as clarity in *menu prompts, easy-to-understand patient educational materials, consent forms in relevant languages, easily understandable signage to get to a clinic, and the friendliness of the staff.* For many older cancer patients, navigating the physical environment of a cancer center or clinic may be complex, time-consuming, and arduous, especially if they are not feeling well or have physical limitations. For example, *what does it take for a*

Table 4 REAL framework

Element	Description
Relatable	Communications are important and significant for patients – information resonates with their everyday lives and "worldview." It is highly relevant according to their beliefs, values, and background
Engaging	Communications are interesting and appealing. The messages "catch" their attention and patients are drawn to them
Actionable	Information is specific and points to an action, such as toward a decision or behavior or a task
Literacy-friendly	Communications are clear, straightforward, and easy-to-understand. They allow patients to assimilate the information and to do something with it

patient to park, register, provide information, get their blood work and other tests done, and then locate the clinic where they will see his/her provider? An excellent guide to assessing one's health care environment and implementing empowering patient strategies and organizational policies that support such a climate can be found at the following link: https://cdn1.sph.harvard.edu/wp content/uploads/sites/135/2012/09/healthliteracyenvironment.pdf (Rudd and Anderson 2006).

Effective communication is explicitly connected to health literacy and helps to promote positive, productive, and satisfying patient-provider interactions. To aid this mindset, the REAL framework is a helpful tool or mnemonic that serves as a constant reminder of the importance of effective communication. The utility lies in its simplicity – that is, often the best communications are those that are ***r**elatable, **e**ngaging, **a**ctionable, and **l**iteracy friendly* (See Table 4).

Special Topic: Role of Effective Communication in Clinical Trial Participation and Research

Clinical trials are now commonplace in oncology care and are essential for testing the safety and effectiveness of promising treatments. However, participation in therapeutic clinical trials is low with only 2–3% of cancer patients nationwide ever enrolling in a trial (Hamel et al. 2016; Mendelsohn 2010; Murthy et al. 2004; Stewart et al. 2007). Although 61% of new cancer cases occur among elderly, they comprise only 25% of the patients enrolled in randomized clinical trials (RCTs) (Mahipal et al. 2015). Underrepresentation in pivotal research limits generalizability, and in fact, may result in misleading conclusions about older adults including racial/ethnic minority populations, rural patients, and patients with low socioeconomic status (Roth et al. 2016; Stewart et al. 2007; Baquet et al. 2006, 2008; Baquet 2012; Vanderpool et al. 2011). Impediments to recruitment, enrollment, and retention of underrepresented populations (including the elderly) to cancer clinical trials, as well as innovative efforts to ameliorate such hindrances have been extensively documented (Hamel et al. 2016; Nipp et al. 2016; Trevino et al. 2013; Sohal et al. 2015; Fouad et al. 2016). Barriers to participation in clinical trials are complex and may be attributable to lack of provider recommendation to participate, patient's cultural beliefs and attitudes toward research, lack of knowledge about the importance of clinical or biomedical research to the health of the community, and/or insufficient and inappropriate consent process (Ford et al. 2008; Hamel et al. 2016), in addition to stringent protocol exclusion criteria that are driven by presence of comorbidities and preclude qualification especially among the elderly and racial-ethnic minorities.

As such, a persistent question has been the concern over frailty and potential poorer tolerance of chemotherapy among some elderly patients (Extermann 2012; Muffly et al. 2013; Extermann et al. 2017). Thus, the question whether older patients can safely undergo aggressive regimens has been investigated. A systematic review by Kumar et al. (2007) found that enrollment of elderly in experimental RCTs was not associated with increased harm to this patient population. Overall, results suggested that survival in one trial that exclusively enrolled elderly patients favored the newer treatments (hazard ratio [HR], 0.69; 95% CI, 0.47–1.02; $p = 0.06$). Similarly, in trials enrolling elderly participants at a rate of more than 40%, survival and event-free survival favored the innovative treatments (HR = 0.91;

95% CI, 0.84–0.99; $p = 0.03$; and HR = 0.85; 95% CI, 0.72–1.01; $p = 0.07$, respectively). Treatment-related mortality was similar in both the innovative and standard treatment groups. Thus, increased participation of the elderly remains an important ideal, and may help to find safe new treatments as well as identify ways to assess treatment tolerance and clinically applicable measures to support this cohort of patients (Kumar et al. 2007; Extermann 2012; Muffly et al. 2013; Extermann et al. 2017).

Although clinical trial participation continues to be an important and challenging topic for cancer patients, family members, clinicians, researchers, study sponsors/funding agencies, and policy makers, some studies have shown that racial-ethnic minorities enroll to treatment oncology clinical trials at comparable rates as Whites when they are provided access, are approached, and meet eligibility criteria (Tejeda et al. 1996; Wendler et al. 2005). Furthermore, there is evidence that older patients are comparably receptive to clinical trials (relative to younger patients less 65 years), enroll in trials when asked, and when they are eligible (Ayodele et al. 2016). Research in prostate cancer treatment decision-making suggests that 63% of patients preferred to take an active role in decision-making (and decide on their own after consulting their provider), 29% preferred a collaborative role with their provider, and 8% favored a passive role where the provider tells them what to do (Gwede et al. 2005; Diefenbach et al. 2002). Thus, clinician awareness of the varied communication and decision-making styles of cancer patients is important, and clinicians need to take extra time to make sure that patients ask questions, and involve family members in the decisions. Ultimately, the provider should be ready to accept the fact that patients' decisional support needs may vary widely, and that effective communication may be compromised if there is discordance.

By far the greatest challenge is how to adequately reach and provide access to all patients who could *potentially* benefit from participating in clinical and prevention research. A number of successful communication strategies have been proposed to address participation in oncology clinical trials through community oncology networks (Roth et al. 2016), multilevel approaches (Hamel et al. 2016; Eggly et al. 2017), and patient navigator programs (Durant et al. 2014; Fouad et al. 2016) to address barriers. Given the complexity of the problem of clinical trials participation among older cancer patients and among cancer patients overall, success depends on sustained long-term efforts at all levels (patient, family/social networks, providers, health systems, policy, and community). There needs to be heightened attention to new or emerging communication challenges and concerns for older cancer patients given the proliferation of new (adaptive) study designs in precision oncology trials (Sohal et al. 2015; Ondra et al. 2017; Liu et al. 2017). With the increasing complexity of contemporary clinical trial designs and emphasis on genomics, precision medicine, biospecimens, and biomarker-driven therapies, there are new or difficult questions facing multidisciplinary oncology clinical and research teams with regards to communications to older cancer patients and their families. Table 5 summarizes selected questions and perspectives that may present in the discussion of clinical trial participation in the context of genomic research and precision oncology care.

These and other related questions call for a variety of effective strategies as summarized in the preceding section. Future research also should continue to investigate whether there are subgroups of older cancer patients that require greater attention due to language, cultural factors, literacy, or other contextual influences. Interventions can then be tailored or targeted for these unique attributes to increase equitable participation in research and potential to add rich data in this era of precision medicine and patient-family centered care.

Summary

This chapter highlights the inherent and essential value of effective communication for promoting patient and family participation and engagement in their well-being, healing, and quality of life across the cancer care continuum. The

Table 5 Selected communication questions for older adults in oncology clinical trials and precision cancer care

Key points	Questions
Precision medicine helps to discover unique therapies that treat an individual's cancer based on the specific genetic make-up of their tumor Providers have a key role in helping patients and family members understand and deconstruct research and precision oncology care in ways that are clear and useful	• *Do older cancer patients understand the terms "precision/personalized medicine?"* • *What do older cancer patients think about the role of genomic information when cancer is not hereditary? Is the notion of cancer/tumor genes (*versus *germline genetics) a well-understood concept by older cancer patients?* • *Are there different communication styles or approaches needed with older adults, immigrant populations, or limited English proficiency individuals in this era of genomic research?* • *As new clinical trial designs are introduced, do older cancer patients understand the associated consent forms? For example, adaptive trials that call for breaks in treatment (when patient/disease is responding well) but the cancer is not eradicated; does the concept of adaptive personalized medicine resonate with older adults who may believe the traditional paradigm that all cancer must be eliminated?* • *Clinical, behavioral, or prevention trials involving biobanking of biospecimens are pivotal to advancing genomics research and precision cancer prevention/care.* • *Do older adults have privacy concerns with the approaches involved in the collection, storage, and future testing for the sake of advancing science (with no apparent personal benefit)?* • *What fears do older patients, especially racial/ethnic minorities, have about precision medicine and genomics research?* • *How can oncologists simplify communications on these topics with older adults, particularly with nontrusting patients?*

emergence of a changing multicultural demographic landscape coupled with an increase in the number of older cancer patients and the remarkable advances in cancer care and research and technology create multiple opportunities and teachable moments for improving communication with older cancer patients. At the individual level (patient-provider interactions), communications that foster trust, empathy, compassion and appreciation of differences and similarities in worldview (cultural origins and prevailing perspectives) are likely to produce effective understandings among patients. Use of plain language and teach-back approaches are critical tools in older adult oncology settings. As the proportion of older patients treated on a clinical trial increases, and as genomic precision medicine becomes mainstream, greater use of these effective communication strategies is needed. Oncology practitioners thus must embrace "Universal Health Literacy Precautions" and routinely employ available consensus communication guidances with each of their older cancer patients. The hope is that patients and their families can find value and compassion in the information exchanged between them and their oncology providers and can have a meaningful quality of life that most matters to them during all aspects of their cancer journey.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Decision Making and Safety Issues in Older Cancer Patients

- ▶ Geriatric Screening in Cancer Patients
- ▶ Healthcare Informatics and Technology in Managing the Older Cancer Patient
- ▶ Population Trends in Aging and Cancer
- ▶ Research Methods: Clinical Trials in Geriatric Oncology
- ▶ Research Methods: Outcomes and Survivorship Research in Geriatric Oncology
- ▶ Research Methods: Quality of Life and Patient-Reported Outcome Research in Geriatric Oncology
- ▶ The Older Cancer Patient: Religious and Spiritual Dimensions

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The Older Cancer Patient: Religious and Spiritual Dimensions

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Lodovico Balducci

Contents

Abstract

The goals of care are based on the values of each individual: setting the goals of care is a spiritual endeavor. Accordingly, this chapter examines the definition of religion and spirituality, the influence of religion and spirituality on the management of the older person, and the clinical assessment of religion and spirituality.

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In general religion and spirituality have been associated with better tolerance of chronic diseases and more satisfactory caregiving experience in patients with chronic diseases and their families, and all providers need to recognize that medical emergency that is referred to as spiritual distress can be properly managed by a chaplain. Spiritual distress is a cause of poor quality of life and may lead to treatment failure from desperation and lack of motivation.

Religion and spirituality may play a specially important role in the management of older cancer patient as with aging there is an increased interest in the meaning of life and in spiritual

accomplishments (gerotranscendence). Each person should have adequate evaluation of spiritual and religious resources, and the practitioner should be experienced in utilizing these resources appropriately to improve a patient outcome and to support the patient's quality of life.

Keywords
Religion · Spirituality · FICA · Religious evaluation · Older patient · Cancer

Introduction

Setting the goals of care is the first step in the management of serious and incurable diseases (Magnuson et al. 2016; Temel et al. 2016). The goals of care are based on patient's immediate preferences and long-term aspirations related to the treatment (Justin 1987). Preference and aspirations are influenced by each person's spiritual and religious beliefs, that is, by his/her values. A value history is thus implicit to some extent when setting the goals of care. This process is particularly important for the older cancer patients. When the benefits of treatment are reduced and the risks increased, the preservation of meaningful quality of life may become the primary purpose of all medical interventions (Vallet-Regi et al. 2017)

Whether they are explicitly declared or are implicit in a person's behavior and plans, values represent the transcendence of human life, as they provide the frame of reference that allows to judge if life is worth living in each beholder's eye (PDQ Supportive and palliative care editorial board 2016; Koenig 2015). Thus, the delivery of personalized care requires a spiritual connection of patient and provider, which may involve a discovery of the meaning of the disease, of pain and suffering, and of death. There is almost universal agreement in all cultures that this connection is beneficial at multiple levels (PDQ Supportive and palliative care editorial board 2016; Koenig 2015; Memaryan et al. 2016; Gielen et al. 2017; Sherman et al. 2015a; Jim et al. 2015). It may improve adherence to treatment and treatment outcome in addition to patient satisfaction and quality of life. Indeed, suffering and imminent death may represent a healing experience for patients with terminal cancer and their caregivers.

A threefold challenge to personalized care is present nowadays. The first is globalization and the consequent cultural diversity. In the days of old communities were stable over time. Medical care was provided in the same village or in the same neighborhood, and patients and providers might have worshiped in the same church and shared the same values, which were implicit in each encounter. This is rarely the case today, and providers need to be aware that the patients' values and beliefs may be quite different from and even at odds with their owns, and personalized care entails understanding, acceptance and respect of this diversity (Balducci et al. 2017). The second is the fragmentation of medicine into multiple specialties and subspecialties. The scarcity of primary care physicians, whose role is becoming every day more nebulous and whose professional time every day more taxed, and the intervention and interaction of different providers in the management of the same patient may prevent the development of an ongoing relation of trust necessary to negotiate a value-based plan of care (Kuluski et al. 2013; Kocher and Chigurupati 2016). For older individuals used to rely on the advice of a single provider, this change has been particularly disorienting and disconcerting. The third challenge is the mounting use of technology in medical practice. The universal adoption of electronic health records has reduced the face-to-face time for patients and providers (DeRoches et al. 2008). As important, increasing reliance on precision medicine, practice guidelines, and clinical pathways have changed the perception of and the expectation from the provider. Rightly or wrongly, patients are seeing the physician more as a technologist of the human body than as an authoritative and trustworthy counselor.

In this chapter we plan to provide a blueprint for the assessment and management of spiritual needs of older cancer patients. Based on a review of the literature and our personal experience, we assume these needs have become more widespread and unfulfilled in the current medical reality. We also hold that catering to the spiritual needs is essential to healing (Silbermann et al.

2010; Balducci 2012), the ultimate goal of care. Healing refers to the personal experience of the disease and may be achieved in all circumstances, even and mostly when cure is out of reach.

After an overview of the construct and assessment of spirituality, we will explore the role of the practitioner of oncology in addressing the spiritual wants of older cancer patients.

Religion, Spirituality, and Health Care

After trying to define religion and spirituality, we will briefly review the impact of these exquisitely human domains on health preservation and health-care delivery.

Definitions

While an operational definition is wanted, there is general agreement that religion and spirituality are different albeit interrelated dimensions (PDQ Supportive and palliative care editorial board 2016; Koenig 2015). Religion involves the belief in a transcendent power and a number of behaviors, including prayer, meditation, rituals, and social interactions, which allow a person to establish a relation with and become close to this supreme power. This relation may be multifaceted and include worship, petition, and even expressions of love, anger, and disappointment. Communal celebrations are typical, but not necessary expression nor are they exclusive of a religion. Many individuals may profess a belief in a god without being part of any defined "community of faith." A religious community may represent an important support for a patient, especially an older one with limited social resources. It has been recommended that the presence of such community be investigated as part of the medical history (Puchalski 2012).

Spirituality is a relation with transcendence that may be found without and within oneself, which may or may not take the aspect and the name of a deity. The relation with transcendence involves the affirmation of the sacred (from the Latin "*sacer*" that means hallowed, reserved to a special and unique use). For example, in a monogamous relation, the partners sacrifice, that is, they make sacred, their sex to each other. Any violation of this commitment compromises the "sacredness" of the relation and ultimately may destroy its transcendent, spiritual aspect.

Recent studies have found some correlation between religiosity and spirituality and neuroanatomy. They are controversial and are mentioned to allow the reader to follow this new field of investigations. Some authors demonstrated that individuals prone to depression have a thinner cortical cortex at the brain MRI, and religious and spiritual individuals had a thicker than normal cortex (Miller et al. 2014). Following a number of transversal studies suggesting that circulating levels of oxytocin were associated with increased religious and spiritual involvement (Erdman 2016), a randomized placebo-controlled study of middle-aged adults was conducted (Van Cappellen et al. 2016). Individuals receiving intranasal oxytocin showed increased engagement in meditation, prayer, and church attendance (Van Cappellen et al. 2016).

Assessment

Some of the difficulties of assessing the spiritual domain of care are immediately apparent. To start with the theology of different religions may be quite different from and sometimes at odds with each other. For example, the three Western monotheistic religions (Judaism, Christianity, and Islam) teach some form of social justice, based on the assumption that all believers (and in some cases all human beings) have the same value in front of God. The requirement of social justice is conspicuously absent in some of the Eastern religions. The supreme aspiration of Western religions is some type of union with the deity after death, whereas for Hinduism it is the Karma, that is, the final release from the cycle of reincarnation, and for Buddhism it is the Nirvana, a peace founded on the absence of passions. Each main religion is subdivided into different denominations, with different specific beliefs, that have been the causes of many religious wars, some of which persists in our times. Within each religious

persuasion, the expression of spirituality may take different manifestations. For example, Roman Catholicism encompasses the contemplative spirituality of hermits and the active spirituality of missionaries. Second, the assessment parameters are particularly fluids. For example, church attendance, participation in the communal religious activities, and even adherence to a moral code of conduct, such as the ten commandments, may represent an inadequate estimate of a person religiosity and spirituality (Jack et al. 2016; Delkeskamp-Hayes 2005). Despite these difficulties, a number of instruments for assessing religiosity and spirituality produce consistent and reliable results, as long as spirituality is distinguished from humanism, morality, and mental welfare and maintains the relation to transcendence affirmed through the sacred (Koenig 2008) as specific characteristic.

A review of the instruments utilized to assess religiosity and spirituality is beyond the scope of this article, and the reader is referred to recent reviews (PDQ Supportive and palliative care editorial board 2016). Suffice it to say that most of them have been employed exclusively for research purposes, that they may involve quantitative as well as qualitative approaches, and that some of them emphasize participation in religious activities, while others are more focused on spirituality. One of these instruments, the FICA (Puchalski 2012) (an acronym for Faith, Importance, Community, Assessment), has been adopted by many practitioners in the initial assessment of patients, because it is simple and brief and provides information of immediate relevance to patient management, such as the presence of a support community.

The studies of the interactions of religion and spirituality with health maintenance and outcome may essentially be divided into five groups (Koenig 2015):

- Epidemiological studies that correlated the belonging to and attendance of a church/religious community, and outcome
- Studies involving an assessment of personal religiosity and spirituality through standardized instruments and outcome
- Studies of the influence of specific religious and spiritual practices, such as prayer and meditation on personal well-being
- Studies of the feasibility and effectiveness of a religious/spiritual intervention
- Studies of the influence of the disease on religious and spiritual growth and development

Effects of Religion and Spirituality on Health

Table 1 summarizes the various health dimensions that may be influenced by religion and spirituality according to a recent systematic review (Koenig 2015). For what concerns the mental health, the majority of studies indicated that religion and spirituality were helpful to deal with a gamut of

Table 1 Dimensions of health that may be influenced by religion and spirituality

Mental health
Coping with adversity
Positive emotions
Depression
Anxiety
Psychotic disorders/schizophrenia
Bipolar disorders
Personality traits
Substance abuse
Social problems
Health behavior
Cigarette smoking
Exercise
Diet
Weight
Sexual behavior
Physical health
Mortality
Coronary heart disease (CHD)
Hypertension
Cerebrovascular disease
Dementia
Immune function
Endocrine function
Cancer
Physical functioning
Self-rated health
Pain and somatic symptoms

adversities including cancer, other serious diseases, and end-of-life situations. Likewise, the promotion of beliefs that foster hope, optimism, meaning, and purposes and that foster positive character traits, such as forgiveness, gratefulness, and kindness/compassion was found generally beneficial and devoid of adverse effects. More variable were the results related to well-being and happiness, self-esteem, sense of control, and altruism, but the majority of studies found a positive rather than a negative relationship between religion and spirituality and each of these domains. These findings should dispel the common worry that religion may lower one's sense of self-esteem, by promoting guilt or self-deprecation. Religiosity and spirituality had minimal effects on depression, except for one study that deserves mention (Miller et al. 2012). The authors followed for 10 years the adult offspring of depressed patients and found that the risk of depression was decreased by 90% for individuals for whom religion and spirituality had high importance. Spiritual interventions appeared to reduce prevalence and severity of anxiety, and in the majority of the investigations, religion and spirituality had a positive effect on risk of suicide and of substance abuse. The results related to bipolar and psychotic disorders were inconclusive. Religiosity and spirituality by and large promote positive personality traits, including extroversion, consciousness and openness to new experiences, and agreeableness, and disfavor the negative ones, such as psychoticism and neuroticism. Religion and spirituality promoted social stability in the majority of cases, by disfavoring criminality and divorce and supporting caregiving and social involvement.

Religion and spirituality supported healthy behaviors including exercise and healthy diet and discouraging cigarette smoking and risky sex.

Of 121 prospective studies, 82 (76%) reported a positive relation between religiosity/spirituality and longevity, and none of the 17 studies of highest quality indicated a negative relationship. Three systematic reviews of the existent literature demonstrated that religiosity and spirituality were associated with a 37% decline in mortality. It is difficult to disregard these results as statistical flukes, and it is reasonable to conclude that spiritual health is associated with a better and longer life. This conclusion is consistent with the fact that religion and spirituality promote healthier lifestyles, may improve the immune defenses, modulate cardiovascular reactivity to stress (Bertson et al. 2008), and suppress the inflammatory status that is a hallmark of aging (Robins et al. 2016). In addition, religion and spirituality were associated with decreased prevalence and improved outcome of chronic diseases, such as cardiovascular diseases, cancer, and cerebrovascular diseases, and might have slowed cognitive decline in older individuals.

Religion, Spirituality, and Cancer

Three recent meta-analyses have examined the influence of religion and spirituality on physical (Jim et al. 2015), mental (Salsman et al. 2015), and social (Sherman et al. 2015b) health of cancer patients.

These reviews recognized three religious/spiritual domains: affective, cognitive, and behavioral. In addition they included an "other" category that comprised studies in which these domains could not be clearly determined. The affective dimension concerned religion/spirituality as a source of spiritual well-being and spiritual distress. The behavioral one included actions and conducts pertinent to religion and spirituality, such as church attendance, prayer, meditation, and acceptance of and adherence to a moral code. The cognitive domain encompassed individual beliefs such as attributes of the deity, religious fatalism, and opportunity for spiritual growth.

These studies found that

- Overall religiosity and spirituality bore a significant association to physical and functional well-being and to physical symptoms. In particular spiritual well-being was associated with improved and spiritual distress with poorer physical health. Likewise, belief in the opportunity for spiritual growth led to a better physical health (Jim et al. 2015).
- Overall religiosity and spirituality and their affective and cognitive components were significantly associated with all domains of mental well-being, including emotional well-being,

general distress, depression, and cancer-related distress (Salsman et al. 2015).
- Overall, religion and spirituality were significantly correlated with social well-being, social distress, and social support (Sherman et al. 2015b) in social roles, relationships, activities, and perceived quality of this involvement.
- While religion and spirituality seemed to have altogether a positive effect on physical , mental, and social health, spiritual distress was a cause of deteriorating health and may even have led to poorer disease outcome through depression, decreased treatment adherence, and impaired social support. Recognition and management of spiritual distress may represent an important intervention that in some cases may be lifesaving. Common causes of spiritual distress included grief, loss of faith, loss of meaning, feelings of having been abandoned by god, having disappointed god through sin, or being unable to offer an effective and meaningful prayer, to have lost the relation with the deity. The studies of the relationship between religion, spirituality, and cancer outcome are inconclusive (Salaman et al. 2015). It has been proposed that a meta-analysis of the issue as well as defined taxonomy of religion and spirituality assessing the affective, behavioral, and cognitive domain may throw some light on the issue. At present we can assume that religion and spirituality by and large may have a positive effect on the physical function and the quality of life of cancer patients (PDQ Supportive and palliative care editorial board 2016) though in some circumstances they may cause distress, which should be timely recognized and managed. At present it is not clear whether this improvement in quality of life and physical function purports improved outcome nor whether interventions to foster spirituality in cancer patients are beneficial in terms of survival.

Some important practical messages emerged from this review:

- Religion and spirituality are important dimensions in the life of many cancer patients and do influence their quality of life.
- Religion and spirituality may provide important resources in the management of cancer patients, and practitioners should be attuned to assess and exploit them. In particular a discussion of these issues may make patient-physician communication more effective, may improve patient's trust, foster adherence to treatment, and improve the function, the mental health, the social health, and the quality of life of the patients.
- Religion and spirituality may be a source of distress that may compromise quality of life, cause depression, and diminish the motivation to receive any form of care, prevent healing, and ultimately worsen treatment outcome. As part of good health-care delivery, it behooves the practitioner to recognize and investigate the signs of spiritual emergencies.(Puchalski et al. 2009)
- In all cases the physician should make room for and endorse the religiosity and spirituality of each patient. When a specific intervention is needed, beyond the practitioner area of expertise, such as to help the patient overcome a sense of guilt that saps all attempts to provide care or to convince the patient to receive medical treatment if he/she refuses this treatment for religious reasons, the practitioner may refer the patient to the clinical chaplain. Clinical pastoral training enables chaplains to minister to patients of all religious backgrounds and also others such as humanists, agnostics, and atheists and to address the spiritual concerns of individuals without religious beliefs (Mclean 2015).

Religion, Spirituality, Aging, and Cancer

Aging is Dynamic

The life expectancy in the western world is progressively increasing (Walter and Schonberg 2014), in a world in which cultural and technological changes are increasingly more rapid. Seemingly, the religious and spiritual interests of

the baby boomers, who have grown in an increasingly secular and culturally diverse world, may be quite different from those of the previous generation, the current octogenarians, and nonagenarians. In this section we will review the influence of aging on religion and spirituality and the influence of religion and spirituality on older cancer patients and on their caregivers, recognizing that this is a work in progress, affected by rapid cultural changes, not unlike any other areas of medicine. Also, the data we have are based on selected populations and may not be generalizable.

Religion, Spirituality, and Aging

We will examine the influence of religion and spirituality on successful aging , coping with diseases, and disease outcome.

The concept of successful aging has been debated for at least 30 years, since it became clear that the prolongation of survival should have been associated with preservation of independency, function, and quality of life (Freedman and Spillman 2016). Originally, successful aging had been constructed mainly in medical and functional terms (Freedman and Spillman 2016; Edlund 2014). In the last few years, it was realized that a sense of meaning and accomplishment provides the majority of older individuals with a feeling of self-worthiness necessary to endure all age-related losses and to motivate them to remain active and productive (Carver and Buchanan 2016; Trivedi et al. 2016). The assurance that a person may always provide a unique contribution to the society irrespective of age, disease, and disability is essential to the self-esteem of older patients with chronic diseases. A recent systematic review of the literature (Carver and Buchanan 2016) identifies a number of domains outside the medical and physical ones, associated with "successful aging." These included engaging, resilience, optimism and positive attitude, religiosity and spirituality, self-efficacy and self-esteem, and gerotranscendence. Interestingly, religiosity and spirituality were positively correlated with the presence of all elements of successful aging, suggesting that they may represent the fount of successful aging, at least for some individuals. In the meantime, some older persons felt that they had aged successfully even in the absence of religiosity and spirituality. Religiosity and spirituality appear as an important, but not exclusive source of successful aging. Of special interest is the positive interaction of religion/spirituality and resilience, an essential skill to adapt to the unavoidable losses of aging in the medical, functional, emotional, and social domains. This positive interaction has been reported in multiple studies.

The concept of gerotranscendence is germane to this chapter (Tornstam 2005). It implies that aging is associated with a mounting search for meaning that may be found in organized or informal religion, in spiritual practices, in relations, and in humanistic endeavors. Clearly religion and spirituality represent one of the available and time-honored responses to this search. With the aging of the population, a number of fascinating research questions emerge from this construct: Is gerotranscendence a universal event or is it limited to a generation of individuals dwelling in a Western world with a Judeo Christian background? Is the development of gerotranscendence consistent and progressive over time?

Religion/Spirituality, Diseases, and Aging

We have already established how religion and spirituality may be associated with decreased mortality rate, decreased incidence and prevalence of chronic diseases, and improved ability to cope with these diseases. As the risk of chronic diseases increases with age, these data pertain mainly to the older population. Likewise we have reported how religion and spirituality are associated with a decreased risk of suicide, a common cause of death for the aged (Waem et al. 2003).

A number of studies examined the influence of religion and spirituality on depression (Johnstone et al. 2012; Unterrainer et al. 2014; Lac et al. 2017;

Sachdeva et al. 2015), cognitive decline (Sachdeva et al. 2015), coping with the diagnosis of HIV infection in older individuals (Dolittle et al. 2016; Vance et al. 2011), and adaptation of lesbians, gays, bisexuals, and transgender to aging (Orel 2014; Kim et al. 2017; Erosheva et al. 2016; Griebling 2016). Though not directly related to cancer, each of these conditions may complicate the management of cancer in older individuals.

There is universal agreement that religion and spirituality are associated with decreased incidence and severity and better tolerance of depression. This finding is extremely important as depression may compromise the adherence to and the effectiveness of cancer treatment and may also delay or prevent palliative care. The relation of religion/spirituality with cognitive decline is controversial, but the majority of studies indicate that they may be associated with a delay and improved acceptance of cognitive decline. With the aging of the population and the improved treatment of HIV infection, many patients who have contracted the infection when younger survive into an advanced age. In addition the risks of spreading HIV and other sexually transmitted diseases to older individuals are increased due to a number of factors. Thanks to improved health maintenance and sexual rehabilitation, the sexual activity of the population has become more prolonged. Many older individuals are single as they have lost a lifetime partner through death or divorce and may engage in sex with different partners, especially those living in retirement communities where the incidence of sexually transmitted diseases is particularly high (Minichiello et al. 2011). Religion and spirituality appears to be an important resource to face the real or supposed stigma related to HIV, to comply with HIV treatment, and to avoid risky sexual behavior after the diagnosis. Aging gays and lesbians may face particular challenges. Even if homosexuality is becoming more socially accepted, the stigma related to this sexual preference persists, especially in small and closed communities. In addition, these individuals may want the availability of an extended family including children and grandchildren that provide an informal network of social support. Hopefully, the ratification of gay marriage may prevent in the future this social isolation in old age. Religion and spirituality are associated with improved acceptance of this solitude. In addition, organized religion may provide much needed social support, as Christian and Jewish communities have begun to offer ministries to and support group for sexual minorities.

While most studies revealed a positive effect of religion and spirituality in these areas of aging, it is important to remember that they may also be associated with unwanted consequences. For example, guilt may enhance depression and discourage HIV-infected or homosexual individuals from seeking treatment. Some of them may feel that cancer is the right punishment of their sinful behavior or may be ashamed to reveal a condition condemned by most religious persuasions. Homosexuality is still unacceptable in many Christians and Jewish communities and in virtually all Islamic communities. A blank recommendation to join a church is unwise; rather it is important to help patients to find the religious community and the spiritual practices more congruent with their conditions.

Religion Spirituality, Aging, and Cancer

Older cancer patients may face some challenges related to their age (Vallet-Regi et al. 2017). Aging involves progressive reduction in the functional reserve of multiple organs and systems, increased prevalence of comorbidity, and in many cases, reduced social and economic resources. As a consequence the complications of most cancer treatments and especially of cytotoxic chemotherapy are more common and severe in the aged. Treatment may even be more costly as it involves the utilization of expensive antidotes to treatment toxicity, such as the use of hematopoietic growth factors or more prolong hospitalization after surgery (Vallet-Regi et al. 2017).

Emotionally, aging may involve depression and fatalism. It is not uncommon for older individuals to avoid cancer screening or to delay clinical investigations of new symptoms such as pain or constipation, which are considered,

erroneously, as expected manifestations of normal aging (Balducci 2016). Consequently, the majority of cancers are diagnosed at a more advanced stage in older than in younger persons. Likewise older individuals may delay cancer treatment due to the convictions that this treatment is more toxic than beneficial, has minimal effects on survival, and may compromise quality of life and functional independence. These beliefs may be reinforced by acquaintances and even by health-care providers with limited knowledge of new advances in cancer treatment. Diagnostic and treatment delays are commonplace for elderly without independent transportation who have to impose on younger family members or pay a hired driver to reach the clinics. Economic considerations may also play a role, as modern treatments are more and more expensive and cancer is a more and more common cause of "financial toxicity" that may lead to bankruptcy (Huntington 2016). Even when the insurance pays all direct medical-related costs (which is rarely the case), the indirect and medically unrelated costs may be substantial for older individuals. Last but not the least, older individuals may have more difficulties to understand the rationale and the mechanics of cancer treatment due to cognitive decline as well as to hearing and visual impairments. These different unfavorable elements are woven to each other like the threads of a carpet design. The complexity of treatment-related decisions may be overwhelming for the older patients and their families (Vallet-Regi et al. 2017).

A limited number of studies focused on older cancer patients have demonstrated that spiritual and religious beliefs allow a more realistic appreciation of the benefits and risks of cancer treatment and acceptance of the disease and its outcome and may increase the motivation to receive treatment (Caplan et al. 2014; Ripamonti et al. 2016). All in all religion and spirituality may provide a peace of mind that allows older individuals to choose the course of action more appropriate with their personal circumstances and more congruent with their personal values. In addition a religious community may represent a critical source of emotional and social support for older cancer patients and their caregivers.

Religion, Spirituality, and the Caregiver of the Older Cancer Patient

The home caregiver is essential for the successful treatment of older individuals, including those that at the beginning are fully independent, as the treatment itself may cause functional deterioration and mandate the intervention of the caregiver. The caregiver has multiple roles (Rodyhouse and Wilson 2017; Penson et al. 2000; Kurtz et al. 2004; Haley 2003; Mittnick et al. 2010) that include providing emotional as well as physical and social support (taking the patient to the clinics, helping the patient negotiate the most appropriate course of action with the health-care provider, responding timely to medical emergencies, assuring the patient general welfare, especially nutrition and hygiene, and fostering adherence to treatment). In addition when many different members are involved, the caregiver may assuage unavoidable conflicts and disagreements and may act as the family spokesperson. Indeed the caregiver is the practitioner's most powerful ally, and it behooves the practitioner to promote the caregiver well-beings. The management of older patients involves the management of the caregiver in the majority of cases (Mittnick et al. 2010).

The data concerning the health of the caregivers of older cancer patients is limited (Lai et al. 2017), but it is reasonable to use the data concerning the caregivers of patients with other chronic diseases and in particular dementia. We know that the complications of caregiving include increased mortality, increased incidence and severity of depression, increased prevalence of comorbidity, as well as disruption of social and personal relationships. Marriages and other intimate relationships may be compromised and even destroyed as a result of caregiving.

A recent systematic review (Gijsberts et al. 2011) showed that religion and spirituality are helpful to preserve the caregiver's mental and physical health, and indeed organized religion appeared associated with improved survival and decreased risk of complications. A religious/spiritual perspective provided the caregiver with a meaning for her/his sacrifice in taking care of an

older relative, reinforced her/his motivations, and prevented depression and discouragement. Being part of a religious community might have had at least two positive effects: community volunteers were available to give respite to the caregiver and relieve the burden of caregiving. Also the religious community afforded much needed positive reinforcement, by praising the caregiving effort and acknowledging its important and unique role in promoting the cause of humanity. Perhaps the major cause of caregiver frustration is indeed lack of support, respect, and acknowledgment in a secular culture that pays lip service to the sacredness of human life and considers the sick and the disabled as disposable and as an economic burden. Subsequent studies confirmed these finding (Yoon et al. 2016; Kim et al. 2015).

Spiritual and Religious Interventions

Even in the absence of clinical studies, some common sense directions may be derived from this brief reviews:

- Religion and spirituality play an important role in the welfare of many patients with serious and terminal diseases and especially of older cancer patients. It behooves all practitioners dealing with these diseases to become familiar with the patient beliefs, values, and aspirations and to include these beliefs in the individualized plans of care. We recommend the adoption of the FICA in the initial assessment of each patient. This simple instrument that can be executed in few minutes provides information as to the patient beliefs and as to the availability of a religious or other spiritual community such as church, temple, or mosque or family, friends, yoga group, or other support group able to provide spiritual, emotional, and social support.
- Practitioners should be able to differentiate spiritual emergencies from the medical and the emotional ones and to provide proper support or to involve the proper specialist in the management of these conditions. The proper specialist is generally the hospital chaplain. In some case it may be the religious leader of the patient religious community or a trusted friend or family member.
- The extent to which a practitioner may intervene in the religious/spiritual aspects of a patient life is variable and depends in part on the degree of comfort the petitioner has with his/her own spirituality. Under no circumstances, the practitioner should try to use professional authority for proselytism or for disdaining or belittling a patient's beliefs. At the meantime he/she should be able to address a patient's question with religious implications. For example, a practitioner should investigate further common patient's statements such as "I will do what God wants me to do." Whether a practitioner should oblige a patient's request to pray with her/him is a matter of personal choice. In any case the focus of the practitioner should be on the patient's and not on her/his own beliefs.
- The management of older cancer patients may involve the management of the caregiver as well. It behooves the practitioner to identify and exploit the spiritual and religious resources available to the caregiver.

Conclusions and Perspectives

Undoubtedly religion and spirituality play an important role in the management of many patients with chronic and terminal diseases such as cancer. In the same time, they may be a cause of spiritual distress compromising the patient's quality of life and the adherence to and the effectiveness of treatment. Consequently, as part of personalized care, the practitioner needs to assess whether these domains pertain to the patient or whether they may represent a source of support or of distress and to intervene accordingly. As the management of older cancer patients implies the management of the caregiver, this assessment should extend to the caregiver as well. While some people may consider this assessment as intrusive and violating of the patient's privacy, all studies available show that the opposite is the case. Most patients with cancer and other chronic

diseases welcome this inquiry, confirming the statement of the Italian novelist, essayist, and movie director Pier Paolo Pasolini: "the most important answers concern the question that one does not care to ask!"

The mechanic of this assessment depends on the working environment, but it will always entail a team work. For example, the FICA may be executed by a nurse or a social worker, the social worker should be aware of the available religious and spiritual resources, and a chaplain should be at hand to intervene.

A number of important and urgent research questions emerge from this brief review:

- How do specific beliefs influence the quality of life and the well-being of older cancer patients? In particular is the belief in forgiveness and in love as agape instrumental to peace of mind? Is the emphasis on family duties as is emphasized by Islam and conservative Jewish community important?
- Can we try an objective assessment of spirituality, based on beliefs, practices, and behavior, instead of personal statements? Qualitative research and especially content and language analysis may be instrumental to address this question.
- Is gerotranscendence a cultural or a universal phenomenon?
- Can we identify biological correlates to religion and spirituality that may pertain to aging?

Exploring these and other related questions may involve different research methods, questionnaires, patient interview, biological assays, but mainly it requires a team of individuals committed to promote physical health as a component of total health, convinced that healing is always possible even when cure is not achievable.

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Part VIII

Research Methods in Geriatric Oncology

Tamas Fulop and Martine Extermann

Research Methods: Epidemiologic Research in Geriatric Oncology

63

Esther Bastiaannet

Contents

Abstract

Despite an increase in the number of studies, there is still a lack of evidence-based medicine for older cancer patients, especially for the nonfit and oldest (80 years and over) cancer patients. Randomized controlled trials (RCTs) are still the gold standard in medicine to assess treatment effectiveness and are considered to be the most robust study design to assess treatment effects. Although RCTs are difficult to perform in older cancer patients, it is important to continue work on developing and using alternative designs. Still, some comparative effectiveness questions cannot be answered by existing RCTs, nor they will be studied in future RCTs because of ethical, financial, or other constraints. Observational studies could be an alternative source of data to compare treatment effectiveness in these questions. However, one of the major challenges in observational data is confounders that affect the outcome of the study and differ in proportion between the two treatment groups; effective methods to control for this confounding are essential in nonrandomized studies. A number of strategies including propensity scores and matching are used to control for measured confounders in observational research; however, control for unmeasured confounders presents a greater challenge; the instrumental variable method might provide a better estimate for treatment effectiveness, providing that certain assumptions are not violated.

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Randomized controlled trials · Data extrapolation · Observational studies · Comparative effectiveness research · Confounding by indication · Instrumental variable

Introduction

The number of published geriatric oncology papers has increased in the last years, although the proportion remains low as part of all published oncology papers. Most of the papers concern data from observational studies, usually retrospective data analyses, but there are a few prospective (randomized controlled) trials in older patients. Despite an increase in studies, there is still a lack of evidence-based medicine for older cancer patients, especially for the frail or oldest (80 years and over) cancer patients. This limited evidence from randomized controlled trials (RCT) complicates the development of guidelines for the treatment of older patients. This is further complicated by the fact that the population of older cancer patients is characterized by a large individual variation in physical and mental conditions due to differences in comorbidities, functional status, geriatric syndromes, and socioeconomic aspects resulting in decreased physical reserve and a strong influence of personal preferences in the decision-making process (Bastiaannet et al. 2010; Louwman et al. 2007; Bouchardy et al. 2007; Decoster et al. 2015). In addition, cancer and its treatment may further decrease this physical reserve (Decoster et al. 2015). Observational studies usually show that older patients have a worse survival and receive less aggressive treatment than their younger counterparts. Both overtreatment and undertreatment of the older cancer patients could influence the survival of this heterogeneous group of patients. The use of a geriatric assessment in older cancer patients may identify health and functional problems; besides, some studies have shown that several domains from the geriatric assessment are associated with the outcome (Wildiers et al. 2014; Puts et al. 2012; Decoster et al. 2015).

One of the central aims of medical research is to estimate the effectiveness of one treatment versus another in certain patient groups. RCTs are still the gold standard in medicine to assess treatment effectiveness and are considered to be the most robust study design to assess treatment effects. New drugs also need to be assessed in the older cancer patients as specific adverse effects might occur that could change the ratio of toxicity versus benefit (Wildiers et al. 2013). Aging is a highly individualized process that results in changes in organ function, which could affect the pharmacokinetics of anticancer drugs and may alter the drug metabolism and treatment tolerability (Wildiers et al. 2013; Wildiers et al. 2003). Pharmacokinetic studies are therefore needed specifically for older cancer patients to study these aspects. In general, clinical trials should be including patients from the entire age range of the cancer population; however, the heterogeneity of the older population generally does not allow this (Wildiers et al. 2013). Specific trials for subgroups of older patients are therefore needed, with appropriate control arms depending on the setting (Wildiers et al. 2013). As an alternative, to capture older patients who are not included, large observational studies in the nonfit older population should be considered, preferably linked to randomized trials (Wildiers et al. 2013).

Some important effectiveness questions in geriatric oncology concern comparing no treatment with treatment (Wildiers et al. 2013) However, several challenges can exist with this RCT design. First, patient participation in a trial of treatment versus no treatment is generally more difficult than participation in a trial of treatment A versus B (as the impact of random assignment is larger), and selection bias and crossover can occur (Wildiers et al. 2013). Another aspect is that funding is more difficult to obtain for these kind of studies as there is generally no benefit for the industry (Wildiers et al. 2013). Although RCTs are difficult to perform in older cancer patients, it is still important to continue work on developing and using alternative designs, especially for the nonfit and oldest elderly (Wildiers et al. 2013).

Still, some comparative effectiveness questions cannot be answered by existing RCTs, nor

will they be studied in future RCTs because of ethical, financial, or other constraints (Baiocchi et al. 2014). Observational studies could be an alternative source of data in these questions to compare treatment effectiveness (Baiocchi et al. 2014). However, one of the major challenges in observational data is confounders, defined as variables (known pre-treatment) that affect the outcome of the study and differ in proportion between the two treatment groups; effective methods to control this confounding are essential in nonrandomized studies (Baiocchi et al. 2014; Greenland 2000). A number of strategies including propensity scores and matching are used to control for measured confounders in observational research; however, control for unmeasured confounders presents a greater challenge (Baiocchi et al. 2014;D'Agostino 1998).

This chapter discusses the problems with RCTs and extrapolation of study results to the older cancer population, the lack of new RCTs in geriatric oncology, outcome measurements, and challenges in observational research, as well as potential use of observational data in geriatric oncology.

Data from Randomized Controlled Trials

As one of the few RCTs without an upper age limit, the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial provided an unique opportunity to study the association between age and disease-specific mortality (van de Velde et al. 2011; van de Water et al. 2012c). The TEAM trial is a randomized, phase 3, multinational, open-label study conducted in postmenopausal breast cancer patients with estrogen receptor-positive tumors, progesterone receptor-positive tumors, or both. Patients were randomized to receive either exemestane or tamoxifen, followed by exemestane for a total of 5 years. This study (van de Water et al. 2012c) showed that the disease-specific mortality and breast cancer relapse was higher in older breast cancer patients as compared to the younger patients included in the trial. This is despite the fact that disease-specific mortality as proportion of all-cause mortality decreased with age. The authors discuss several possible underlying mechanisms to explain these results: first, older patients may experience undertreatment; several studies showed that older breast cancer patients have a lower chance to receive standard care (Yancik et al. 2001; Bastiaannet et al. 2010; van de Water et al. 2012a). Second, a previous analysis of the TEAM study showed that older patients discontinued study medication more frequently and received less often subsequent therapy (van de Water et al. 2012b). However, this study showed that discontinuation (within the first year) was not associated with disease-specific mortality (van de Water et al. 2012b). Next, older patients may experience overtreatment; in this situation, adverse events of the breast cancer treatment may result in mortality attributed to breast cancer, e.g., due to toxicity. However, in the study, breast cancer relapse was shown to increase with age, so overtreatment is not likely to explain the findings. The authors also speculate that breast cancer in the older patients might have a more aggressive biology; the older patients did present with larger tumors but nodal status was similar. It was, however, not possible to test this hypothesis in further detail in this study and other studies suggest the opposite (Diab et al. 2000; Wildiers et al. 2007). Besides, adjustment for both treatment and tumor characteristics did not diminish the association between age- and disease-specific mortality. Consequently, other unknown factors might have contributed to the findings, e.g., the immune response to the tumor or the response to therapy which needs further research (Zitvogel et al. 2006; Lichtman et al. 2007).

Extrapolation of Study Results to the General Older Population

Inclusion in clinical trials is often selective to ensure the internal validity of the study, although this may compromise the external validity (Rothwell 2005). For the above-described TEAM trial, it was possible to make a head-to-head comparison of the included patients with breast

cancer patients of corresponding age from the general population (Van de Water et al. 2014). The study confirmed that patients who participated in the trial had more favorable patient and tumor characteristics than patients from the general population; however, for patients aged 65–74 years, both patient groups had a comparable overall survival and thus the selective inclusion could be overcome by taking into account these characteristics. On the contrary, in patients aged 75 and over; differences in overall mortality between the groups could not be explained by patient, tumor, or treatment factors, and unmeasured mechanisms may have a role in the selective inclusion (Van de Water et al. 2014).

In general, the reason for the selective inclusion of older patients in RCTs depends on several factors. Eligibility criteria are the most important to hamper the inclusion of older patients or patients with comorbidities (Van Spall et al. 2007). A recent study (Zulman et al. 2011) showed that in RCTs published in the five major medical journals, 20% excluded patients based on age. For the remaining studies, a large proportion excluded patients with age-related diseases. Besides the inclusion criteria, reluctance of physicians to include (Townsley et al. 2005; Kemeny et al. 2003; Kornblith et al. 2002) and willingness of patients to participate in RCTs may further hamper the inclusion of older patients. Besides, for some older patients, factors related to the trial logistics may play a role (Townsley et al. 2005).

The International Society for Geriatric Oncology (SIOG) as well as many researchers and clinicians have made a plea for new studies in older cancer patients that also address other endpoints, next to survival and recurrence, as functional and cognitive decline and quality of life (de Glas et al. 2014a; Wildiers et al. 2013; Pallis et al. 2011, 2010; Balducci 2000; Biganzoli et al. 2012; Aapro et al. 2009). It may however take several years from the initiation of a trial to the publication of the results. Consequently, new evidence in 10 years is most likely to come from studies that are initiated at this moment (de Glas et al. 2014a). A study published in 2014 with respect to breast cancer presented an overview of all current clinical trials at that moment in breast cancer, with a special focus on older patients (de Glas et al. 2014a). To study this, the clinical trial register of the United States National Institute of Health (www.clinicaltrials.gov) was assessed in November 2013 for all phase II-IV clinical trials with respect to breast cancer which were currently including patients or planning to start (de Glas et al. 2014a). The study showed that of the 463 included trials, only 9 (2%) studied breast cancer in older patients. A large proportion of the trials did not have an upper age limit; however, a majority excluded patients based on performance status. The most common endpoints of the studies were overall survival, disease-free survival, and response to therapy, although the studies in older patients more frequently included endpoints as quality of life functional status and cognition (see Fig. 1) (de Glas et al. 2014a).

There are a number of possibilities when it comes to choosing the endpoints in clinical trials including older patients with cancer, and this requires a careful reflection on the ultimate goals of the studied therapies (Wildiers et al. 2013). As shown in the paper from de Glas et al. (2014a) and Wildiers et al. (2013), the majority uses traditional endpoints as overall survival, disease-free survival, recurrence, or breast cancer survival. Overall survival is a crucial endpoint, but disease-specific survival is as most important as deaths resulted from other causes occurring more frequently in the older population (Wildiers et al. 2013). However, the SIOG position paper states that although these endpoints are important, patient-related endpoints are crucial to assess risks and benefits of treatment in older patients (Wildiers et al. 2013; de Glas et al. 2014a). Composite endpoints allow the integration of multiple endpoints, and could have advantages in RCTs including older patients; quality of life, preservation of functional capacity, cognitive function, and independence are most important for the older population and should be included (Wildiers et al. 2013; de Glas et al. 2014a; Hurria and Lachs 2007). In addition to these endpoints, incorporating a geriatric assessment in the trial is essential to understand the effect of treatments (Wildiers et al. 2013). According to the SIOG position paper, patients across the entire age

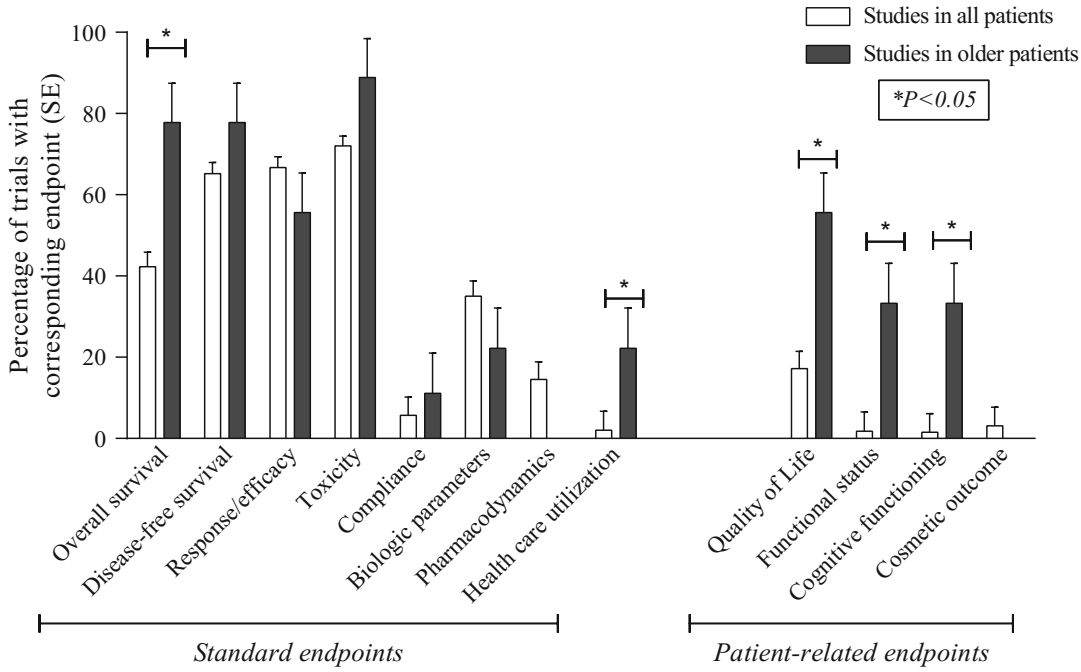

Fig. 1 Endpoints of studies in older patients compared to studies in all patients (Reprinted from de Glas et al. (2014a))

spectrum should be included in trials studying treatments which are expected to be used across all age categories. However, several treatments are not suitable for unfit or frail elderly due to (expected) higher or even unacceptable toxicity; in this setting, elderly specific trials are needed to study appropriate therapy in this group of patients, e.g., comparing modified approaches of adapted chemotherapy with palliative or supportive care (Wildiers et al. 2013).

In general, patient participation in a trial comparing treatment versus no treatment can be challenging; other possible treatment designs might be more appropriate. Several attempts of specific RCTs in the older patients have failed in the past for several reasons. As a consequence of the above challenges, we will not be able to provide a large proportion of the older cancer patients with an evidence-based treatment recommendation (de Glas et al. 2014a). Observational studies – provided that adequate methodology is used – could serve as an alternative to RCTs in older cancer patients and fill some of the knowledge gaps in geriatric oncology, as they are more representative for the entire older cancer patient population (de Glas et al. 2014a; Wildiers et al. 2013; van de Water et al. 2011, 2014).

Observational Studies

Cohort Data from Cancer Registries

One of the main advantages of observational data, especially from cohort data obtained from cancer registries with a high completeness percentage, is that all older patients in the population are included. National differences in the treatment and survival of younger and older patients can be shown, as well as time trends for countries. Studies from Europe have shown that older patients are diagnosed at a higher stage, receive less aggressive treatment, and have a decreased survival as compared to younger patients, and moreover, this survival has not increased at such a fast rate as for younger patients (studies from the Netherlands) (Bastiaannet et al. 2011, 2010). With the inclusion of a large number of patients, trends within the older population in several age categories can be assessed. Studying time trends for both

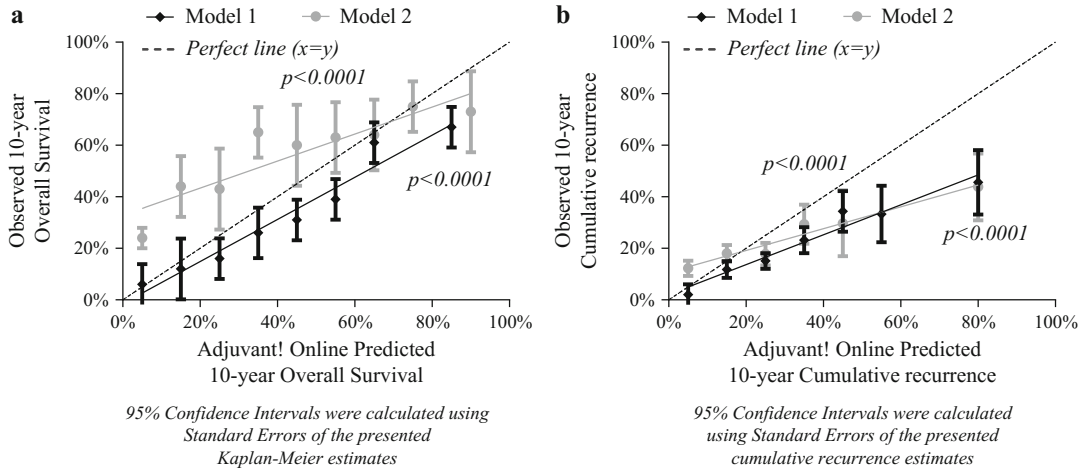

Fig. 2 Observed versus predicted 10-year (**a**) overall survival and (**b**) cumulative recurrence (Reprinted from de Glas et al. (2014c))

treatment and survival in cohort data with a high completeness can show interesting patterns. One of the studies using this method investigated time trends in surgical treatment, overall survival, and relative survival in older patients with resectable breast cancer diagnosed between 1995 and 2011 in the Netherlands (n = 26,292) (de Glas et al. 2014b). The study showed that the proportion of older patients who did not receive surgery increased considerably in the study period; however, overall and relative survival did not change in this period in the Netherlands (de Glas et al. 2014b). The findings of this study suggest that the current therapies, which include the omission of surgery, do not influence the survival. This was confirmed by comparing hospitals with different treatment strategies on outcome; again no differences in both overall and relative survival were shown (de Glas et al. 2014b). Although the study has some limitations, an important one is that the increased omission of surgery was not the only change in treatment strategy over time which limits the attribution of survival trends to the omission of surgery alone, showing these trends can hint to important treatment effects (de Glas et al. 2014b).

Another application of cohort data is the validation of prediction models; usually designed with a cohort of younger patients, for their use in older patients. In breast cancer patients, the correct identification of patients who have a higher risk of breast cancer recurrence and mortality is important to select patients who might benefit from adjuvant therapy (de Glas et al. 2014c). In practice, the Adjuvant! Online prediction tool is the best known (Ravdin et al. 2001). However, this model was developed with a study population of breast cancer patients in the age range 35–69 years from the Surveillance, Epidemiology, End-results (SEER) registry (n = 34,252) (Ravdin et al. 2001). The study of de Glas et al. (2014c), validating Adjuvant! Online in a cohort of older breast cancer patients, indeed showed that the prediction model does not accurately predict overall survival and disease recurrence in older patients with early stage breast cancer (Fig. 2). An important advantage of registry data as performed in this study is that an (large) unselected cohort of older patients can be included. Development of an improved prediction model specifically for older patients is important for several cancer types; this could improve the outcomes and individualize clinical decision making (de Glas et al. 2014c).

International Comparisons

Observational data are also suitable to make international comparisons between regions or counties

to study differences in treatment and survival. One of the larger studies that included an age-specific analysis was the study of EUROCARE, including data from 24 cancer registries in 14 European countries ($n = 114{,}312$) (Allemani et al. 2012). In most part of Europe (northern, western, and southern parts and the UK), survival increased with increasing age up to the age of 69 years, but decreased sharply for older patients (Allemani et al. 2012). In eastern Europe, survival already started to decrease after the age of 50 years and was very low for the oldest age group. The differences between the age categories were most pronounced for northern and western Europe, and less in southern Europe and the UK (Allemani et al. 2012). Another international comparison, comparing several European countries and USA, showed large differences in locoregional treatment of older breast cancer patients (Kiderlen et al. 2012). Further detailed analyses, preferably by using country as pseudorandomization, are needed to study the most effective treatment strategies for older patients. This comparative effectiveness research could provide clues to the most optimal strategy, especially if treatment strategies are different in countries with similar health care systems.

Treatment Effectiveness

One of the major challenges to study treatment effectiveness using observational data are the methods to control for confounding, which is inherent to analyzing observational data for treatment effectiveness. Confounders are defined as variables, known before treatment, that affect the outcome of the study but differ in proportion between the two treatment groups (Baiocchi et al. 2014; Greenland 2000). A number of strategies, including propensity score and matching, are used to control measured confounders in observational research; however, control for unmeasured confounders remains a challenge (Baiocchi et al. 2014; D'Agostino 1998). The instrumental variable (IV) method was developed to control these unknown and unmeasured confounding factors (Baiocchi et al. 2014; Stuart 2010). An IV is defined as a variable that mimics treatment allocation as in a randomized controlled trial (Greenland 2000; Bennett 2010). There are however a few assumptions to which the factor must fulfill. Country may be a suitable IV as place of residence determines the allocation of a patient to one of the cohorts; under the assumption that there are (large) differences in treatment strategy, that patient and tumor characteristics are equally distributed and that the health care systems of both countries are similar.

In more detail, these are the three assumptions which should be met when considering a factor like country as IV. The first assumption states that the IV should be related to the chance of a certain treatment or treatment strategy. In general, a larger contrast leads to a better IV analysis. When comparing countries, it is usually the complete treatment strategy under investigation as cancer management consists of different combinations of neoadjuvant treatment, surgery, radiotherapy, and adjuvant systemic treatments. To assess the strength of the countries used as instrumental variable, an F-statistic can be calculated by performing a regression analyses which predicts treatment as a function of the instrument and covariates (Bennett 2010). An F-statistic of more than 10 is often used to indicate that the instrument is not weak, although there are some discussions in the literature on the use of F-statistics (Bennett 2010). The second assumption is that the IV country should not be related to the prognosis of the patient. So, there should be no differences in the two countries with respect to characteristics of the patients and tumor that are associated with prognosis. If there are large differences in variables which are associated with the outcome, stratification on these variables could provide a solution. The third assumption is that the IV should not have an effect on the outcome other than through the chance to receive a certain treatment (strategy). This means that there should be no important differences between countries with respect to other aspects of the health care system which could influence the outcome. Finding the most appropriate comparisons between countries can be challenging, but worthwhile as bias from confounding by indication in traditional

analyses is large (Bennett 2010;Newhouse and McClellan 1998;Martens et al. 2006).

Using calendar time is another method to assess treatment effectiveness in observational research (Baiocchi et al. 2014). Treatment strategies for most cancer types have changed over the past decades and have been assessed together with changes in outcome over time. Although this technique probably results in more reliable estimates than direct comparison of treatments (Mdege et al. 2011), there might be several factors that can lead to bias in these kind of studies, e.g., information bias (with more reliable data collection in recent years) or other factors explaining the changes in outcome than treatment (e.g., changes in diagnostic work-up) (Baiocchi et al. 2014). Consequently, the use of calendar time is most useful and reliable if a large change in clinical practice occurs in a short period (Baiocchi et al. 2014). This is also the concept of a stepped wedge design, where a change in treatment or a new treatment or intervention is randomly introduced over a certain period of time (Dekkers 2012).

One of the most applied IV statistical analyses technique is the two-stage least squares estimation (Bennett 2010). The first step in this analysis is to obtain a regression estimate by regressing treatment on the instrumental variable country with adjustment for relevant measured confounders. In the second step, the predicted value of the treatment is used in a regression of the outcome, adjusted for the same confounders as in the first step. Standard techniques for regression analyses are available in some software packages; however, solid techniques to analyze survival data are still pending. The GRACE (Good ReseArch for Comparative Effectiveness) and ISPOR (International Society for Pharmaco-economics and Outcomes Research) guidelines and checklist do provide guidance with respect to comparative effectiveness studies in general (Dreyer et al. 2010; Johnson et al. 2009).

As already mentioned by Hernán and Robins, there are some good reasons for skepticism that an analytic method solves one of the major problems in epidemiological research (Hernan and Robins 2006). The effect estimate of the instrumental variable will be biased if country as an instrument does not meet the three main assumptions, but the assumptions (specifically the third) are difficult or not empirically verifiable (Hernan and Robins 2006). Moreover, any bias as a result of these violations will be amplified if the association between country and exposure is weak (Hernan and Robins 2006; Brookhart et al. 2010). At least, studies using an instrumental variable should include a clear description of the assumptions and results to determine whether the instrumental variable is valid (Davies et al. 2013). However, specifically in geriatric oncology, it is recognized that RCTs have important limitations in real-world decision making (Armstrong 2012; Van de Water et al. 2014), as a result of restrictive enrolment criteria and the fact that RCTs are often not feasible in the older population. The instrumental variable method, with further enhancement of the method over time, could serve as a potential solution to perform specific analyses in geriatric oncology, and could provide clues to the most optimal treatment strategy and initiate specific RCTs and tailored treatment for the older cancer patients.

Competing Risks of Death

In many of the studies, cause-specific endpoints such as recurrence or cancer-specific mortality are used (de Glas et al. 2014a, 2016). However, an important consideration in studies with older patients that use these cause-specific endpoints is that the risk of dying from another cause before reaching the endpoint of interest is high (Berry et al. 2010; Pallis et al. 2011). The most commonly used method to estimate survival probabilities over time is the Kaplan-Meier method which can deal with censored follow-up times (de Glas et al. 2016). An important assumption of this method is independent censoring where it is assumed that patients with censored times have (at any time) the same survival prognosis as patients who are still in the study (Verduijn et al. 2011; de Glas et al. 2016). However, in the competing risk setting, this assumption does not hold as patients who die of other causes have a probability of zero to reach the cause of interest in these studies (de Glas et al. 2016). An alternative is the

cumulative incidence competing risks (CICR) method (Andersen et al. 2012; Putter et al. 2007; de Glas et al. 2016), which holds the assumption that patients who experienced a competing event are no longer at risk for the endpoint of interest of the study and estimates the actual probabilities of reaching different endpoints (cumulative incidences) (Verduijn et al. 2011; de Glas et al. 2016). The different statistical time-to-event methods such as the Cox proportional hazards model and the Fine and Gray model also deal with competing events in different ways (Andersen et al. 2012; Putter et al. 2007; Berry et al. 2010; de Glas et al. 2016). The Cox proportional hazards model is the most appropriate when assessing the relative effect size in etiologic studies, while the Fine and Gray model should be used to estimate effects on absolute risk in predictive research and populations with a high frequency of competing events. These challenges are especially present in studies of older patients with cancer types as prostate cancer or low risk breast cancer as the risk of competing events is especially large in these populations and less applicable in studies that investigate highly aggressive tumor types such as pancreatic or lung cancer as the risk of dying from the cancer is high in these populations (de Glas et al. 2016).

For individuals with a cancer diagnosis, one would ideally like to have reliable disease-specific mortality information (Dignam et al. 2009); however, attributing cause of death depends on the judgment of the physician completing the death certificate and the coding medical registry clerk and can be confusing (Dekker et al. 2014). The accuracy of cause of death statements has been debated in several studies (Harteloh et al. 2010; Welch and Black 2002; Brown et al. 1993; Ederer et al. 1999; Dekker et al. 2014). Brown et al. showed that the proportion of non-cancer mortality was considerably higher in cancer patients than in the general population (Brown et al. 1993). This issue is particularly seen in the older population as determining cause of death can be notoriously difficult in this group, as unexpected or unexplained deaths may be attributed incorrectly to the cancer and the risk of competing potential causes of mortality substantially increases with age (Hu et al. 2013; Goldoni et al. 2009). Additionally, cause of death extracted from death certificates of patients with cancer is not always accurate. Relative survival is frequently used as an alternative, and does not require cause of death information (Dignam et al. 2009; Dickman et al. 2004; Ederer et al. 1961; Henson and Ries 1995). Relative survival is calculated as observed all-cause survival in the cohort divided by expected survival estimated from the general population matched by age, sex, and year and is a good alternative to cancer-specific survival in observational data from older cancer patients.

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Research Methods: Translational Research in Geriatric Oncology

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Abstract

Cancer is predominantly a disease of aging, and older adults with cancer represent the majority of cancer diagnoses and deaths in the United States. Despite dramatically increasing numbers of older adults developing cancer, our understanding of this potentially vulnerable population remains limited. We are ill prepared to care for this surging demographic, and the translation of scientific discoveries arising in the lab or clinical research into clinical applications to care for the aging population has never been more important. This chapter will focus on proposed biomarkers of functional age that could complement existing assessments of older adults with cancer. First, we will discuss biological markers of aging such as systemic inflammatory markers and markers of senescence. Second, we will review the role of body composition and imaging for evaluating sarcopenia. Next, we focus on cardiovascular performance and discuss the potential importance of gauging exercise capacity. Lastly, we address potential methodologic challenges and design considerations related to translational research in older adults with cancer. Translational research offers several novel avenues to improve our assessments of older patients to aid in the assessment of the risks and benefits of treatments. Further development of these promising areas is necessary to improve the quality of care for this growing and vulnerable population.

Keywords

Translational research · Geriatric oncology · Biomarkers of aging · Sarcopenia · Cardiovascular fitness · Cellular senescence

Introduction

Older adults represent the majority of cancer diagnoses and deaths in the United States (Surveillance Epidemiology and End Results (SEER) program). By the year 2030 it is expected that nearly 70% of all cancer cases will be in adults 65 years of age or older (Smith et al. 2009). Despite these dramatic numbers, our understanding of this population remains limited (Scher and Hurria 2012). We are ill prepared to care for this surging demographic, and the translation of scientific discoveries arising in the lab or clinical research into clinical applications to care for the aging population has never been more important.

Aging is a heterogeneous process with resultant wide differences in the health status in patients of the same chronological age. These age-related differences contribute to the large variability in treatment tolerance and outcomes seen in older patients. Age-related differences are sometimes readily apparent from the "eyeball test" in assessing patients from the door of the exam room, such as the use of wheelchair, but often outward appearances can be deceiving. Many older patients with cancer rated as having a "normal" performance status have important impairments that go unrecognized (Jolly et al. 2015). Due to inadequate routine measures of tolerability, many older patients do not receive chemotherapy and other cancer therapies based on chronological age alone, despite evidence that some older adults derive similar benefits as younger patients (Sargent et al. 2001). Evaluating a patient's functional age and estimating treatment tolerability can be challenging and requires a detailed and thorough assessment of an individual patient.

Table 1 Potential biomarkers of interest

Biomarker	Source	Test	Associations with	
			Frailty/ function	Mortality
Inflammatory markers (CRP, IL-6, TNF-α, D-dimer)	Serum or plasma	ELISA	Yes	Yes
Telomere length	Leukocyte DNA	PCR, Southern blot, FISH, STELA	Yes	Yes
$P16^{INK4a}$	Peripheral T-lymphocyte RNA	PCR	Unknown	Unknown
Body Composition/sarcopenia	CT, MRI, DEXA, BIA	Commercially available body composition software	Yes	Yes
Maximal oxygen consumption (VO_2 max)	O_2 and CO_2 of inhaled and exhaled air	Incremental exercise testing	Yes	Yes

Modified from Hubbard et al. (2014)
Abbreviations: *CRP*, C-reactive protein; *IL-6*, interleukin-6; *TNF-α*, tumor necrosis factor-α; *ELISA*, enzyme-linked immunosorbent assay; *PCR*, polymerase chain reaction; *FISH*, fluorescence in situ hybridization; *STELA*, single telomere length analysis; *CT*, computed tomography; *MRI*, magnetic resonance imaging, *DEXA*, dual-energy x-ray absorptiometry; *BIA*, bioelectrical impedance analysis

Many tools exist that can aid in assessing functional age and in predicting the risk of morbidity and mortality in older patients. Geriatric assessment provides a detailed evaluation of a patient's functional status, cognition, nutritional status, comorbidity, and social support, thus providing a broader overall understanding of individual characteristics that may impact morbidity and mortality (Hurria 2009). There is a growing literature on the use and benefits of geriatric assessment in older patients with cancer (Wildiers et al. 2014). Short detailed geriatric assessments have been developed and validated for use in cooperative group settings and in community oncology centers (Hurria et al. 2011; Williams et al. 2014). All older adults with cancer are recommended to undergo a geriatric assessment to objectively appraise their health; however, geriatric assessments can be time consuming, and models to incorporate geriatric assessment into routine care are not widely implemented (Magnuson et al. 2016). Frailty is a geriatric syndrome of increased vulnerability for adverse outcomes, and although related to chemotherapy toxicity and long-term survival in older adults with cancer, frailty assessment is rarely employed in clinical practice (Cohen et al. 2016; Guerard et al. 2017). Biomarkers may be able to help fill these gaps. The ideal biomarker would reflect a patient's functional reserve and aid in prediction of tolerance to treatment. Many proposed biomarkers exist (see Table 1) with variable amounts of supporting evidence.

This chapter will focus on proposed biomarkers of functional age that could complement existing assessments of older adults with cancer. A summary of proposed biomarkers is presented in Table 1. First, we will discuss biological markers of aging such as systemic inflammatory markers and markers of senescence. Second, we will review the role of body composition and imaging for evaluating sarcopenia. Next, we focus on cardiovascular performance and review the potential importance of gauging exercise capacity. Lastly, we address potential methodologic challenges and design considerations related to translational research in older adults with cancer.

Potential Biomarkers of Aging

Systemic Inflammatory Markers

Markers of systemic inflammation have been extensively studied as potential biomarkers of functional age. Aging is characterized by a

pervasive low-grade and chronic inflammation, coined as "inflammaging" (Franceschi and Campisi 2014). As most age-related diseases such as atherosclerosis and diabetes are related to chronic inflammation, inflammation is a risk factor for both morbidity and mortality in older adults (Franceschi et al. 2000). These markers of inflammation, which include interleukins (most prominently IL-6), C-reactive protein (CRP), and tumor necrosis factors (TNF-α), correlate with measures of frailty, functional decline, and survival (Franceschi and Campisi 2014). As TNF- α and IL-6 can stimulate production of prothrombotic factors that are notably increased along with inflammatory markers (Kanapuru and Ershler 2009), for the purposes of this chapter, we will also include markers of coagulation system such as D-dimer and soluble vascular cell adhesion molecule (sVCAM) with systemic inflammatory markers. Pro-inflammatory markers increase with advancing age, even in healthy individuals (Fagiolo et al. 1993; Sindermann et al. 1993), and are proposed to accelerate the aging process (Franceschi et al. 2007; Vasto et al. 2007).

Several studies have demonstrated the relationship of inflammatory markers with clinical measures of frailty. In a large analysis from the Cardiovascular Health Study, frail older adults had significantly elevated levels of CRP, factor VIII, and D-dimer compared to non-frail patients that persisted even after controlling for age, sex, race, and comorbidities (Walston et al. 2002). Another study of 110 patients over the age of 75 years of age found similar elevations in TNF-α, IL-6, and CRP with increasing frailty (Hubbard et al. 2009). These markers have also been shown to correlate with physical function and functional decline in older patients. In a study of physical function decline in older adults, Cesari et al. found high levels of IL-6, CRP, and IL-1RA were significantly associated with poor physical performance and reduced muscle strength (Cesari et al. 2004). In another study by Cohen et al., high levels of IL-6 and D-dimer were associated with declines in measures of function and a twofold increased risk of mortality among community dwelling older adults (Cohen et al. 2003). Thus, these inflammatory markers may be beneficial in identifying frail older adults and those with functional decline.

Although inflammatory markers can be collected and easily measured during cancer management, the cancer itself can alter and produce inflammation (Hubbard et al. 2014). This greatly limits the utility of inflammatory markers in oncology and is counter to the principles of an ideal biomarker that should be independent from specific pathologic conditions (Falandry et al. 2013). Nonetheless, several studies have explored the use of inflammatory markers in patients with cancer. In a study by Brouwers et al., inflammatory markers were correlated with increasing chronologic age, worse Eastern Cooperative Oncology Group (ECOG) performance status, and impairments in instrumental activities of daily living (IADL) in patients with breast cancer (Brouwers et al. 2015). Markers of inflammation were also associated with poorer global quality of life and increased fatigue in a study of adults with acute myeloid leukemia. The role of inflammatory markers in older adults with cancer remains uncertain, and whether these markers can predict individual's tolerance to cancer treatment or functional decline associated with cancer treatment warrants further study. Although a focus of age-related research for over two decades, markers of inflammation have not assumed a major role in clinical care. Future studies designed to evaluate if any single marker or combination of inflammatory markers have an independent role in predicting outcomes and/or improving management in adults with cancer are needed.

Markers of Senescence

When cells undergo DNA damage, the cell can activate a response pathway leading to permanent cell cycle arrest (Hubbard et al. 2014). This state of irreversible growth arrest, known as cellular senescence, can be triggered by multiple mechanisms including telomere shortening or epigenetic derepression of the INK4a/ARF locus (Collado et al. 2007). These mechanisms serve to limit aberrant cellular proliferation and protect against the development of cancer. As we age, we

accumulate more and more senescent cells; therefore, measures of cellular senescence could be used as surrogates for physiologic aging. There is also a connection between senescence and increasing levels of chronic inflammation. Senescent cells can secrete a large number of cytokines, chemokines, and other pro-inflammatory proteins known collectively as the senescence-associated secretory phenotype (SASP) (Coppe et al. 2008). SASP related factors are proposed to increase inflammation in the surrounding microenvironment and ultimately contribute to the aging process. Although there is no established circulating marker of cellular senescence, other markers associated with the senescence process, including telomere length and $p16^{INK4a}$, have been explored as possible biomarkers of aging.

Telomeres are protein structures located at the ends of eukaryotic chromosomes that are required for genome stability and progressively shorten overtime with cell division. Short telomeres trigger DNA damage checkpoints that mediate cellular senescence and eventually lead to mitotic arrest known as senescence (Sharpless and DePinho 2004). As telomeres shorten with increasing age and have been correlated with aging-related disease, telomere length has been proposed as a biomarker of aging (von Zglinicki and Martin-Ruiz 2005). In a seminal study of older adult residents of Utah who had donated blood, shorter telomeres in blood DNA were associated with poorer survival (Cawthon et al. 2003). The mortality rate of individuals with shorter telomeres was nearly twice that of those with longer telomeres. The role of telomere length in carcinogenesis and as a predictor of cancer prognosis has also been explored. In a recent systematic review and meta-analysis of seven individual studies with a total of 956 patients with colorectal cancer, short telomere length in peripheral blood leukocytes was significantly and independently associated with poorer overall survival (Hazard Ratio 2.01, 95% CI 1.46 to 2.77, $p < 0.001$) (Jia and Wang 2016). Short telomere length has also been associated with negative prognosis in patients with breast cancer, soft-tissue tumors, and lung cancer in several retrospective studies (Pallis et al. 2014). However, many prospective studies have failed to demonstrate similar results (Pallis et al. 2014). The dysfunction of telomeres may also represent an important role as a biomarker. Telomere dysfunction similarly limits the proliferative capacity of cells with resultant senescence or apoptosis. Several protein markers (including CRAMP, stathmin, EF-1alpha, and chitinase) have been identified as secreted from telomere-dysfunctional bone marrow cells (Jiang et al. 2008). These markers, which can be detected in serum, were able to discriminate between young and old individuals as well as those with age-related disease (Jiang et al. 2008). Although several studies have explored telomere length or dysfunction as a biomarker of aging, the overall results are inconclusive (Mather et al. 2011). Nonetheless, telomere length remains a compelling marker of interest in search for markers of biologic age given its correlation with aging and age-related disease.

The expression of the tumor suppressor $p16^{INK4a}$ sharply increases with age and has also been proposed as a potential biomarker of aging. Expression of $p16^{INK4a}$ codes for a protein that blocks cyclin-dependent kinase, ultimately leading to cellular senescence and permanent cell-cycle arrest (Liu et al. 2009). Although $p16^{INK4a}$ is expressed in most mammalian tissues, it is most readily measured from whole blood via quantitative real-time polymerase chain reaction of T-lymphocyte RNA. Gene expression of $p16^{INK4a}$ increases nearly tenfold with aging over the life span and has also been significantly associated with tobacco use and physical inactivity as well as correlated with the inflammatory marker IL-6 (Liu et al. 2009). This promising biomarker is the focus of several ongoing studies to evaluate its usefulness as a predictor of toxicity and outcomes.

Impact of Cancer Therapies on Biomarkers of Aging

The use of molecular biomarkers not only allows for a better assessment of physiologic aging, but may also provide a surrogate outcome for the aging process itself. Surgical procedures are associated with a cascade of cytokine and acute phase

responses, typically measured by either IL-6 or CRP, and the degree of inflammatory response appears associated with the magnitude of the operative procedure (Watt et al. 2015). For example, simple cholecystectomy procedures have been shown to be associated with modest increases in CRP (52 mg/L), while larger increases in CRP have been associated with colorectal cancer resection (123 mg/L) (Watt et al. 2015). Although these short rises in inflammatory markers after surgery are concerning, these are not likely to result in long-term accelerated aging. Radiation therapy causes radiation-induced injury to normal tissue by depleting tissue stem cells and progenitor cells while also damaging the vascular endothelial microvessels (Kim et al. 2014). This results in the excessive generation of reactive oxygen species and the production of pro-inflammatory cytokines (Kim et al. 2014). The long-term implications of radiation are best demonstrated in survivors of childhood cancers with the accelerated development of secondary malignancies (such as breast cancer) and other comorbidities (Bhatia et al. 2015). Chemotherapy is also another major cause of accelerated aging. Chemotherapy preferentially targets rapidly dividing cells, such as tumor cells, but also results in side effects and toxicities as a result of its indirect effects on normal healthy tissue (Beeharry and Broccoli 2005). While patients may tolerate the acute side effects of chemotherapy, the long-term unintended impact of cytotoxic chemotherapy is only now becoming apparent. Telomeres in individuals treated with cytotoxic chemotherapy are shorter than age-matched control individuals without exposure to chemotherapy (Beeharry and Broccoli 2005). The attrition of telomeres has also been shown to correlate with the intensity of cytotoxic chemotherapy (Diker-Cohen et al. 2013). In another recent study by Sanoff et al., significant increases in $p16^{INK4a}$ expression were demonstrated in 33 women with early stage breast cancer undergoing adjuvant chemotherapy (Sanoff et al. 2014). This rise was comparable to 14.7 years of chronological aging and suggests a potential gerontogenic effect of chemotherapy. Telomere length was not affected by chemotherapy in this study. This finding was collaborated by a cross-sectional study of breast cancer survivors that demonstrated a similar $\log_2$-increase in $p16^{INK4a}$ with the administration of chemotherapy. The long-term impact of the potential accelerated aging phenomenon associated with some cancer therapies remains unknown and is an area of increasing research.

Conclusions

Many promising novel molecular biomarkers exist that may ultimately aid in the assessment of older adults with cancer. There is a clear need to incorporate biomarkers into oncology trials, and many trials are beginning to incorporate the aforementioned markers. The ideal marker would provide additional information to our standard oncologic evaluation and be easily repeated at various time points throughout treatment without undue harm. The best predictive power is likely to be achieved by utilizing a panel of markers that stratify patients into risk or frailty groups (Hubbard et al. 2009). These novel biomarkers also offer an opportunity to study the unintended pro-aging effects of cancer treatments on patients. Further understanding the long-term impacts of these gerontogenic effects and finding ways to minimize these effects are needed.

Body Composition and Sarcopenia

Introduction

Age-related loss of muscle mass and function, known as sarcopenia, is a complex age-related condition associated with an increased risk for adverse outcomes. Rosenberg et al. were the first to introduce the term sarcopenia, to describe the loss of muscle mass with aging. The term sarcopenia is a combination from the Greek words: *sarx* (flesh) and *penia* (loss) (Rosenberg 1997). A step further was made by Baumgartner et al. who investigated the extent of the problem posed by muscle loss seen with aging in describing the age-related loss of muscle mass seen in older adults using dual-energy X-ray

absorptiometry (DEXA) to compare appendicular skeletal muscle mass in older adults to a younger reference group in New Mexico (Baumgartner et al. 1998). Investigators found a marked decline in muscle mass in older adults with more than half of the octogenarians two or more standard deviations below the younger reference group. They also showed that low muscle mass was associated with self-reported physical disability (Baumgartner et al. 1998).

Although the precise underlying mechanisms causing changes in body composition with aging are not yet clear, after the third decade of life, approximately 1% of muscle mass is lost every year (Brzeszczynska et al. 2016). Sarcopenia has been associated with functional impairment, disability, reduced health-related quality of life, loss of independence, and mortality (Gale et al. 2007; Visser et al. 2005; Janssen et al. 2002; Rolland et al. 2008). The yearly financial burden of sarcopenia is estimated at ~$18.5 billion in the USA alone (Janssen et al. 2004). In recent recognition of sarcopenia as a distinct medical condition, an ICD-10 has been established and made available for use as of October 1, 2016 (M62.84). A variety of factors contribute to the development of sarcopenia with aging, including clinical factors (comorbid disease and medications), biological factors (inflammation, hormonal changes, genetics), and behavioral factors (lifestyle and living conditions) (Rolland et al. 2008). Inflammatory cytokines as described above, such as IL-6 and TNF-α, may promote muscle wasting and malfunctioning of skeletal muscle by increasing the systemic inflammatory process and in conjugation with oxidative process in aging adults (Brzeszczynska et al. 2016).

Sarcopenia in Oncology

Although the presence of sarcopenia has been associated with adverse outcomes in numerous chronic diseases, recently there has been increasing interest in the impact of sarcopenia in oncology. Muscle loss in patients with cancer is additionally complicated by cancer-related cachexia. Muscle wasting is a frequent consequence of cancer cachexia along with weight loss, fatigue, and anorexia (Evans et al. 2008). Cancer cachexia is primarily mediated by an activated pro-inflammatory response (with high level of IL-6 and TNF-α) with resultant increased protein catabolism (Rolland et al. 2011). Subclinical changes in weight and lipid metabolism have been shown to start as early as 2 years before a cancer diagnosis is made (Kritchevsky et al. 1991). Of note, the impact of cancer on metabolism and energy imbalance varies greatly by tumor type and stage (Petruzzelli and Wagner 2016). Although cancer cachexia and sarcopenia are clearly distinct concepts, the two conditions overlap. In clinical practice in oncology, the contribution of cachexia or the sarcopenia process in the loss of muscle mass in older adults with cancer is rarely clear. Many factors contribute to the loss of muscle mass seen in patients with advanced cancer (Evans 2010). Recent research into the underlying mechanisms of muscle loss between older adults with and without cancer has demonstrated that in patients with cancer there is blockade of satellite cell maturation, upregulation of apoptotic factors, and reduced oxidative stress defense genes not seen in healthy older adults (Brzeszczynska et al. 2016). This particular study offers a glimpse into the varied underlying mechanisms in muscle loss related to sarcopenia versus cancer cachexia, but more research is needed to understand the similarities and differences between the two conditions to better inform potential interventions. Targeting common pathways of muscle loss in both cancer cachexia and sarcopenia may be most effective in reducing losses in muscle mass and strength in patients with cancer (Rolland et al. 2011).

Assessing Sarcopenia

Many tools are available to aid in the assessment of sarcopenia and body composition. These tools range from simple anthropometric measures to advanced imaging. See Table 2 for a list of commonly used modalities. The gold standard for assessment of body composition, particularly outside the field of oncology, is DEXA.

Table 2 Selected commonly used body composition techniques with pros/cons listed of each approach

Technique	Pros	Cons
Anthropometry	Easily obtained and inexpensive	Relatively insensitive and significant interobserver variability
BIA	Portable, safe, and inexpensive	Relies on population-specific regression equations and less accurate in altered states of hydration
DEXA	High precision and accuracy to differentiate total body fat, lean muscle, and bone Safe for repeated measures	Differences between manufacturers and software versions Unable to quantify muscle density
CT	Highly accurate quantitative and qualitative measurements Useful in clinical settings where used as part of standard medical care	Large radiation exposure and rarely used without other clinical indications Costly and requires specialized personnel
MRI	Excellent resolution images Most accurate method to detect body composition at tissue-organ level Safe	Costly and requires specialized personnel Cannot accommodate very large patients
Deuterated creatine dilution	High accuracy and less bias in interpretation	Requires specialized equipment and personnel Primarily only research tool to date
Ultrasound	Portable, safe, and inexpensive	Lacks standardized techniques causing significant interobserver variability More qualitative than quantitative results Requires specialized personnel

Modified from Prado et al. (Prado and Heymsfield 2014)
Abbreviations: *BIA*, bioelectrical impedance analysis; *DEXA*, dual-energy x-ray absorptiometry; *CT*, computed tomography; *MRI*, magnetic resonance imaging

DEXA provides precise quantification of whole-body and regional composition with minimal exposure to radiation that is safe for repeated measures (Prado and Heymsfield 2014). More advanced imaging techniques are routinely utilized in oncologic care as part of cancer staging, disease monitoring, or surveillance and can be used to quantify body composition. Standardized and practical methods for quantifying body composition from computed tomography (CT) imaging has been developed (Mourtzakis et al. 2008). The L3 landmark from cross-sectional imaging has been identified as the strongest predictor of whole body fat and fat-free mass when compared to DEXA (Mourtzakis et al. 2008). The advantage of using advanced imaging modalities, such as CT or magnetic resonance imaging (MRI), is the ability to provide additional qualitative measurements of muscle and fat beyond purely quantitative measures (Aubrey et al. 2014). Muscle attenuation provides indirect information regarding the composition of muscle that is otherwise only available from muscle biopsy. The attenuation of muscle is inversely related to muscle fat content and can be utilized as a surrogate measure of muscle "quality" (Aubrey et al. 2014). Recent research has developed an integrated measure that combines both muscle quantity and attenuation termed Skeletal Muscle Gauge (Weinberg et al. 2016). Figure 1 illustrates the visual differences between two older adults in terms of skeletal muscle quantity and attenuation. Both patients A and B have a similar body mass index (BMI), but patient B has evidence of low muscle mass and low muscle attenuation. Additional practical tools for measuring muscle mass, such as ultrasound and bioelectrical impedance analysis (BIA), can be performed at the bedside and are preferred methods for clinical practice when advanced imaging is not available (Rubbieri et al. 2014).

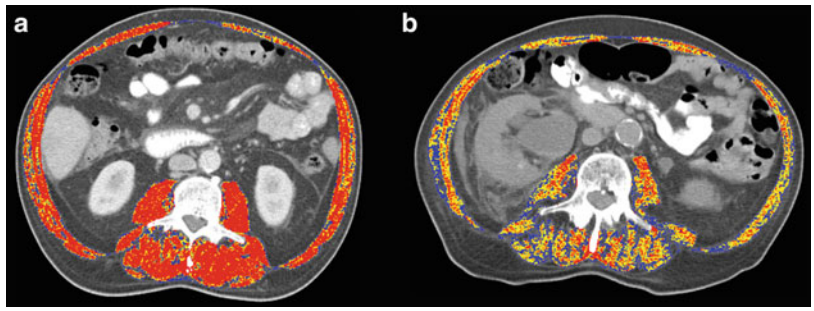

Fig. 1 Representative abdominal computerized tomography (*CT*) images highlighting skeletal muscle differences. Depicts two older adults at the L3 cross-sectional area with the same BMI (BMI = 24), but different quantity (skeletal muscle index A = 47.3 vs. B = 35.3 cm^2/m^2) and composition of skeletal muscle (mean skeletal muscle density A = 36.2 vs. B = 11.6 Hounsfield Units [HU]). The red area represents skeletal muscle within the normal range of radiodensity (+30 to +150 HU), the yellow represents +1 to +29 HU, and the blue represents 0 to −29 HU. Abbreviations: *BMI*, body mass index

More novel research methods, such as deuterated creatine dilution, can estimate total body muscle mass from urine collection of D_3-creatinine enrichment that is strongly correlated with estimates from MRI or DEXA (Clark et al. 2014).

As the consensus definitions of sarcopenia include measures beyond muscle quantification alone, it is important to incorporate measures of strength and physical performance to more accurately define sarcopenia (Cruz-Jentoft et al. 2010; Studenski et al. 2014). The rationale for incorporating measures of muscle strength and performance in the definition of sarcopenia is from the observation that the relationship between muscle strength and mass is non-linear, and muscle strength is not solely a function of muscle mass (Goodpaster et al. 2006; Delmonico et al. 2007). In particular, CT-based muscle mass poorly correlates with impairments in physical function and performance on Timed Up and Go (TUG) (Williams et al. 2017). Well-validated measures of muscle strength and performance exist that can be easily performed in the clinical or research setting. Handgrip strength is the simplest available measure of muscle strength and correlates well with leg strength, poor mobility, and disability in activities of daily living (Lauretani et al. 2003). However, handgrip strength in older adults can be less reliable as it is impacted by common comorbidities and the compensatory use of hands and arms by frail older patients (Rantanen et al. 1998). Other alternative measures include stair climb power or knee flexion/extension, but these can require additional equipment. Several measures of physical performance are available, including usual gait speed, Short Physical Performance Battery (SPPB), TUG, and 6-minute walk test (Cruz-Jentoft et al. 2010).

Impact of Sarcopenia on Outcomes in Oncology

Emerging literature in oncology has described the association of sarcopenia with adverse outcomes (Kazemi-Bajestani et al. 2015; Rier et al. 2016). A recent meta-analysis that included 7843 patients from 38 studies demonstrated overall survival was significantly shorter among sarcopenic cancer patients (HR = 1.44, p <0.001) as well as cancer-specific survival (HR = 1.93, p <0.001). Inferior survival was shown among both early and late stage solid tumors as well as in a variety of different types of malignancies (Shachar et al. 2016). Also of note, many studies across the literature have shown the more subtle sarcopenic obese patients to be particularly at-risk for poorer survival compared to non-sarcopenic obese patients (Prado et al. 2008).

Several studies have demonstrated the inverse relationship between chemotherapy or biological

treatment and muscle mass with higher toxicities rates (Kazemi-Bajestani et al. 2015). The association of chemotherapy toxicity with lower muscle mass or lean body mass is most apparent in therapeutics dosed based on BSA. Prado and colleagues studied 5-flouracil/LBM ratio and showed that higher toxicities were in patients with lower lean body mass; this observation was particularly significant in females (Prado et al. 2007). Another study on patients with metastatic breast cancer receiving first line taxanes-based chemotherapy demonstrated that sarcopenic patients had higher percentage of hospitalizations, dose adjustments, and grade 3–4 toxicities (Strulov Shachar et al. 2016). Antoun et al. also showed higher dose-limiting toxicity in biological oral drugs that are given in fixed doses such as sorafenib for metastatic renal cell cancer. In his study dose-limiting toxicity was significantly higher in sarcopenic patients whose BMI <25 kg/m^2 than patients who were not sarcopenic and/or BMI >25 kg/m^2 (41% vs. 13%, $p = 0.03$) (Antoun et al. 2010). Mir et al. demonstrated that dose limiting toxicities occurred more frequent in patients with sarcopenia and advanced hepatocellular carcinoma ($n = 40$) and showed that median AUC of sorafenib was significantly higher in sarcopenic patients ($p = 0.013$) (Mir et al. 2012).

Sarcopenia in the surgical patient prior to cancer surgery appears to also be a predictor for surgical complications. Peng et al. demonstrated in a large series of patients undergoing liver resection for colorectal liver metastasis ($n = 259$) that sarcopenic patients had an increased risk of major postoperative complications (OR 3.33; $p = 0.008$) (Peng et al. 2011). Low muscle mass in patients with colorectal cancer undergoing surgery ($n = 234$) showed a longer length of stay (15.9 vs. 12.3 days, $p = 0.04$) and low muscle mass was also an independent predictor of surgical infections (odds ratio [OR] 4.6, $p < 0.01$) (Lieffers et al. 2012). Not only was sarcopenia associated with increased postoperative infection risk and prolonged length of hospital stay, but this finding was especially pronounced in older adults (29.6% vs. 8.8%, $p = 0.0005$, and 20.2 vs. 13.1 days, $p = 0.0008$) (Lieffers et al. 2012).

Conclusions

As sarcopenia is highly prevalent in patients with cancer, particularly the elderly, and associated with adverse outcomes, this has many potentially important clinical implications. Many decisions in oncology require a careful balance of the risks and benefits of treatment, and the presence of sarcopenia may impact the risk/benefit balance of many treatments. The presence or absence of low muscle mass could influence and alter treatment decision-making in some settings and allow for a more personalized oncologic treatment approach. Identifying patients that are sarcopenic or at risk for sarcopenia (pre-sarcopenic) may also help target potential interventions that could help mitigate adverse outcomes. The research field of body composition in cancer holds great promise in better assessing and treating older adults with cancer, yet the research of body composition and geriatric oncology has many unanswered questions. How is the mechanism of muscle loss different between aging patients with and without cancer? How should sarcopenia be defined in oncology? Are the adverse trajectories the same in sarcopenic older versus younger adults with cancer or is it even worse? How can we best treat and help to maintain muscle mass? The use of body composition in assessing older adults with cancer is a promising avenue to provide more personalized oncologic treatment that could ultimately improve outcomes.

Cardiovascular Aging

Introduction

In current practice, assessment of performance status, either by Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group (ECOG) scale, is a part of our routine evaluation of patients with cancer. These simple measures are the basis of clinical trial eligibility for most trials, yet are mostly subjective and lack sensitivity to detect impairments in older adults with cancer (Jolly et al. 2015). Due to these drawbacks, these measures are frequently

supplemented with other more objective measures of overall physical functioning. Cardiorespiratory fitness is an objective measure of global cardiovascular function and reserve that reflects the ability of the cardiopulmonary system to deliver adequate oxygen and substrate to active skeletal muscles for adenosine triphosphate resynthesis. Assessing peak oxygen consumption (VO_{2peak}) via incremental cardiopulmonary exercise test with gas-exchange measurement is the gold standard assessment of cardiorespiratory fitness and exercise capacity (Hurria et al. 2016a). As aging is associated with a progressive decline in the health of the cardiovascular system (North and Sinclair 2012) and emerging literature has demonstrated the inverse relationship of VO_{2peak} with all-cause mortality in a variety of adult populations (Jones et al. 2010; Kavanagh et al. 2002), cardiorespiratory fitness represents a possible useful marker of physiologic aging.

Assessing Cardiorespiratory Fitness

Assessing VO_{2peak} or VO_{2max} is most often performed with the use of cardiopulmonary exercise testing. Cardiopulmonary exercise testing involves the measurement of ventilation and respiratory gas parameters during exercise (Albouaini et al. 2007). A non-rebreathing valve is connected to a mouthpiece to prevent inspired and expired air from mixing. There are many different protocols used for testing cardiopulmonary exercise, but most often utilize either a treadmill or cycle ergometer. Patients undergo progressive increases in workload while having gas exchange continuously measured. VO_{2max} is reached when VO_2 remains steady state despite an increase in workload (Sagiv 2012). VO_{2peak} is the peak VO_2 at peak exercise (American Thoracic and American College of Chest 2003). Although VO_{2max} is considered the best index of aerobic capacity and the gold standard, in many clinical situations a clear plateau may not be achievable before a symptom limitation to exercise (Noakes 1998). Therefore, VO_{2peak} is often used as an estimate for VO_{2max} and for practical purposes the terms are used interchangeably. As VO_{2peak} is more often measured in the clinical setting and predominately used in recent publications in oncology, we will use the term VO_{2peak}. Accurate estimation of VO_{2peak} requires an all-out effort by participants to fully stress the aerobic system and is typically performed in an exercise physiology laboratory with a strict protocol. Per the Fick principle, VO_{2peak} is the product of cardiac output and arteriovenous oxygen difference ($VO_2 = [SV \times HR] \times [CaO_2 - CvO_2]$). Thus, VO_{2peak} reflects the maximal ability of a person to take in, transport, and use oxygen (Albouaini et al. 2007). VO_{2peak} is impacted by several factors including genetic factors, quantity of muscle, age, sex, and body size. VO_{2peak} can be affected by training and is typically expressed in liters/minute and as a percentage of the predicted value (American Thoracic and American College of Chest 2003). The safety and feasibility of cardiopulmonary exercise testing in patients with advanced cancer has been demonstrated (Jones et al. 2007). Given the intensity required to obtain VO_{2peak} testing, this test can be a challenge for older adults and especially those with comorbidities. Anyone with unstable angina, uncontrolled hypertension, syncope, or the presence of serious cardiac dysrhythmias should not be allowed to perform exercise testing (American Thoracic and American College of Chest 2003). Also, patients that are unable to exercise due to either orthopedic or neurological conditions are unable to undergo exercise testing. Submaximal testing with measurement of oxygen uptake kinetics may be a reasonable alternative and practical approach to assessing exercise capacity for some older adults (Alexander et al. 2003). Formalized exercise testing guidelines are also available from the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) and are a good source for a more comprehensive overview of exercise testing methodology (American Thoracic and American College of Chest 2003).

Cardiorespiratory Fitness in Oncology

There is growing interest and literature on cardiorespiratory fitness in adults with cancer; however,

the methods of performing and reporting data is frequently inconsistent and does not always comply with national and international guidelines (Jones et al. 2008). The purpose of performing cardiopulmonary testing in oncology usually falls under two broad categories: (1) as a prognostic measure to be used in risk stratification or (2) as an outcome measure to assess the impact of an exercise intervention or the impact of cancer treatment on cardiorespiratory fitness.

In a seminal article by Jones et al., the authors investigated the prognostic significant of preoperative cardiopulmonary fitness (VO_{2peak}) among patients with potentially resectable non-small cell lung cancer (NSCLC). For patients in the highest tertile of VO_{2peak} (>1.29 L/min^{-1}) compared to the lowest (<0.96 L/min^{-1}), the adjusted hazard ratio for all-cause mortality was 0.56 (98% CI, 0.39–0.80) and remained significant whether or not the patients underwent resection (Jones et al. 2010). In a separate study by Moyer et al., investigators examined the value of cardiopulmonary exercise testing in predicting complications in patients with gastroesophageal cancer undergoing resection. Higher rates of cardiopulmonary complications occurred in patients with low anaerobic thresholds compared to patients with higher levels (42% vs. 20%) (Moyes et al. 2013). Similarly, in another study of patients undergoing major colonic surgery (90% oncological surgery), a higher VO_{2max} was associated with decreased postoperative morbidity (West et al. 2014). In their final multivariable model, an increase of 1.0 ml kg^{-1} min^{-1} in VO_{2max} was associated with a ~20% reduction in the odds of surgical complications (West et al. 2014).

The impact of cancer and its treatments on cardiopulmonary fitness has also been investigated. Although no prospective observational studies of exercise capacity have been performed, the usual care arm in the context of randomized controlled clinical trials of exercise training allows for an exploration of longitudinal changes in patients undergoing cancer treatment. In a study by Courneya et al. of an exercise intervention in patients with breast cancer undergoing adjuvant chemotherapy, an approximate 5% decline in VO_{2peak} was measured from baseline to the completion of chemotherapy (Courneya et al. 2007). Other studies of chemotherapy have found similar declines in cardiopulmonary fitness across multiple different tumor types including breast, rectal, and esophagogastric malignancies (Sinclair et al. 2016; West et al. 2015). Other anticancer treatments have been associated with declines in exercise capacity. In a study of men with advanced prostate cancer, 6 months of androgen deprivation therapy with or without radiation therapy was associated with a 10% decline in VO_{2peak} (Segal et al. 2009). As VO_{2peak} declines approximately 10% every decade, this suggests that chemotherapy may cause nearly a decade of physiologic aging. Most concerning is that declines in cardiopulmonary function seen in adults with cancer may not improve even years after the completion of therapy. In a cross-sectional study of breast cancer survivors, patients with breast cancer had marked impairments in VO_{2peak} across the entire survivorship continuum compared to age-matched healthy sedentary women (Jones et al. 2012). The average VO_{2peak} of women with early-stage breast cancer was 22% less than that of the women without breast cancer with an average follow-up of 27 months after the completion of primary adjuvant therapy (Jones et al. 2012). The clinical importance of these declines in the long term remains unknown but are alarming and require further research.

Exercise as a Countermeasure to Improve Cardiorespiratory Fitness in Oncology

The field of exercise interventions in oncology has dramatically increased over the last few decades with nearly 100 published studies investigating the impact of structured exercise in oncology (Sasso et al. 2015). In healthy, non-cancer populations, aerobic exercise is the most effective therapy to improve VO_{2peak} (Jones et al. 2009); however, few trials have examined the impact of exercise on exercise capacity in oncology (Hurria et al. 2016a). The available literature is predominately derived from interventions in women with early breast cancer. Several studies have

demonstrated the safety (low adverse rates), tolerability (high adherence rates), and feasibility of aerobic training in patients with cancer (Hurria et al. 2016a). A recent meta-analysis of six randomized controlled exercise studies involving 571 patients showed improvements in VO_{2peak} compared with non-exercising controls (Jones et al. 2011). These exercise interventions frequently abrogated the declines in VO_{2peak} observed in the usual care group (Courneya et al. 2007; Jones et al. 2013). As exercise interventions in clinical trials vary greatly, from generic home-based exercise prescriptions to supervised tailored exercise treatments, more research is needed to determine the optimal timing, type, and schedule of exercise (Hurria et al. 2016a). Among the field of "exercise oncology," it is felt that individualized and non-linear training holds the greatest promise to improve outcomes, and randomized clinical trials comparing the impact of generic versus individualized interventions are ongoing (Sasso et al. 2015). Given the heterogeneous aging process and the wide ranging differences in health status between older individuals, generic exercise prescriptions can be challenging and less impactful. More tailored interventions are necessary for older adults with cancer that are adaptable to individual patients.

Conclusions

Assessments of cardiorespiratory fitness hold great promise in providing additional prognostic information in adults with cancer. Guidelines for accurately and safely measuring cardiorespiratory fitness are available (American Thoracic and American College of Chest 2003), but more work is necessary to learn how to best adapt these tests to older and more frail adults. Several studies to date have shown marked impairments in exercise capacity during and years after the completion of cancer therapy in adults, but the long-term implications of these declines are not yet known. Exercise interventions appear safe, tolerable, and potentially efficacious in offsetting these impairments in exercise capacity related to cancer therapy. Determining the optimal exercise training for patients with cancer and understanding the long-term clinical impact of declines and/or improvements in exercise capacity are areas of high research priority.

Methodology and Design Considerations

Many obstacles exist in studying older adults with cancer that directly pertain to and impede translational research. First and foremost, although older patients make up the majority of new cancer diagnoses and cancer deaths, they are underrepresented in the majority of cancer clinical trials (Scher and Hurria 2012). Sixty percent of individuals diagnosed with cancer are over the age of 65; however, they make up only 36% of the patients enrolled on US Food and Drug Administration (FDA) registration trials (Talarico et al. 2004). As a result, there is less safety and efficacy data regarding cancer therapeutics for this growing population compared to younger patients and also less opportunity to perform translational research in the older adult cancer population as a part of clinical trials (Hurria et al. 2014). Besides improving the participation rate of older adults on clinical trials, studies that focus specifically on older adults with cancer are also needed to help fill knowledge gaps and optimize care.

Due to the heterogeneous nature of older adults, adequately defining the population of interest is necessary for all clinical studies. The specific inclusion of older and/or frail patients in clinical trials is made more difficult by a lack of consensus regarding both "older" and frail. There is no precise age that denotes "older" patients, and many of the participants in cancer clinical trials are the most robust and healthiest of older patients with nearby access to specialized cancer centers (Gross et al. 2005). When considering age alone and the lack of representation on cancer clinical trials, those aged >75 are especially unlikely to be included (Scher and Hurria 2012; Talarico et al. 2004). Similarly, defining frail patients or those patients with less reserve and more vulnerable to develop cancer treatment toxicity is hindered by the lack of a validated and practical definition for

use in clinical studies (Hurria et al. 2014). The most commonly employed measures of frailty include the Fried phenotype and the Rockwood method; however, how these methods apply to identify at-risk older adults with cancer is less understood (Fried et al. 2001; Rockwood and Mitnitski 2007). For geriatric oncology specific studies, there is growing interest in defining frailty using validated chemotherapy toxicity tools to identify those at greatest risk for chemotherapy toxicity (Extermann et al. 2010; Hurria et al. 2016b).

Depending on the study and question of interest, thinking broadly about confounding variables that may be more prevalent in older adults is important. Many older adults face unique challenges ranging from loss of peers and loved ones to loss of functional and mobility independence to multimorbidity and polypharmacy. These stressors can vary from individual to individual, and this variability must be incorporated into study design. Comprehensive Geriatric Assessment is recommended for use in older adults that assesses a broad range of domains relevant to the older patient, including social support, nutrition, physical function, comorbidity, medications, etc. (Wildiers et al. 2014). This holistic evaluation includes many potential confounders common among older adults and should be included in studies of the geriatric oncology population.

Several study designs have been proposed to help fill the knowledge gaps in treating older adults with cancer. Randomized controlled trials (RCTs) still remain the gold standard to ascertain the superiority of one treatment or approach over another; however, RCTs are particularly costly and require large sample sizes. Embedded studies, otherwise known as correlative or ancillary study, are placed within the infrastructure of a larger parent study and can help provide additional metrics or translational aspects specific to older adults even if they are not the focus of the overall study. A prospective cohort study can help answer many questions regarding the toxicity and feasibility of certain treatment regimens or intervention strategies, but is unable to identify the best treatment as there is no randomization. Additionally, an extended trial design is a novel method that could be employed for trials in which a drug or intervention is deemed superior, yet failed to accrue an adequate number of older adults (Hurria et al. 2014). Although this method has not yet been employed to date, it offers the opportunity to fill the knowledge gap on the tolerability of a new therapy or intervention in older adults while not altering the structure or focus of the original trial.

Selecting the most pertinent and appropriate endpoints for clinical trials is also critically important (Wildiers et al. 2013). Many clinical trials focus predominantly on efficacy outcomes such as tumor response or overall and progression-free survival; however, many older adults emphasize quality of life and functional independence as much as or than survival (Wedding et al. 2007). In order to accurately balance the benefits and risks of a treatment or intervention in older adults many factors are relevant beyond efficacy measures alone. Older adults are less willing to trade increased survival for current quality of life (Yellen et al. 1994) and maintaining cognition and function is paramount (Fried et al. 2002). Measuring functional endpoints such as maintenance of functional capacity and/or incorporating composite endpoints that can take into account multiple dimensions of treatment benefit can be beneficial when designing studies for older adults with cancer (Wildiers et al. 2013).

General Conclusions

The aging of the United States population and abroad is resulting in a dramatic increase in older adults with cancer (Smith et al. 2009). Many challenges exist in treating older adults, but none more apparent than the need to better assess the aging process and improve our ability to predict the variability in outcomes evident in older patients (Hubbard et al. 2014). Translational research offers several novel avenues to improve our assessments of older patients to potentially aid in the assessment of the risks and benefits of treatments. Biomarkers obtained from peripheral blood, such as markers of inflammation, have been correlated with chronological age, frailty, and functional decline (Walston

et al. 2002; Brouwers et al. 2015). Sarcopenia has been associated with increased chemotherapy toxicity, surgical complications, and inferior survival, and body composition analysis from routine imaging could easily improve our ability to estimate risks with minimal additional resource allocation (Kazemi-Bajestani et al. 2015; Rier et al. 2016). Cardiopulmonary exercise testing and assessments of VO_{2peak} have been associated with surgical outcomes and overall mortality (Jones et al. 2010; Moyes et al. 2013; West et al. 2014). These tools not only help assess older adults, but also offer insight into the impact of cancer and its treatments on physiologic aging (Hurria et al. 2016a). Translational research may help identify subgroups of patients at high risk for adverse outcomes that can be targeted for intervention. Translational research must also consider the methodology challenges and design considerations relevant for studying older adults. Further development of these promising avenues of translational research are necessary to improve the quality of care for this growing and vulnerable population.

Cross-References

- Biomarkers of Aging (With a Clinical Potential in Oncology)
- Cellular Senescence and Tumor Promotion
- Hematopoiesis and Aging
- Musculoskeletal Aging, Sarcopenia, and Cancer

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Research Methods: Clinical Trials in Geriatric Oncology

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Abstract

For various reasons, older adults are underrepresented in cancer clinical trials. As the selection criteria in randomized controlled trials are well controlled, younger and fitter patients are usually only eligible, making it difficult for clinicians to draw conclusions on the effects of drugs in older, frail, or unfit adults. With an aging world population, more attention needs to be focused on geriatric oncology, but the challenge lies in designing trials that capture the heterogeneity of an entire population, particularly the elderly and frail.

Separate trials for older patients are needed that incorporate more appropriate end points and suitable control arms. Pharmacokinetic studies should also be undertaken given the effect of aging organs on drug pharmacokinetics. How to design such trials in the absence of global standardized geriatric assessment tools and definitions is, however, challenging.

Randomized or single-arm phase II trials in older adults can provide important information on efficacy and toxicity where a phase III randomized controlled trial (RCT) is not feasible. Observational cohort studies are proposed as an adjunct to RCTs. Large and well-designed observational cohort studies can capture relevant and clinically meaningful data in real-world settings on older patients ineligible for RCTs.

Better clinical trial design is crucial to understanding the impact of new cancer therapies on older patients. Trials in older cancer patients should be compulsory.

Keywords

Observational cohort studies · Older patients · Randomized · Trial · Geriatrics

Introduction

Cancer is a complex disease associated with aging and so it is not surprising that the majority of new diagnoses and cancer deaths occur in people over the age of 65 years (Hurria et al. 2014). The world's population is also aging with the over-65-year-olds making up the fastest growing segment. By 2050, it is estimated that the number of people aged 65 and over will be 16% of the global total, which was just 5% in 1950 (United Nations 2010).

In the USA, for example, 65-year-olds made up 13% of the population in 2010. By 2030, it is estimated that this will increase to 20% and that by 2050 the number of 65-year-olds will have doubled. Eighty-five-year-olds are the most rapidly increasing segment of the US population and are projected to make up 21% of the country's population by 2050 (Hurria et al. 2015). As a further example, the projection over the next 40 years is that the proportion of the Australian population over 65 years will almost double. To put these figures into perspective, Australians aged 65 and over are expected to increase from around 2.5 million in 2002 to 6.2 million in 2042. For Australians aged 85 and over, the projected increase is from 300,000 to 1.1 million over the same period (The Australian Government, the Treasury 2016).

Despite these statistics, older adults are underrepresented in cancer clinical trials, and this raises clinical questions with regards to the efficacy and tolerability of cancer drugs in older people because they respond differently to cancer treatments compared to their younger counterparts (Hurria et al. 2015). It also raises questions about how to accurately define older patients and recruit them to clinical trials, given the heterogeneity of the group. With an expected increase in

cancer incidence and prolonged life expectancy of diagnosed individuals (Hurria et al. 2014), there is an obvious need to pay greater attention to geriatric oncology and to clinical trials in this population.

This chapter discusses the importance of trial designs that incorporate older adults into the development of new anticancer treatment strategies. A need also exists for trials that evaluate geriatric assessment and related interventions, but this is beyond the scope of this topic.

Definitions of "Older" and "Frailty"

Given the heterogeneity of older adults, the ability to accurately define older patients entering clinical trials is problematic. In 2012, the Cancer and Aging Research Group held a conference in collaboration with the National Cancer Institute, the National Institute on Aging, and the Alliance for Clinical Trials in Oncology (USA) from which the following definitions were recommended:

Older: Based on age alone, older patients are defined as aged 75 years or more for the purpose of study design and recruitment.

Frail: Based on a geriatric definition of frailty, frail patients are defined as older individuals who are at higher risk for cancer treatment toxicity because of associated conditions such as functional losses, cognitive impairment, or physiologic changes (Hurria et al. 2014).

These definitions alone, however, do not provide enough substance and a complete geriatric assessment should be mandatory in registration trials and encouraged in all trials that recruit older people. Without a geriatric assessment, it is impossible to know the characteristics of older trial patients or to whom the data can be extrapolated – were they older and fit only, or were they older and a mix of fit and frail? The European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B (CALGB) groups have proposed geriatric assessment tools, but other options exist, and there is no current universally accepted standard (Wildiers et al. 2013). Adopting a universal approach to definitions is just one of the challenges of geriatric cancer trials.

Implications of Underrepresentation of Older Patients in Cancer Trials

Multiple research studies have shown that older adults have historically been underrepresented in cancer clinical trials. Various reasons exist including physician recommendation, transportation or caregiver issues, "excessive" visits, financial aspects, restrictive eligibility criteria, trial design, perception of aggressive therapy, and limited expectation of benefit (Lichtman 2012b). Compared to younger patients, older patients are more likely to experience severe toxicities resulting in treatment discontinuation or receive a reduced dose which could dilute or affect the true treatment benefit. Older patients are also more likely to have comorbidities that can result in death from noncancer causes. Together, these issues have resulted in age limits and strict trial inclusion criteria which have excluded large numbers of older patients from clinical trials (Wildiers et al. 2013).

More recent evidence suggests that the lack of data in older cancer patients remains a concern (Scher and Hurria 2012; Hurria et al. 2014, 2015). For example, a review of the patient information leaflets of 24 cancer drugs approved between 2007 and 2010 showed that only 33% of the trial participants were aged 65 years, compared with almost 60% of the cancer population for the same age range (Scher and Hurria 2012).

National Cancer Institute (NCI) sponsored trials emanating from the USA have not fared better over time. From 1997 to 2000, of the 59,000 research participants in 495 NCI trials, only 32% were older adults compared with 60% of patients with cancer. Despite calls from as far back as the 1980s to pay more attention to geriatric oncology (Kennedy 1998), data from the NCI show that the percentage of older adults enrolled onto cooperative group trials between 2001 and 2011 has remained at just 20% (Hurria et al. 2015). Another study (Le Saux et al. 2016) showed that the

proportion of phase III trials reporting at least one analysis dedicated to elderly patients has grown since the creation of the International Society of Geriatric Oncology (SIOG): 46.7% between 2011 and 2014 versus 19.3% between 2001 and 2004. However, these data were mostly extracted from subgroup analyses and therefore the evidence can only be considered as preliminary.

Underrepresentation of older adults in cancer clinical trials has significant clinical implications. Organ function is affected by the aging process which, in turn, affects drug pharmacokinetics and metabolism (Wildiers et al. 2003). The biology of certain cancers also changes with aging. These factors, combined with the comorbidities expected in an older population, may result in substantial differences in the efficacy and safety of cancer treatments (Wildiers et al. 2013). While there is an increased understanding that chronological age and physiological age can differ substantially, many older adults receive less aggressive treatment, or chemotherapy less frequently than recommended by practice guidelines, because of questions surrounding tolerability and benefit (Hurria et al. 2014, 2015).

The underrepresentation of older cancer patients, coupled with a routine lack of reporting of age-related issues in clinical trials, often leaves clinicians with unanswered questions: Which patients experience serious adverse events? Do older patients experience more toxicity than their younger counterparts? Are there certain toxicities that are more prevalent in older patients? Do older patients complete treatment to the same extent as younger patients? Do older patients derive as much benefit from treatment? (Lichtman 2012a). Generally, there is a significant lack of information on the safety and efficacy of cancer treatments in older patients.

Recently, in an effort to respond to the crucial need for meaningful data in older patients, interest in geriatric oncology has been gaining momentum (Lichtman 2015). The Cancer and Aging Research Group (CARG), in collaboration with the National Institute on Aging (NIA) and the NCI, the American Society of Clinical Oncology (ASCO), and SIOG, have held a series of conferences to examine research priorities in geriatric oncology and provide recommendations on improving the evidence base in older patients with cancer (Hurria et al. 2014, 2015; Lichtman 2015; Mohile and Wildiers 2012). This has led to discussion on clinical trial design, wider eligibility criteria, and how to select the most appropriate endpoints relevant to the older population.

Suitable Endpoints in the Older Population

Endpoints are essential in clinical trials to assess the effectiveness of therapy. In oncology, well-established and standard clinical endpoints exist for randomized controlled trials (RCTs). While endpoints such as overall survival (OS) and disease-free survival (DFS) in the curative/adjuvant setting are gold standard, they may not be the most appropriate measures to balance the benefits against the risks of treatment in the elderly.

Table 1 provides a summary of the pros and cons of standard endpoints in randomized controlled cancer trials (Wildiers et al. 2013).

Overall Survival (OS)

OS is viewed as the gold standard among endpoints in cancer RCTs. It is a distinct and easy to measure end point, but its relevance in the elderly is complicated by noncancer-related deaths. It also does not take into account the importance of quality of life (QoL) parameters from the patient's perspective.

Disease-Specific Survival (DSS)

DSS better indicates how many patients die as a result of disease and how many die as a result of other causes, although this can be subjective as the cause of death may be difficult to evaluate. Trials should ideally report DSS in addition to OS as DSS can evaluate the "true benefit" of an anticancer therapy (Wildiers et al. 2013).

Table 1 Relevant end points in clinical trials in the older cancer population

Endpoint	Definition	Current situation	Pro	Con
Overall survival (OS): Time or proportion	Time from diagnosis of treatment situation/ study entry until death or rate of patients alive at a specified time point	Considered as the gold standard in clinical trials, especially when evaluating the superiority of new treatments	Remains hardest endpoint, also in elderly Easy and distinct to measure High impact for patients	"Oncological" relevance in elderly can be hampered by increased number of non-cancer related deaths (all life ends with death) Does not include aspects of quality of life
Disease-specific survival (DSS): Time or proportion	Time from diagnosis of treatment situation/ study entry until death from the index disease or rate of patients without death related to the index disease at a specified time point	Important to collect besides OS since it gives better insight into the contribution of non-cancer related deaths	Cancer treatment primarily aims at decreasing cancer death	Some cancer treatments might also influence non-cancer related deaths (e.g., treatment related mortality) May lead to an overestimation of the true benefit for patients in presence of competing risks (e.g., treatment benefit in localized prostate cancer) The reason for their death will be of no/minor meaning for patients Reason of death can remain unclear
Co-primary endpoints	Combination of two or more equal primary endpoints	Rarely used in oncology	Allows capturing more than efficacy alone	Difficult statistical design since the correlation between different endpoints is rarely known Might increase sample size
Composite endpoints	Combination of different endpoints in one defined endpoint	Rarely used in oncology (example is "skeletal related events"), but should be more encouraged. Example of TFFS and TTF here below	Can take into account multiple dimensions in the definition of "treatment benefit," including efficacy and toxicity Simple and efficient statistical design Allows also separate reporting of the different endpoints as well	Requires individual components of the composite that are clinically meaningful and of similar relative importance Difficult interpretation if there are divergent results for each component separately
Treatment failure–free survival (TFFS) and time to treatment failure (TTF):	TFFS is the time elapsed between randomization and early treatment discontinuation due to any reason (including disease progression,	Often used in addition to OS	Integrates efficacy and toxicity	Difficult to distinguish between efficacy and toxicity (e.g., toxic, but very effective) Treatments might be stopped for other

(*continued*)

Table 1 (continued)

Endpoint	Definition	Current situation	Pro	Con
Time or proportion	treatment toxicity and early death), disease progression, death (from any cause), or any other event of interest. TTF is similar but deaths from other causes are not considered as events			reasons (e.g., "chemotherapy holiday")
Quality of life related endpoints: Level at a specified time point or time until deterioration compared to baseline	Evaluation of the quality of life through validated instruments at baseline and during the course of the disease/treatment/ study	Often used as secondary endpoint in clinical trials, but should be more promoted as primary endpoint or part of a composite endpoint	QoL may be more important than duration of life for many older individuals	Difficult to measure and to determine clinically relevant cutoffs that make a therapy worthwhile or not
Maintenance of functional capacity/ dependence: Level at a specified time point or time until deterioration compared to baseline	Evaluation of the evolution of functioning and (in) dependence through validated instruments during the course of the disease/treatment/ study	Rarely measured in oncology trials, but crucial to include	Main contributor to quality of life in elderly cancer patients	No general consensus on optimal measurement and clinically relevant cutoffs that make a therapy worthwhile or not

Coprimary Endpoints

Coprimary endpoints enable researchers to capture more than efficacy alone. Multiple single endpoints can be chosen as coprimary endpoints of equal importance, and a statistical design, albeit difficult, can be built to test each separately. Coprimary endpoints, however, require a larger sample size if the trial objective is to have positive results for at least one or all coprimary endpoints, and the type I or II error, respectively, must be adjusted for multiple testing (Wildiers et al. 2013).

Composite Endpoints

A composite endpoint in a RCT is when multiple single endpoints are combined so that an event is triggered if any of the endpoints occur. Composite endpoints enable other parameters of interest, such as QoL or the ability to carry out daily tasks, to be incorporated. All components of a composite endpoint should be analyzed and reported separately. The separate reporting of endpoints is essential to facilitate cross-study comparisons (within limits) or to generate assumptions for future trial designs. The major advantages of a composite endpoint are the simple statistical design based on a single endpoint (i.e., the composite one) and the resultant increase in statistical efficiency.

An interesting example of a composite endpoint in older individuals is therapeutic success. This endpoint combines efficacy, toxicity, and patient compliance with treatment and is defined as a patient receiving at least three cycles of chemotherapy at the planned dose (without dose reduction) and schedule (no treatment delay

beyond 2 weeks) and having a response (either complete or partial) without experiencing grade 3 or 4 toxicity according to the Common Toxicity Criteria. Variations on this definition are possible. As an endpoint, therapeutic success is particularly interesting in the metastatic setting to compare toxicity, which in this situation should ideally be low, against a supposed treatment benefit. In the curative setting, however, higher levels of toxicity may be generally more acceptable if there is a considerable survival benefit. The adjuvant setting is also more challenging for composite endpoints given that toxicity is short term compared to the potential long-term benefit of treatment. While looking simultaneously at toxicity and efficacy has its advantages and disadvantages (therapies may be temporarily toxic, requiring dose reduction, but they may also be efficacious), therapeutic success is useful in settings where significant differences in toxicity between two treatments are expected and require further investigation.

Despite major advantages in terms of statistical design and efficiency, composite endpoints are not risk free. More information on the pros and cons of composite endpoints can be found in Kleist (2016) (Wildiers et al. 2013).

Treatment Failure–Free Survival and Time to Treatment Failure

Treatment failure–free survival (TFFS) and time to treatment failure (TTF) are well-known composite endpoints. TFFS is defined as the time that elapses between random assignment and early treatment discontinuation because of any reason (including treatment toxicity and patient refusal), disease progression, death resulting from any cause, or any other event of interest. While TTF is similar, only disease-specific and treatment-related deaths are considered events.

TFFS and TTF are interesting endpoints in elderly cancer trials. Both enable toxicity to be taken into account rather than just concentrating on efficacy. Older patients may prefer quality over quantity of life, so it is important to be able to capture treatment discontinuation due to toxicity. Treatment breaks or "chemotherapy holidays" that are unrelated to toxicity or disease progression should be taken into consideration rather than being viewed as treatment failures. Similarly, early treatment discontinuation should not be seen as a failure in situations where significant toxicity is followed by positive disease outcomes (Wildiers et al. 2013).

QoL-Related Endpoints

Improving or maintaining QoL is a major goal of cancer treatment. In the palliative setting in particular, the main aim should be to reduce the symptoms and discomfort arising from progressive disease such as loss of functionality, pain, and deterioration of overall QoL.

Health-related QoL (HRQoL) is a multidimensional parameter that focuses on the impact of health status on QoL. HRQoL is a major concern for patients with cancer and it can be influenced by symptoms due to cancer as well as treatment induced toxicity (Bottomley et al. 2003). While younger patients with children may prioritize survival over quality of life and therefore be willing to accept greater toxicity, it has been shown that older patients are less willing to compromise their HRQoL for an increase in survival potential (Wildiers et al. 2013; Yellen et al. 1994).

As a measure of outcome, HRQoL is appropriate in elderly trials and should be captured in all trials of palliative chemotherapy in older patients regardless of the primary endpoint of the trial. It is, however, fraught with issues on how it can be optimally measured given its complexity. How the different measures of QoL, such as physical, emotional, and social functioning, can be combined into one score, how they can be made relevant to older people, and which cut-offs are suitable endpoints are not well defined (Wildiers et al. 2013).

In an attempt to provide an instrument that focuses on HRQoL issues that affect older people with cancer, the European Organisation for Research and Treatment of Cancer (EORTC) QoL Group developed an elderly-specific questionnaire module to supplement its general QLQ-C30 core questionnaire (Wheelwright et al. 2013). Another valuable approach, incorporating

QoL considerations into treatment comparisons, is quality adjusted life years (QALY).

Compared to composite endpoints, quality of life adjusted survival approaches address the situation in which each component of the composite endpoint may not be equally important. One method for assigning weights that reflect the patient's perspective is to incorporate HRQoL into survival analyses. This endpoint is also interesting because it enables economic evaluations using cost-utility analyses (Cole et al. 1993; Glasziou et al. 1990). However, QALYs assume a certain consistency with choices over time, and the relation to individual and social preferences for health remains unclear (Woodward et al. 2013).

Preservation of Functional Capacity/ Independence

An endpoint closely related to HRQoL is the preservation of independence and function, and it should be a major aim of elderly patient cancer management. As survival has been shown to be linked with functional capacity, incorporating this measurement into outcome events would be highly valuable (Reuben et al. 1992; Wildiers et al. 2013).

Cognitive Function

Cognitive function can also be an important endpoint for older patients. In a French prospective study, approximately half of the patients experienced objective cognitive decline after adjuvant therapy for breast cancer (Lange et al. 2016). Cognitive deficits may affect a patient's quality of life and their compliance to treatment.

Surgical Trial Endpoints

A number of elderly cancer patients do not receive standard surgery as they are considered unfit for surgery due to an inaccurate estimation of their risk. The Pre-Operative Assessment of Cancer in the Elderly (PACE) assesses operative risk and is recommended for all elderly patients prior to surgery (Audisio et al. 2008). While surgical trial endpoints in the elderly are relevant, they should be accompanied by long-term outcome endpoints.

Improving Cancer Trial Design in Older Patients

Age Limits

The evidence demonstrates that cancer clinical trials do not adequately represent older adults and yet it is in this growing subset of the population that the use of cancer drugs will greatly increase as the population countries continues to age. In registration studies, drugs intended for use across the entire adult age spectrum should have outcomes evidence across the same age range. Therefore, trials should include older patients without an upper age limit and a minimum cohort of all older patients. Failure to do so creates a selection bias towards younger patients, or to older patients who may have been eligible for the trial on the basis that they are fitter. In this situation, the trial conclusions are unable to be generalized across the entire population, and this is especially true for patients who are considered older and frail.

While increasing the number of older patients into trials, specifically registration or phase III studies, sounds relatively easy, there are numerous factors at play. Ensuring sufficient accrual of older patients may require a trial to remain open once it has met its target until a minimum number of selected older patients have been enrolled. Documented information on the fitness status of the older enrolled patients is important, as is documentation on ineligible patients, so that the results can be correctly interpreted across the older subset.

The characteristics of the drugs under investigation may also pose an issue. Some standard treatments (control arm) are not suitable for unfit or frail older patients, or even those who are fit, because of their expected toxicity risks or other competitive risks. These include, but are not limited to allogenic bone marrow transplantation – high-dose cytarabine, anthracycline, or cisplatin; major

surgery; and concurrent chemoradiotherapy. In many ways, a "catch 22" situation arises out of the drugs being compared – a RCT with a "heavy" control arm and a "soft" experimental arm will never include frail older patients; a RCT comparing two "soft" treatments is unlikely to include fitter older patients who may be candidates for a "heavier" standard treatment. In such situations, specific trials in the frail or older patient that modify a chemotherapeutic or biologic regimen and compare it against supportive or palliative care may be a better approach. Another option, depending on the setting, could involve comparing standard therapy to less aggressive therapy or to no therapy (Wildiers et al. 2013).

Phase III Versus Phase II Trials

While phase III studies are gold standard in clinical research regardless of age, phase III RCTs are usually reserved for younger populations as designing trials that address the heterogeneity of older populations is challenging. Due to an enhanced risk of toxicity or other adverse events that could hamper drug development, there is probably also reluctance from the pharmaceutical industry to develop significant trials (registration or other) in older patients, despite an aging global population offering huge market potential.

The ability of phase II trials to provide insight into the efficacy and toxicity of cancer drugs in older adults may, however, provide an adequate solution. A randomized phase II study in elderly unfit patients could serve to quickly establish if a drug is too toxic compared to the results of a phase III study in younger and fitter patients. Similarly, if a phase II study in older unfit patients produced efficacy and toxicity results in line with a previous phase III study in younger patients, there may not be a need to repeat the phase III trial again in the older unfit population. Elderly-specific clinical trials are therefore relevant for unfit patients. As the definition of frailty is not consensual, stratifying patients according to their life expectancy, toxicity risk (using the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH score)) and geriatric covariates (such as activities of daily living or nutritional status, etc.) may enable data to be extrapolated to clinical practice. The difficulty with this approach is the selection of an appropriate control arm, but this could be overcome by leaving the control arm to the investigator's discretion.

In the event that an appropriate control arm is not feasible, a single arm phase II study with toxicity as an end point is a possible practical solution. Despite single arm phase II studies being less robust than randomized phase II or phase III data, a single arm phase II elderly study would at least provide an indirect comparison of the efficacy and toxicity data from previous studies as well as information on relevant end points, as previously discussed. While they are not perfect, single arm phase II studies are sometimes the only feasible option and do translate across to clinical care. The adoption of the R-miniCHOP (rituximab plus low-dose cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients over the age of 80 years with B-cell lymphoma is one such example (Wildiers et al. 2013; Peyrade et al. 2011).

Pharmacokinetics and Phase I Trials

Aging organs affect the pharmacokinetics of drugs and the metabolic process which often causes enhanced drug toxicity compared to that seen in younger patients. Having a thorough understanding of the pharmacokinetics of anticancer drugs in older and frail patient populations is therefore highly valuable. Pharmacokinetic and phase I studies specific to these populations should be designed for new drugs and could run parallel to standard phase I trials or shortly thereafter, assuming the results of standard studies have shown promise.

Another interesting concept is to progressively increase the inclusion criteria in phase I/II trials. The drug or regimen being evaluated is administered first to patients in good condition. Cohorts of patients with increasing comorbidities or functional limitations are subsequently added, providing thresholds for dose reductions or changes. Geriatric assessment tools such as the CRASH

Table 2 Issues in clinical trials design in older cancer patients

Randomized controlled trials (RCT) remain the gold standard when possible
Clinical trials should preferably integrate the whole age range including fit and frail older individuals
Elderly specific clinical trials in older cancer patients are required if standard therapy is different from younger patients
Trials on treatment strategy comparing different strategies (e.g., therapy vs. best supportive care) should be encouraged
Randomized phase II or even single arm phase II trials in specific subsets of older patients can provide insight in the range of efficacy and toxicity in older populations, but ideally need to be confirmed in large phase III trials that might be very hard to perform for various reasons (insufficient interest from sponsors/investors, difficulty to find sufficient patients,. . .)
Not all questions can be answered with randomized trials, and large observational cohort studies or registries even in the community can provide further insight for the frail population with much less selection bias (preferably in parallel with or linked to RCTs)
Comparable/uniform geriatric assessment should be integrated in future trials in geriatric oncology
Regulatory authorities should require evaluation of efficacy and safety of new drugs also in older/frail patients

score and the CARG (Cancer and Aging Research Group) score could be incorporated into this approach in order to predict chemotherapy toxicity, but stratifying patients using risk indicators is hindered by the exact definition of frailty or vulnerability which is still not universally clear. Table 2 summarizes the key issues in clinical trial design for older cancer patients (Wildiers et al. 2013).

Randomized Controlled Trials, Observational Cohort Studies or Both?

Randomized Controlled Trials (RCTs)

The history of clinical trials dates back to approximately 600 BC. Credit for the first modern randomized trial is usually given to Sir Austin Bradford Hill, a professor of medical statistics who pioneered the design while evaluating the use of streptomycin as a treatment for tuberculosis. Today, RCTs are seen as the gold standard for establishing the efficacy of one intervention over another and this is due to the randomization process which reduces the risk of bias. Stolberg and colleagues define RCTs as quantitative, comparative, controlled experiments in which a group of investigators studies two or more interventions by administering them to groups of individuals who have been randomly assigned to receive each intervention (Stolberg et al. 2004).

RCTs require carefully controlled environments, populations, resources, and time. To achieve a controlled environment, RCTs have strict inclusion and exclusion criteria which limit the heterogeneity of each study arm. Patients are then randomly assigned to one intervention (control) or another (comparison) so that the only known major variable is the exposure to the intervention being tested. While this is excellent for quality control, the results of randomized trials have the potential to establish a new standard of care that may not necessarily be applicable across broad populations, particularly the elderly (Mohile and Wildiers 2012). A good example of this is the BCIRG001 trial. It demonstrated that adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) is superior to 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) in node-positive breast cancer (Mackey et al. 2013). Despite the superior OS and DFS of the TAC regimen, it was not taken up as a treatment option in older patients principally due to its toxicity profile. The cut-off age in the trial was 70 years.

While there are many clinical questions in geriatric oncology that require investigation, their assessment within the context of a RCT is challenging. For example, what are the outcomes in older patients with indolent prostate cancer who undergo surgery versus those who do not? Does adjuvant chemotherapy in older breast cancer patients provide a worthwhile benefit versus no chemotherapy? Treatment strategy trials, such as those in which an active intervention is compared to no intervention, find recruitment difficult compared with trials that compare one intervention against another. Selection bias and crossover due

to "resentful demoralization" may also occur when patients are aware of a new treatment not available to them and comply poorly with the standard treatment. For example, the CASA and ACTION adjuvant breast cancer chemotherapy trials, which compared chemotherapy to no chemotherapy, did not meet their accrual goal due partly to poor patient acceptance. Conversely, the CALGB 49907 trial that compared the efficacy of standard chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil [CMF] or doxorubicin plus cyclophosphamide [AC]) with capecitabine in women with early-stage breast cancer aged 65 years or older was more feasible (Mohile and Wildiers 2012). The impact of the assigned intervention on a patient also needs consideration – the impact of being assigned to an active treatment versus no treatment in older patients is far greater than being assigned to either one of two possible active treatment arms.

There are novel trial designs available that address the difficulties encountered when patients recruited to RCTs do not receive their preferred treatment. The most well-known is the post-randomization consent design, proposed by Harvard School of Public Health statistician Marvin Zelen (1927–2014). The Zelen design randomizes patients before consent to participate in the trial has been obtained. There are two types of Zelen design: the single and the double consent method. In the single consent approach, only study participants allocated to the nonstandard intervention are asked for consent to receive the new intervention. If they refuse, they are given standard (control) therapy. In the double consent method, the control arm participants are also given the opportunity to refuse treatment and can access the alternative approach. While the Zelen design may be more ethical in some circumstances and remove the bias due to "resentful demoralization," there are inherent issues with Zelen's design. As consent for randomization is not sought, "consent bias" can arise because participants can refuse consent after allocation, and crossover may be more likely as patients are fully aware of the treatment to which they have been assigned (Torgerson 2004).

Fixed 2:1 or Bayesian adaptive randomization trials (Thall and Wathen 2007) are other designs that may be more attractive to patients and clinicians as the number of patients assigned to the effective, or supposedly effective, treatment is higher. These trial designs can therefore provide a solution to the expected poor accrual rates.

While the issues discussed above are relevant across all ages, and treatment strategy trials are challenging, it is important to continue to find novel solutions and experiment with designs applicable to the older unfit population. While there is currently no ideal trial design, one practical solution may be to invest more in large observational cohort studies.

Observational Cohort Studies

At the 2011 SIOG meeting in Paris, an international group of leaders recommended that observational cohort studies be developed to increase the much needed evidence in geriatric oncology. An observational cohort study prospectively follows a group of individuals who have specific features in common over a defined period of time. Unlike registries which monitor events, the information collected in observational cohort studies is prospectively defined for outcomes, sample size, and duration of follow-up. Used in conjunction with RCTs, robust observational cohort studies have the potential to provide timely and cost-effective data on efficacy, safety, and compliance in real life older patients (Mohile and Wildiers 2012). The key word here is "robust" as careful consideration needs to be given to the design of observational cohort studies so that clinically meaningful results can be obtained.

Single Versus Multicenter Observational Cohort Studies

Single-center cohort studies in older patients, while useful, provide limited meaningful information as individual treatment centers tend to use the same, and potentially biased, approach. Large, multicenter observational cohort studies are therefore preferred as they have the ability to provide useful data about the consequences of specific treatment decisions. However, because the treatment approach towards older cancer patients

between centers and countries no doubt differs, it is vital that these studies collect similar, if not identical, data across different tumor types and settings to enable the creation of large databases and cross-trial comparison. The EORTC minimum data set has been proposed for this purpose (Mohile and Wildiers 2012; Pallis et al. 2011).

Overcoming Bias in Observational Cohort Studies

Observational studies can provide important, unbiased, and accurate information on the toxicity of new drugs or therapies in the general older population. However, caution is required when an evaluation of efficacy compared to other treatment strategies is the goal. The sheer fact that treatments are not randomly assigned in observational cohort studies means that they are subject to bias and that the causal effect from treatment may not be entirely accurate. An example of this is the 2016 publication of an analysis by McGale and colleagues on the causal effects of radiation therapy on breast cancer according to the SEER public-use data set versus the meta-analyses of randomized trials of radiation therapy or not from the Early Breast Cancer Trailist's Collaborative Group (EBCTCG) (McGale et al. 2016). Despite the SEER data set being one of the largest and most detailed data sets available, the analysis found major qualitative differences between the EBCTCG and SEER data. The SEER data showed that radiation therapy after mastectomy in women with one to three positive nodes causes death from breast cancer and that radiation therapy prevents mortality from all causes except breast cancer, including from heart disease and from accidents and violence. These results contradict the results of randomized trials, prompting the authors to conclude that nonrandomized comparisons are liable to provide misleading estimates of treatment effects and require careful justification each time they are used (McGale et al. 2016).

Careful study design is therefore vital if clinically meaningful results are to be obtained from observational cohort studies. One way to help overcome issues with bias and still collect valuable additional data is to establish a RCT and to include ineligible patients, or those who declined, in a parallel observational cohort study.

Table 3 Observational cohort studies – considerations for improved trial design (Mohile and Wildiers 2012)

Include patients ineligible for a RCT into an observational cohort study
Include sensitivity analyses – to assess the effects of decisions on outcomes
Include propensity score analyses – to compare the characteristics of patients with a healthy control group
Ensure a prospective design and capture defined outcomes as they occur
Prospectively collect confounding variables and power the study so that it can be adjusted for these variables
Ensure that comparison groups across the cohorts are as similar as possible
Consider pre- and post-comparisons at individual level to foster validity

RCT randomized controlled trial

Integrating patients into an adjunct observational cohort study would increase the quality of the RCT because the patient selection would be better described. In practice, this would offer clinicians a broader understanding of the types of patients in whom the results of the RCT can be generalized (Wildiers et al. 2013). Additional considerations to improve the design of observational cohort studies are listed in Table 3.

In contrast to the McGale publication, the EURECCA Breast Cancer Group study (Derks et al. 2017) is a well-conducted cohort study with interesting results. Data from national and regional population-based or hospital-based cancer registries were collected from six European countries. 214,673 patients with nonmetastatic invasive breast cancer (BC) aged $\geq$70 years at the time of diagnosis were included. For patients aged 70–79 years with stage I BC, the large variation in adjuvant endocrine therapy use between countries (17.9% in The Netherlands vs. >80% in other countries) was not linked to the variation in relative survival. In stage III BC, the proportion of patients receiving chemotherapy in The Netherlands (16.6%) was considerably lower than in Belgium (52.6%). For patients aged 70–79 years with stage III BC, a high proportion of chemotherapy was linked with a significantly better relative survival. This study highlights the fact that some countries tend to over-treat their older stage I BC patients with endocrine therapy (and radiotherapy) with no impact on survival,

while other countries tend to undertreat their stage III BC patients where survival can be positively impacted with chemotherapy.

So while observational cohort studies can give bias, if well designed they can be used to collect data relevant to older populations including efficacy, safety, adherence to treatment, patient-reported outcomes, HRQoL, resource utilization, and patterns of care and cost. As shown, they can enhance the quality of RCTs and potentially inform and guide RCTs that compare different treatment approaches in older patients with cancer. Finally, as older cancer patients with comorbidities are usually excluded from RCTs, observational cohort studies can address this shortcoming by evaluating the relationship of comorbidities or underlying health problems with cancer treatment outcomes (Mohile and Wildiers 2012).

Expanded Access Programs

Expanded access programs (EAPs) make investigational new drugs available, under certain circumstances, to treat a patient(s) with a serious disease or condition who cannot or who can no longer participate in a controlled clinical trial. While the primary intent of an EAP is to provide treatment rather than to collect data, EAPs are useful in that they can provide real life safety data and give information on the wider use of the drug by different patient subtypes. For example, in the TARGET trial, the proportion of patients aged over 70 years receiving sorafenib for renal cell carcinoma was 12% (Escudier et al. 2007), but in the real life EAP it was 29% (Stadler et al. 2010).

Conclusion

Despite an aging world population, older adults are underrepresented in clinical trials leading to selection bias and difficulty in drawing conclusions on the effects of interventions in this segment. The oncology community is now more aware of this issue, but the challenge lies in designing trials that capture the heterogeneity of an entire population, particularly the elderly and frail.

Separate trials for older patients with cancer are needed incorporating pharmacokinetic studies, appropriate end points, and appropriate control arms. OS is a crucial end point, but DSS should be recorded in all cancer trials with older patients to capture deaths from causes other than cancer. Composite end points allow additional parameters, such as QoL, preservation of functional capacity, and independence, to be recorded, all of which are important for older adults.

Randomized or single-arm phase II trials in older adults can provide important information on efficacy and toxicity where the feasibility of a phase III RCT is hindered by insufficient interest from sponsors or lack of patient numbers. Large observational cohort studies have been recommended, ideally alongside a RCT, to capture data on ineligible trial patients such as the older and unfit.

Geriatric assessment in elderly-specific trials is important to better understand the characteristics of the elderly population and their fitness, but a global and standardized approach to definitions and assessment tools is required. The European Medicines Agency (EMA) has an established plan to ensure that drugs are examined appropriately in pediatric patients and, in a recent paper, suggest that the same should be devised and compulsory for older adults (Cerreta et al. 2016).

In conclusion, better clinical trial design is crucial to understanding the impact of new therapies on older individuals and to improving care for this growing population.

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Research Methods: Using Big Data in Geriatric Oncology

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Abstract

Big data is widely seen as a major opportunity for progress in the practice of personalized medicine, attracting the attention of medical societies and presidential teams alike as it offers a unique opportunity to enlarge the base of evidence, especially for older cancer patients underrepresented in clinical trials. The methodology to access such data for research and clinical practice is evolving rapidly. In this chapter, the authors share their experience using such data for research and clinical practice. We review key principles in managing and searching such health and research informatics databases. We share methods to conduct research in the basic and translational sciences, clinical research, and personalized medicine for older cancer patients.

Keywords

Cancer in the elderly · Clinical decision making · Big data · Health and research informatics · Geriatric oncology research

Introduction

Big data is one of those words that generate a general understanding, while their definition is harder to pinpoint. A general definition for the purpose of this chapter could be: "A very large, diverse, and rapidly evolving set of data collected in a structured fashion, and retrieved via analytic software." Functionally, big data is that whose scale, diversity, and complexity require new architecture, techniques, algorithms, and analytics to manage it and extract from it. More specifically in our setting, big data is referring to a medical, biological, or population dataset that is relevant to older cancer patients.

Potential Uses in Geriatric Oncology

While a main driver for the creation of large databases accessible by computerized algorithms has been molecular biology, increasingly these databases are being extended or developed specifically for clinical decision support purposes. Data from cancer registries and other sources are integrated in these extensions as well.

Cancer Registries and Insurance Claims Databases

A large dataset that has been extensively used in epidemiologic studies is the Surveillance Epidemiology and End Results (SEER)-linked Medicare database. For example, Barnholtz-Sloan and team evaluated treatment patterns and survival among elderly patients diagnosed with malignant astrocytoma utilizing SEER-Medicare linked data (Barnholtz-Sloan et al. 2008). An advantage from a geriatric oncology point of view is that it is focused on patients aged 65 and above (the Medicare eligible age). While this registry is a population-based one, it has several limitations. The first one is that it doesn't cover the entire United States (US). The SEER registry focuses on nine States and four specific areas to balance a representative sample of the US population. Another limitation is that oral medications (with a few exceptions) are not tracked. Furthermore, it is a claim-based database. For patients in some bundled insurance plans, the information may therefore be limited as well. Histological details are not tracked, and staging is rudimentary. Many developed countries have tumor registries, with various levels of detail on tumor characteristics, treatment, and outcomes. As a general rule, while mortality is tracked extensively, relapse, recurrence, and disease progression are not tracked by cancer registries. Despite these limitations, the

SEER-Medicare database and cancer registries still have a lot of unexplored opportunities to understand and develop the care of older patients. Access to the SEER-Medicare database can be obtained by submitting a new application, a signed/completed SEER-Medicare data use agreement indicating the specific data files of interest, documentation of institutional review board (IRB) approval, and a signed/completed request form if restricted data elements such as patient zip code or patient census tract are needed in order to answer the research question(s).

Some large health maintenance organizations (HMOs) such as the Kaiser Permanente group also have very detailed datasets. Another example of a large claim-based database is the Japanese national receipt database, which combines claims and results of health checkups in older patients (Ishikawa 2016).

Health and Research Informatics Databases

To overcome some of the limitations of the epidemiologic and claims databases, a strong emphasis is ongoing to leverage electronic medical records (EMRs) to build databases with more granular information and links to clinical pathways. These offer powerful potential tools for older patients with comorbidities. Clinical trials, despite ongoing efforts to improve accrual of older patients, still have an underrepresentation of older subjects (Hurria et al. 2014). Evidence for those complex patients could come from these big datasets. The oldest of these projects is the Total Cancer Care (TCC)^{TM} database. The TCC concept was created in 2003 and implemented in 2006 at H. Lee Moffitt Cancer Center and Research Institute (MCC) in Tampa, Florida, and has expanded into a multicentric network of 18 additional institutions (Fenstermacher et al. 2011). More recent databases are CancerLinQ, coordinated by the American Society of Clinical Oncology, and Watson, based at MD Anderson Cancer Center in Houston, Texas, both started in 2013. These large databases collect information from EMR documented patient data and restructure it into a single database that can be used to ask a variety of questions. Parameters including age, comorbidities, treatments, and outcomes can help to focus on populations of interest and provide detailed output. To facilitate this, these big datasets work with large software partners, Oracle, System Application Products (SAP), Microsoft, and International Business Machines (IBM) respectively.

Methods for Effective Big Database Digging

There are various methods for big database digging; however, this section will focus on the top 6 methods that we have found to be effective and successful. Figure 1 highlights the building blocks for effective and successful big database digging and will be referenced throughout this section. One of the first and essential methods for effectively executing a deep dive into a large database with oncology data is to have a basic understanding of relational databases and database design. For example, it is important to know whether you are working from multiple tables, spreadsheets, and/or databases or whether you are working from a single table, spreadsheet, or database. Knowing how multiple tables are linked on the backend of the database as well as a thorough understanding of the individual source systems populating the database is critical. Having this knowledge is one of the key building blocks (Fig. 1) because this knowledge will allow you to determine the database primary key and foreign key(s) and where to extract the data from if you are utilizing a programming language such as structured query language (SQL) or statistical analysis software (SAS).

Secondly, it is important to have an understanding of the cancer language for each cancer site. This building block specifically targets data analysts or a similar employee who is responsible for extracting or summarizing the data in the form of reports, charts, or graphs from the database. Having a firm understanding of the data you are extracting will allow you to accurately interpret and provide guidance to those who plan to

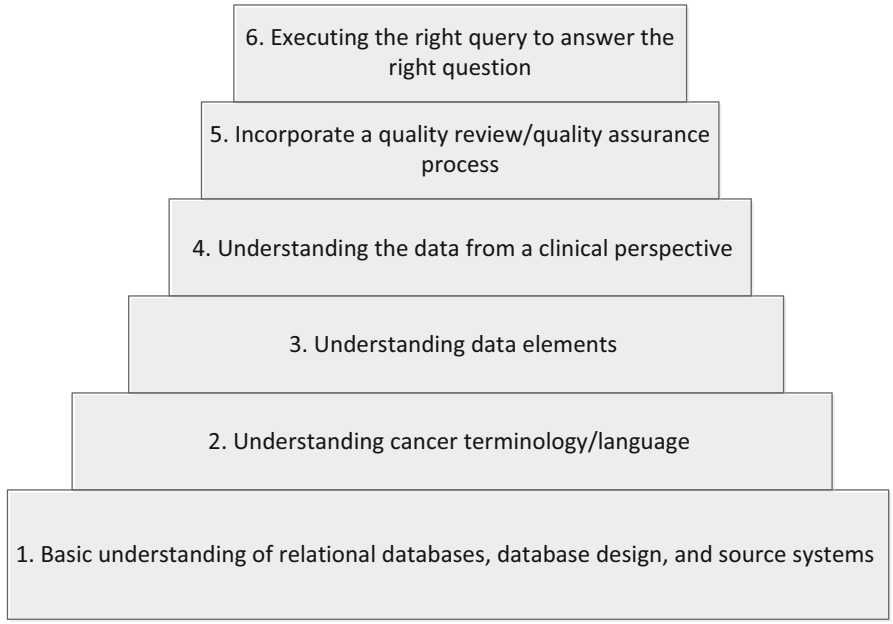

Fig. 1 Top 6 methods (building blocks) for effective and successful big database digging

interpret the data. In addition, successfully understanding this building block will prepare you for the fifth building block, being able to complete a quality assurance/quality review. It is important to have working knowledge of the cancer jargon and know that some of the cancer language has changed over time. This is important when executing a data query to search for cases that meet a specific inclusion/exclusion criterion. For example, when looking for patients that were diagnosed with small cell lung cancer, it is important to have historical knowledge that you need to look for small cell and oat cell using the histology/morphology data element because historically small cell was called oat cell. On the other hand, if you are executing a data query to identify neuroendocrine cases, then you need to include carcinoid because historically neuroendocrine tumors were classified from a histologic/morphology perspective as carcinoid. Without this background knowledge, it is easy to exclude cases that actually meet the inclusion criteria, potentially underestimating your sample size. Hawhee and Williams created an online resource guide for training and education targeting cancer registrars; however, the training guide is useful for anyone seeking cancer-related reading material and training resources (Hawhee and Williams 2016).

Thirdly, it is pertinent to make sure there is complete understanding of the data elements contained within the database. Having an in-depth knowledge of the data elements, the source system that contains the data elements, as well as start and stop dates for the collection of the data elements, is critical. Without this knowledge, it is difficult to understand the capability of data queries that can be executed using the big data. For example, it is important to know the transition of data codes from the International Classification of Diseases, Ninth Edition (ICD-9) to the International Classification of Diseases, Tenth Edition (ICD-10). Also, from a database perspective are the values for ICD-9 codes consolidated into one data element with ICD-10 or do you have to pull data from two different data elements by creating an OR statement in order to accurately execute a data query. In addition to knowing the data elements, it is also important to have a data dictionary available for reference that clearly defines each data element along with other descriptive information about the data element such as data collection start date, data collection end date, data

element permissible values, numeric code, and corresponding description. If you do not have a data dictionary, it is highly recommended that you create one, preferably electronic, and update it every quarter or monthly if data elements are consistently being added.

The fourth building block is to ensure understanding from a clinical, hospital operations, and research perspective. The policies and standard operating procedures of healthcare are often times the driver for the various nuisances in the way that data are collected and coded. Knowing from a high level how data are captured in the electronic health record by the cancer registry and by decision support or financial teams will help ensure that you are accurately interpreting the data. Also, having some knowledge on how the data are entered into the source system (s) will help because this will be beneficial when the data are extracted and there are questions regarding specific data elements and potential missing data.

Next, it is highly recommended to have a quality assurance/quality review (QA/QR) process in place so those working directly with the data queries can collaborate with the clinicians to confirm the data are clinically feasible and interpretation of the data is accurate. During the QA/QR process, it will be helpful to provide a summary at the data element level on the percentage of missing values, blank values, unknown values, and complete values. In addition, it will be helpful to create a process to identify any errors in data entry and the errors being corrected in the source system.

Finally, when executing a query, it is important to know what question(s) you are trying to answer. A clinician and data analyst speak different languages, so it is important for data analyst to understand from a clinical perspective what question is being asked. In addition, it is worthwhile for the clinician to understand the data elements that are readily available that can answer the question(s). In working with data, you will get an answer or number when executing a query, but the key is to make sure that you are answering the right question and you have executed the query accurately.

Specific Research Applications and Methods

Mutations, Gene Expression, Epigenetics

Big data has been used the longest in basic sciences: genome databases, proteomics, metabolomics, and other databases abound. Such databases can be very helpful to explore the biology of aging and cancer, the molecular impact of comorbidities, and more. We list below potentially useful databases. Multiple softwares are available to analyze such data and minimize the false discovery risk (FDR). We recommend using a statistician familiar with these softwares for analysis. The identification of pathways and clinical potential require biological knowledge of the diseases involved. It is also important to have a notion of how the tissue was collected, how the patients were selected, and which clinical correlates are available.

Examples of publicly available big data websites:

GEO database: GEO (Gene Expression Omnibus) is a public functional genomic data repository supporting MIAME-compliant data submissions. Array- and sequence-based data are accepted. Tools are provided to help users query and download experiments and curated gene expression profiles. GEO is an international public repository that archives and freely distributes microarray, next-generation sequencing, and other forms of high-throughput functional genomic data submitted by the research community.

https://www.ncbi.nlm.nih.gov/geo/

GEO database is organized by individual projects, each represented by a (usually) published manuscript. For many journals, it's required to upload your data to GEO before you can get your manuscript accepted for publication.

GEO provides browsing and keywords searching functions. For keyword searching, it returns documents, samples, and datasets whose descriptions contain any of the keyword combinations you are searching for. The search results are displayed as a list of manuscript titles, followed by short descriptions and links to full-

length articles, clinical data, and full-size datasets in different formats. You can select to download datasets as raw cell files and/or normalized expression intensity values in tab-delimited format. These datasets can be used for data mining for new discoveries or for validating biomarkers already developed.

TCGA (The Cancer Genome Atlas) is a collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) that has generated comprehensive, multidimensional maps of the key genomic changes in 33 types of cancer. The TCGA dataset, comprising more than two petabytes of genomic data, has been made publically available, and this genomic information helps the cancer research community to improve the prevention, diagnosis, and treatment of cancer (https://cancergenome.nih.gov/).

Unlike GEO, TCGA is not organized by individual projects, but by disease type. All samples for a certain disease type from multiple projects are incorporated into one big dataset. TCGA provides browsing and querying functions. You can browse their data by primary site, disease type, data category, experimental strategy etc. You can download data from TCGA as well as upload data to TCGA for online analysis.

ICGC (International Cancer Genome Consortium) Data Portal is a confederation of members that share the common goals and principles described in the policies and guidelines document and have agreed to work in a coordinated and collaborative manner within a defined structure. The members of the committees and working groups will help to provide clarity to the ICGC structure as it moves forward. The ICGC Data Portal provides tools for visualizing, querying, and downloading the data released quarterly by the consortium's member projects.

https://dcc.icgc.org/

ICGC contains most of the datasets TCGA has, plus more datasets from non-US countries. ICGC provides keyword search and browsing functions similar to GEO and TCGA. It also provides online data analysis functions such as enrichment analysis, cohort comparison, set operations, and some simple visualization functions.

MetaCore™ is an integrated software suite for functional analysis of next-generation sequencing, variant, CNV, microarray, metabolic, SAGE, proteomics, siRNA, microRNA, and screening data. MetaCore is based on a high-quality, manually curated database of:

- Transcription factors, receptors, ligands, kinases, drugs, and endogenous metabolites as well as other molecular classes
- Species-specific directional interactions between protein-protein, protein-DNA and protein-RNA, drug targeting, and bioactive molecules and their effects
- Signaling and metabolic pathways represented on maps and networks
- Rich ontologies for diseases and processes with hierarchical or graphic output

https://lsresearch.thomsonreuters.com/pages/solutions/1/metacore

IPA (Ingenuity® Pathway Analysis) is a powerful analysis and search tool that uncovers the significance of omics data and identifies new targets or candidate biomarkers within the context of biological systems. IPA has broadly been adapted by the life science research community and is cited in thousands of articles for the analysis, integration, and interpretation of data derived from omics experiments, such as RNA-seq, small RNA-seq, microarrays including miRNA and SNP, metabolomics, proteomics, and small-scale experiments.

https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis/

Potential Application: Diagnostic and Targetable Mutations for Personalized Medicine

The evolution of massively parallel sequencing technology has facilitated the translation of somatic genomic sequencing from being confined to the research realm into standard clinical practice, and its role in both prognostic aspects and treatment direction continues to evolve.

The genetic analysis of tumor tissue and "liquid biopsies" using cell-free DNA (cfDNA) can now be performed at reasonable costs with clinically relevant mapping. The technology has evolved to allow for higher specificity/sensitivity and quicker turnaround times in a cost-effective manner. The benefits of this in terms of prognostic aspects and treatment direction continue to evolve as do the analytic tools facilitating its use and the ability to leverage the data for optimizing future decision making. As cancer centers develop a workflow for integrating genetic tumor analysis into practice, there is also a need to create and maintain databases to store tumor genetic data. These results, in connection with patient characteristics and outcomes, can be used for standard of practice identification of EGFR, KRAS, BRAF, etc. mutations to help with informing both prognosis and classification of specific subtypes of common cancers, as well as tracking response over time and sequential sampling.

Numerous institutions have published their site-specific descriptions of data handling and patient outcomes (Knepper et al. 2017; Radovich et al. 2016; Wheler et al. 2016; Schwaederle et al. 2014). These databases typically include patient demographics, disease characteristics including prior therapies, the type of genetic assay performed, source and date of the tissue acquired for the assay, and the actual gene and mutation results, along with copy number or allele frequencies. Databases may be directly integrated with a site's EMR which may aid in documenting outcomes, or this may be done manually on a regular rolling basis as patients progress through therapies. Since these databases often contain identified patient data, handling and accessing the information must be in compliance with HIPAA and require an IRB application for access. Certain research and shared databases, such as CancerLinQ, are de-identified and require different agreements. The ongoing creation and maintenance of this data provides a valuable resource for addressing some of the current challenges faced by the integration of genetic tumor profiling into standard practice. In the advanced disease setting, big data can be used to identify novel treatment targets for patients who have progressed through multiple lines of therapy or in those with rare tumor types and few standard treatment options and are now incorporated into the standard work-up and management of numerous solid tumors and hematologic malignancies. This approach can also help direct patients into clinical trials, including the novel basket and umbrella trials like the NCI MATCH study.

Challenges include the rare nature of many genetic alterations. Somatic mutations can serve as either prognostic or predictive biomarkers or, in some cases, both. Prognostic biomarkers are measurable variables that provide information about cancer outcomes, including disease recurrence and overall survival, independent of the treatment received (Ballman 2015). For example, in acute myelogenous leukemia (AML), TP53 mutations and internal tandem duplications of FLT3 (FLT3-ITD) are associated with poor outcomes, while CEBPA and NPM1 alterations are associated with more favorable outcomes (Dohner et al. 2015). Predictive biomarkers are measurable variables that are associated with treatment outcomes. These can include alterations that predict benefit from a certain drug or class of drugs, such as epidermal growth factor receptor (EGFR) activating mutations in non-small cell lung cancer (NSCLC) that predict responsiveness to inhibitors of EGFR such as erlotinib and gefitinib. They may also include negative predictive biomarkers associated with resistance to a certain drug or class, such as KRAS mutations in colorectal cancer and the lack of response to monoclonal antibodies that inhibit EGFR, such as cetuximab and panitumumab (Ballman 2015; Bardelli and Siena 2010). Given the importance both prognostic and predictive biomarkers have in cancer management, comprehensive guidelines now incorporate those with robust data into the standard diagnosis and treatment for numerous malignancies. Somatic genetic assessment can also be used in the setting of more advanced disease and/or when there are limited or no treatment options for patients. In these instances, less common alterations can be uncovered and their actionability may be less clear. The goal of clinically interpreting a genetic variant is to determine those alterations considered to be "drivers" of

the malignant process from "passenger" or germline alterations. Cancer cells depend on "driver" mutations that provide a growth advantage to these rapidly proliferating cells, while "passenger" mutations do not have a direct effect on the neoplastic process (Vogelstein et al. 2013). Generally, clinically actionable alterations are defined as those with evidence supporting:

1. Correlation with benefit or resistance to a particular therapy
2. Effect on the function of a gene associated with cancer biology that can be targeted with either an FDA-approved therapy, off-label therapy, or a clinical trial
3. Specific inclusion criteria for a clinical trial
4. Prognostic information that establishes a diagnosis or disease prognosis
5. Germline alteration association with a hereditary cancer syndrome or alters the pharmacokinetic or pharmacodynamic nature of a specific therapy (Meric-Bernstam et al. 2015)

Genetic alterations that cannot be classified as clinically actionable may be considered variants of unknown or almost known significance. Variants of almost known significance (VAKS) are genomic alterations with functional consequences located in a clinically significant gene specifically in an area of the gene known to be clinically relevant (i.e., the tyrosine kinase domain) but has not been reported in the literature previously (Knepper et al. 2017). The strength of a clinically actionable determination is based on the strength of the literature available for the particular genetic alteration. Large, appropriately powered prospective comparative trials with biomarker stratification in the patient's specific tumor type are preferred but are uncommon. Most evidence is from retrospective cohort or case-control trials in addition to case studies or case series. This is partially due to the rare nature of many genetic alterations. Since the clinical interpretation of somatic genetic alterations is only as good as the data informing these recommendations, the generation of datasets across facilities and sharing of this information are essential to optimizing genetic-guided treatment decisions (Table 1).

Specific challenges amenable to leverage of shared data in terms of both findings and outcomes include assigning clinical actionability to specific variants in diverse tumor subsets, prioritizing actionability of variants, and discerning "driver" mutations from "passenger" and germline mutations that may be less relevant to the oncogenic nature of the cancer. Interrogating variants of unknown and almost known significance is also essential and may yield additional treatment options or prognostic information as our understanding of cancer biology continues to grow. Numerous databases exist to help identify germline mutations, pathogenicity of specific alterations, the incidence of mutations across tumor types, and ultimately the guidance toward a treatment recommendation. Several examples of these are listed in Table 2 along with the types of information each may provide. The need to classify variants in a real-time manner to facilitate clinical care underscores the importance of these integrated databases and the ongoing need for continued contribution and data analysis.

The personalized nature of this method of directing treatment may be especially relevant in the senior adult oncology population as it may reveal novel and more appropriate treatment options for individual patients who may have comorbidities or conditions limiting the ability to receive standard therapies (Table 3).

Using HRI for Clinical Studies

A feature common to clinical HRI is an analytic software for retrieval. Such a software may contain two retrieval modes: identifiable data and anonymous mode. Whereas access to identifiable data requires the same IRB approval as retrospective studies, retrieving data in anonymous mode can be leveraged in several ways to strengthen clinical trial design and practice improvement. We list below some examples from the software used at Moffitt's Transmed™.

Table 1 Examples and characteristics of big datasets

Dataset	Data type	Strengths	Weaknesses
Surveillance epidemiology and end results (SEER)/ Medicare	Diagnostic and claims data on patients aged 65 and older enrolled in Medicare. Covers nine US states and four urban areas	Population-wide claims data linked to cancer demographic and clinical data	Does not collect oral medication information
			Does not collect ECOG or KPS (scores used to measure a cancer patient performance status or functional impairment in their ability to complete activities of daily living)
National Cancer Database (NCDB)	Hospital registry data collected from 1,500 facilities	Collects treatment and outcome data for newly diagnosed malignant diseases	Hospital/facility must be accredited by the American College of Surgeons, Commission on Cancer (ACoS, COC)
Health research and informatics enterprise-wide data warehouse – Total Cancer Care (TCC)	Patient consented to the TCC protocol that may or may not have cancer across 19 hospitals/facilities	Collects biospecimen samples (somatic and/or germline)	
		Includes cancer cases as well as noncancer cases (controls)	
		Data and biospecimen collected from 19 hospitals across the United States	
		Molecular or genomic data available	
		Optional completion of patient self-reported data via an electronic patient questionnaire	
The Cancer Genome Atlas (TCGA)	NIH-driven dataset	Public access extensive gene array data	Links to clinical data are limited
CancerLinQ	ASCO-coordinated database	Large set of clinical data linked to private practice oncologists via EMRs	Still in testing/building phase
North American Association of Central Cancer Registries (NAACCR)		All cancer registries are not a SEER state and therefore do not report their data to SEER; however, their cancer registry data may be reported to NAACCR	
		Include registry data from Canada	
State- and hospital-level cancer registry databases		May have additional data available at the patient level that is not available using larger population data such as chemotherapy, hormone therapy, and immunotherapy drug names	
		The option to manually abstract patient level outcome data such as recurrence and progression	

Table 2 Databases usable for precision medicine use

Resource	Website	Potential value
cBioPortal	http://www.cbioportal.org/	Location of a specific variant across the domains of the gene as well as the frequency of gene alterations across cancer types from multiple clinical investigations
Catalog of Somatic Mutations in Cancer (COSMIC)	http://cancer.sanger.ac.uk/cosmic	Interrogation at the level of gene, mutation, cancer type, or cancer histology
OncoKB Precision Oncology Knowledge Base	http://oncokb.org/#/	Integrated database of 418 cancer-related genes in terms of clinical significance, treatment implications, and clinical trials (linked with cBioPortal)
MyCancerGenome	http://www.mycancergenome.org/	Knowledgebase of common cancer-related genes in terms of clinical significance, treatment implications, and clinical trials
PharmGKB	https://www.pharmgkb.org/	Interactive tool related to how genetic variation affects drug response
ClinVar	http://www.ncbi.nlm.nih.gov/clinvar/	Archive of reports focused on the relationships between genetic variations and phenotypes, including both somatic and germline alterations along with levels of evidence
1,000 Genomes Project	http://www.1000genomes.org/	Determining the likelihood of an alterations being germline rather than somatic
Exome Variant Server	http://evs.gs.washington.edu/EVS/	Determining the likelihood of an alterations being germline rather than somatic

Table 3 Tips and pitfalls: all that glitters is not gold

Using HRI to identify a potential population for accrual in clinical trials is highly effective and more accurate than clinical estimates
As diagnostic codes change over time and are not always entered correctly in regular clinical practice, they need to be verified with chart data unless very large scale population analyses are conducted
Tumor tissue samples in gene expression databases such as TCGA are typically microdissected to contain at least 80% of tumor tissue for homogeneity. Certain tumors have heavy inflammatory infiltrates that may affect gene expression in cancer cells in these areas, and this would be missed in such databases
Clearly define the limits of your search. Searches get easily diluted by "tantalizing" data, and the risk of hidden heterogeneities in data is high

1. **Estimating accrual for trial design**. It is often difficult to estimate the potential accrual into a clinical trial. Investigators' estimates of their clinical volumes are notoriously unreliable. Cooperative groups often rely on past accrual rates in similar trials, which tend to be fairly accurate. Some previous phase II data may exist in a given institution, but accrual may be more variably influenced by competing trials, change in treatment or referral patterns, or biologic marker selection. The Transmed software allows the creation of search strategies that can either identify a specific population (capsules) or be used repeatedly (filters). A filter can be created to identify the number of patients seen at the institution with similar cancer types, stages, treatments, and eligibility criteria. We recommend checking 2–3 recent years to account for variability. Once the number is obtained, we recommend applying the following rule of thumb: for survey trials, estimate an accrual of half the number of patients seen. For therapeutic trials, estimate one fourth of patients seen. This allows for the typical patient acceptance rate (Kemeny et al. 2003), as well as for imponderables such as distance from hospital, comorbidities etc. In our experience, estimates obtained this way, while often sobering, are quite reliable upon trial implementation.
2. **Process improvement research**. As big data often includes EMR information, this creates an opportunity for geriatric oncology research. Elements of a geriatric assessment and interventions can be digitalized in the EMR, and outcomes can be tracked over time. Research is still nascent in that area.

Digging for Therapeutic Use in Individual Unusual Cases

Utilizing the methods (building blocks) for effective big database digging provides the foundation for identifying therapeutic use among individuals with unusual cases.

Identifying therapeutic use in individual unusual cases first requires the need for known demographic and clinical characteristics. This also includes gathering requirements or the inclusion/exclusion criteria for the patient cohort of interest. Once this information is known, it is important to work with someone familiar with the data elements and database to extract the data in a predetermined format. For example, there was a case seen at MCC and the patient was diagnosed with both breast cancer and multiple sclerosis. In order to properly treat this patient, the team identified if there were other patients treated at MCC with similar demographic and clinical characteristics. There were other patients identified with similar characteristics, and the clinical team collaborated on the best course of treatment utilizing the availability of retrospective data.

One of the key drivers behind big data efforts in clinical medicine is the ability to help the patients' treatment in real time. One of the efforts underway is to integrate clinical guidelines and pathways into patients' EMRs. The software would analyze information about tumor stage, patient's characteristics, and previous treatment and offer guideline-based treatment suggestions on screen. Research is ongoing to assess issues such as incomplete data and pathway building (e.g. Bettencourt-Silva et al. 2015).

A more ambitious effort, but of particular relevance to older patients is generating real-time evidence for patients who do not match eligibility criteria from the studies on which the guidelines are based. For example, in lung cancer, a substantial number of guideline recommendations have limited validity in patients aged 80 and above (Battisti et al. 2017). Our group piloted an approach using HRI to do remote consultation for a community practice group (Dougoud-Chauvin et al. 2016). The outside oncologist was sending an e-mail with structured patient information. Similar patients were retrieved from TCC, and a summary case report was created with expert comment. Information was collected as to the impact of the information provided. The median turnover time was 2 working days, but the staff effort needed was substantial. Future research efforts should focus on a better selection algorithm to retrieve information, better coding of the disease and treatment phases in HRI (likely using language recognition software), and the generation of data pools for frequently asked questions. Outcomes research should track outcomes beyond modification of decision making.

Conclusions

Big data will play an increasing role in geriatric oncology (and in medicine in general). This is an incredible research opportunity for this highly heterogeneous population. It can be applied to basic science, helping to understand the interaction of aging and cancer and the modification of tumor biology and host-tumor interaction with age. It can be applied for translational research: finding targetable mutations to propose individualized treatments. It can be applied to clinical medicine, for generating evidence for complex patients or for assessing the impact of oncogeriatric interventions. While this is a new research area, the authors drew from their collective experience with this research to provide information to help oncogeriatric researchers leverage these powerful tools efficiently.

Cross-References

- ▶ Aging and Cancer Biology
- ▶ Biomarkers of Aging (With a Clinical Potential in Oncology)
- ▶ Comorbidity in Aging and Cancer
- ▶ Decision Making and Safety Issues in Older Cancer Patients
- ▶ Healthcare Informatics and Technology in Managing the Older Cancer Patient
- ▶ Integrating Geriatric Oncology into Clinical Pathways and Guidelines

- ▶ Pharmacology of Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management
- ▶ Principles of Cancer Targeted Therapy in Older Adults
- ▶ Research Methods: Epidemiologic Research in Geriatric Oncology
- ▶ Research Methods: Outcomes and Survivorship Research in Geriatric Oncology
- ▶ Research Methods: Translational Research in Geriatric Oncology

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Research Methods: Systematic Reviews and Meta-analysis in Geriatric Oncology

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Gary H. Lyman and Marek S. Poniewierski

Contents

Abstract

Cancer is largely a disease of aging with increasing incidence with age for most malignancies and the majority of cancer patients diagnosed after age 65. At the same time, aging is associated with a progressive increase in the number of major medical comorbid conditions that may complicate the disease course and increase treatment-related complications and their adverse consequences. Unfortunately, age restrictions in clinical trials have led to limited data on the special characteristics, comorbidities, and outcomes of older patients with cancer. Geriatric Oncology has emerged as a subdiscipline within oncology with a focus on clinical management and research related to cancer in the older patient.

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Topics in Geriatric Oncology studied in randomized or nonrandomized clinical studies including those captured in systematic evidence reviews and meta-analyses cover a broad range of subjects related to cancer in the elderly. In this chapter, the basic methodology for conducting high quality systematic reviews and evidence summaries including meta-analyses is summarized. Such studies range across areas of prevention and screening, diagnosis and staging, functional assessment including comprehensive geriatric assessment, cancer treatment, supportive care, and survivorship and end-of-life. Systematic reviews start with defining the specific question and then establishing the relevant clinical setting including the target patient population or problem, the exposure, prognostic factor or intervention, any relevant comparison(s), and clinically important outcomes. Subsequently, a rigorous explicit and transparent process of identifying, appraising, and selecting or excluding the relevant evidence is undertaken. The resulting evidence from the systematic review may then be summarized descriptively or, when appropriate, in the form of a formal meta-analysis. Later in the chapter, a summary of reported systematic reviews and/or meta-analyses related to Geriatric Oncology over the past two decades is presented and summarized. Finally, available tools for the conduct, analysis, quality appraisal, and reporting of systematic reviews and meta-analyses are provided for the reader interested in a better understanding of such systematic evidence reviews.

Introduction

The discipline of Geriatric Oncology covers a broad range of topics including prevention and screening, diagnosis and staging, functional assessment studies including comprehensive geriatric assessment, cancer treatment, supportive care, and survivorship and end-of-life, among others. The evidence base for the field of Geriatric Oncology includes the highest level of evidence represented by randomized clinical trials (RCTs) as well as systematic reviews and meta-analyses of such trials. The totality of evidence also includes a range of prospective and retrospective nonrandomized clinical studies related to cancer in the elderly. The methodologic approach to systematic reviews and meta-analyses may vary somewhat depending upon the specific topic and the type of outcome measures captured. Nevertheless, there are important general principles related to systematic reviews and evidence summaries including meta-analyses that should be consistently applied across topics and diseases. These will be reviewed here with a primary focus on studies relevant to Geriatric Oncology.

Overview of Evidence Reviews and Summaries in Geriatric Oncology

The Cochrane Collaboration defines a systematic review as a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review. Statistical methods to summarize the evidence including meta-analyses may or may not be used to summarize and analyze the results of the included studies. Systematic reviews should be objective, systematic, transparent, and reproducible. As in most clinical research, the process starts with defining the specific question(s) and then establishing the relevant clinical setting, including (1) the appropriate patient population or problem; (2) the exposure, prognostic factor, or intervention of interest; (3) any relevant comparison(s); and (4) the clinically important outcomes (PICO) (Richardson et al. 1995). A systematic search to identify studies addressing each research question should be conducted followed by a systematic review, selection, and synthesis of the results pertinent to the question. The criteria for inclusion and exclusion should be objective, explicitly stated, and consistently implemented as well as transparent such that other investigators would likely identify the same studies and outcomes using the same criteria. Future researchers may also update the

review at a later time in order to integrate new findings. This explicit approach minimizes the risk of bias and allows readers of the review to assess the author's assumptions, procedures, evidence, and the validity and applicability of the conclusions.

Systematic reviews may include a formal meta-analysis, which attempts to generate a quantitative weighted summary of the major results from similar but separate individual studies. Meta-analyses may be based on aggregate data as reported in published clinical trials or based upon individual patient data (IPD) from each study, when available. While the later represents an ideal setting for summary analysis and interpretation, few such analyses are feasible, affordable, and available. Therefore, the majority of meta-analyses are based on aggregate patient data reported in published manuscripts and not on IPD from each of the trials (Lyman and Kuderer 2005). The strengths and weaknesses of both approaches are summarized below. While IPD meta-analyses often strive to obtain unpublished data and provide greater opportunities for data checking and updating, such features are not inherent to this approach but largely attributable to the considerable resources and time devoted to such studies (Lyman and Kuderer 2005). Failure to obtain data on all patients and all trials may lead to acquisition bias since the missing studies or patients may not be missing completely at random. As discussed later in this chapter, summary effect measures based on study aggregate and IPD results have been shown to be very similar or identical when based on the same studies and patients. While both approaches permit exploration of study level sources of heterogeneity, only access to IPD permits full exploration of and adjustment for patient characteristics and therefore provides the best opportunity for full exploration of the results across multiple studies. However, the resources, time, and cooperation required for IPD studies will continue to limit their use in many important areas of clinical medicine which can be meaningfully and cost-effectively approached by properly performed aggregate meta-analyses.

Conducting a High Quality Systematic Review

While narrative reviews by subject experts have always been a part of the medical literature, the principles for performing high quality, rigorous systemic reviews have only been made explicit in the past two to three decades and are now widely accepted and practiced by professional organizations and investigators worldwide. A systematic review is an integrated and comprehensive review of the literature on a specific clinical question, characterized by explicit methods of data searching, selection, review, and quality appraisal. Major differences between a systematic review and a narrative review are the transparency of the processes utilized and the greater effort to minimize bias in the former. Systematic reviews are more likely to be guided by explicit statements about the literature search strategy and study selection criteria. Inclusion and exclusion criteria for the review are precisely stated with the overriding goal of reducing the risk of bias in the identification, selection, and reporting of the evidence. A systematic review checklist based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement is provided in Table 1 (Moher et al. 2009). After defining an important question, a systematic search for relevant studies is undertaken. Initial searches often start by identifying existing systematic reviews, practice guidelines, and technology assessments on the topic in question. Systematic reviews proceed through a well-defined series of stages addressing clinical outcomes, including (a) defining the question, (b) searching the literature, (c) screening and selection of eligible articles, (d) critically appraising study quality, (e) data extraction, and (f) data synthesis across acceptable studies (Deeks 2001a, b; Vamvakas 1998). Optimal systematic reviews require a dynamic collaboration between experienced clinicians or content experts and methodologic colleagues familiar with the rigorous methods applied to systematic reviews in an effort to avoid bias and provide reliable and trustworthy summary results.

Table 1 Systematic review checklist (PRISMA)

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	

(*continued*)

Table 1 (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Source: http://prisma-statement.org/PRISMAStatement/Checklist.aspx

A study protocol is compiled detailing the question, goals, and each step planned for the systematic review. This should be thoroughly reviewed and agreed upon *a priori.* The protocol should include details of the search algorithm, the inclusion and exclusion criteria, and the data elements to be extracted ideally into predefined data forms or spreadsheets. A clear record of the systematic review process is important to reflect decision/choices made during the design and conduct of the review and serve as a resource when the results are presented. Prior to finalizing the review process, it is often worthwhile identifying a few recognized studies, e.g., 5–20, that appropriately address the question at hand. The database indexing of these studies can be very informative in finalizing the criteria to be utilized in the final search. The databases to be searched should be prespecified and can include published literature, meeting presentations, and other sources determined by the investigators to be relevant and credible. The time frame of the search (start and end dates) should be specified. Likewise, as noted above, it is important to determine whether previous systematic reviews or technology assessments have been performed related to the same topic and review these critically as well as to inform any novel or updated review. An updated review permits a more efficient and effective use of resources and can build upon and even improve upon rather than simply replicate credible previous work of qualified investigators. An explicit search algorithm should be established often in collaboration with a highly experienced search analyst or experienced librarian. This is often best done by breaking the search into individual important and relevant components and then combining into the overall search algorithm. Search categories might include study design, demographics, disease, stage, other clinical characteristics, treatment, and outcomes, among others. Synonyms, plural forms, and different spellings should be considered. PubMed searches should take advantage of MESH headings and filters provided to

optimize and target the search as desired. The use of Boolean logic for appropriately combining search components is critical. The investigator will have discretion between a more focused search with greater specificity in the interest of time and efficiency but with risk of missing some relevant articles or conducting a very broad and highly sensitive search to minimize missed articles but with the need to eliminate many more irrelevant studies during the subsequent review. It is often useful to further review the citations listed in known eligible studies to extend the review beyond that provided by the electronic database. However, as with the identification of studies by content experts, the potential for selection bias exists and should be guarded against.

Once launched, an exhaustive search for relevant studies should be conducted and careful data collection based on dual data extraction is encouraged to reduce investigator bias. Criteria for study inclusion and exclusion should be defined *a priori* but may be amended early in the search process once the initial studies identified are reviewed for relevance to the topic of interest. Inclusion and exclusion criteria should be justified on the basis of prior studies or clinically or biologically relevant rationale. In general, the broader the search strategy, the more detailed inclusion and exclusion criteria are required. Inclusion and exclusion criteria may address a range of parameters including timeline, research design, disease, patient characteristics, outcomes, etc. While inclusion and exclusion criteria may occasionally be modified early in the search process, once finalized, they should be rigorously and uniformly applied across studies usually starting with review of title and abstract often permitting rapid exclusion of irrelevant studies to the question being addressed. The full text of remaining studies should then be reviewed for eligibility. Both steps are best accomplished with a minimum of two experienced reviewers working independently with a third reviewer resolving any eligibility conflicts. Data extraction from the final collection of eligible studies then should proceed with a minimum of two experienced abstractors working independently to complete the predefined data worksheet with reconciliation of differences resolved by either further review of the manuscript jointly or a third independent reviewer.

Systematic reviews summarize the results from several individual studies, identify reasons for variation in the results across studies, and potentially improve the quality of future primary studies by better defining the methodological inadequacies of previous reports. As will be discussed in the next section, results from individual studies may be formally analyzed first by assessing heterogeneity and, if appropriate, combining of results of similar studies by providing weighted summary estimates of the treatment effect. Observed heterogeneity generally relates to either differences in the population studied or the study methodology employed. Variation in study populations, the clinical settings, as well as the interventions employed can each result in variation in effect estimates. Likewise, variation in the type and quality of study methodology represents an important source of heterogeneity related to the selection of an appropriate population sample, careful measurement and the absence of missing data, and blinding of investigators to test results and the absence of missing data.

A systematic review may be presented as a standalone publication or in support of a formal meta-analysis or clinical practice guideline. As summarized in section "Summary of Major Recommendations/Guidelines for Quality Appraisal or Reporting of Systematic Reviews and Meta-Analyses," several professional organizations and journals have established formal criteria for the conduct and reporting of systematic reviews and meta-analyses. Uniformly, these criteria include presentation of a flow diagram (PRISMA) of the search and inclusion and exclusion results presenting the numbers of studies included or excluded at each step of the process. Ideally, the reasons for study exclusion can be explicitly stated and catalogued to reassure the reader of investigator objectivity. The formatting of the systematic review results is similar to other scientific reports including background and rationale, a discussion of the methodology including the search strategy and algorithm, inclusion and exclusion criteria, the process and steps for study selection and data extraction, quality appraisal, and any

formal summary analysis performed. The methods section should be sufficiently detailed and explicit to permit an independent investigator following the provided search algorithm and inclusion and exclusion criteria to replicate the results presented when applied to the same timeframe. As noted previously, a flow diagram summarizing the types and number of studies identified at each stage of the review should be presented. Ideally, the number and reasons for study exclusion should be provided. The results are presented primarily in tabular form supplemented by useful graphics and annotated for further clarification. Importantly, results for each study should be presented including the name of study, citation, year published, number of participants in each arm, primary outcomes observed, and other relevant study and overall patient characteristics if reported. A formal assessment of the quality of included studies should be presented along with evidence for study consistency or heterogeneity. A discussion of the results in the context of prior studies should be provided including the strengths and weaknesses of the reported studies. It is important to include a discussion of the limitations as well as the strengths and additional issues encountered in the conduct of the review. Potential conflicts of interest and publication bias should also be discussed. Objective interpretation of the final results is important along with identification of gaps in available evidence and need for further studies. All eligible studies included in the final review should be cited in the text. Often some tabular material will, of necessity, need to be presented as appendices or supplemental material online separate from the primary publication.

Evidence Summaries and Meta-analyses

After completing the initial steps of a systematic review including specification of the question, search, study eligibility, and data abstraction, many systematic reviews are then often utilized in a formal evidence summary analysis in the form of a meta-analysis. The purpose of a meta-analysis is to systematically identify, review, and synthesize the results of previous research in order to provide valid conclusions related to the totality of reliable evidence on a subject in order minimize bias from selective citation commonly encountered in narrative reviews. If inconsistency across studies or heterogeneity of results is too great, a formal meta-analysis may not be appropriate and the results should be presented descriptively. However, when appropriately applied, a meta-analysis will have greater power than small individual studies and can sometimes explore any inconsistency of findings across studies and the reasons for heterogeneity. Most commonly, meta-analyses are conducted of similar RCTs or rigorously conducted prospective cohort studies with reasonable controls. The analysis should only proceed when the conditions are appropriate including the identification of relatively consistent and similar studies with reasonable similarity in study design, population characteristics, and management as well as outcomes reported. Summary results reported generally include an estimate of the effect size (standardized mean difference, odds ratio, relative risk, hazard ratio, etc.), variance (standard error or 95% confidence limits), and formal tests for heterogeneity and publication bias. Several generic and specialty software packages are available for conducting meta-analyses but should be applied cautiously by an experienced analyst. The decision to use fixed effects models or more conservative random effects models goes beyond the discussion here but should be decided before conducting final analyses by experienced methodologists. While heterogeneity across studies can be assessed formally for significance, such tests have low power and are generally combined with a measure of the impact of heterogeneity on the overall effect estimate using the inconsistency index (I^2). In general, if significant heterogeneity is present, a random effects model is more conservative and preferred. The summary results are often presented as Forest plots presenting the effect size estimate and variation in that estimate for each study individually and with all studies combined. The area of the box representing the effect estimate is inversely related to the variance or weight

of the study. Subgroup analyses and meta-regression analysis based on study design or population characteristics may be useful in exploring the causes of heterogeneity. Other informative approaches include use of a different effect measure or exclusion of studies considered outliers. However, these analyses should be planned a priori and increase the risk of false positive results. In meta-regression analysis, the treatment effect represents the dependent variable while study design and population characteristics may represent independent or explanatory variables. The potential for systematic error or bias (confounding) or effect modification (interaction) should always be considered. Sensitivity analyses across studies or population factors as well as quality metrics may be useful and may inform subsequent definitive studies. Funnel plots may be presented plotting the effect size of each study against the study sample size to qualitatively assess publication. While the absence of smaller negative studies may represent publication bias, formal tests for assessing publication are available and should be considered. In section "Summary of Major Recommendations/Guidelines for Quality Appraisal or Reporting of Systematic Reviews" below, selected formal guidelines and checklists for the conduct and reporting of meta-analyses are presented.

Special Considerations

Diagnostic and Prognostic Studies

Systematic reviews and meta-analyses of studies of diagnostic accuracy differ from other such analyses in the statistical methods used to combine individual study results. When the results lack significant heterogeneity, sensitivities, specificities, and likelihood ratios can be directly combined (Bland and Altman 1994). Study results may also be summarized as a Receiver Operating Characteristic (ROC) curve reflecting the pattern of sensitivities and specificities at different threshold cut points. The diagnostic odds ratio can also be useful when combining studies in a systematic review, as it often remains relatively constant across various cut points. Summary estimates of sensitivity and specificity or likelihood ratios will underestimate test performance if heterogeneity between the studies arises from variation in the diagnostic threshold (Deeks 2001b). The reference standard must be explicitly defined and be considered diagnostic of the condition. Ideally, the investigator and test interpreter should be blinded to disease status. Separate unblinded recruitment of disease and control subjects results in an overestimate of test performance (Lijmer et al. 1999).

Individual Patient Data Meta-analysis

Although few would argue that properly conducted meta-analyses based on individual patient data has distinct advantages, meta-analyses are most often based on aggregate patient data from completed studies that have been published in the medical literature. Meta-analyses based on aggregate data are far more common and continue to be the mainstay of systematic reviews conducted by many professional societies. A search for individual patient data meta-analyses related to cancer in 2000 revealed 38 of which eight were unpublished (Tierney et al. 2000). A more recent search of Medline by the authors identified 1595 reported meta-analyses related to cancer of which 76 (4.4%) were apparently based on individual patient data not changing significantly over several years (Fig. 1). The considerable use of meta-analyses based on aggregate patient data suggests that they are generally considered relevant and valid to editors, reviewers, and readers. Proceeding with a written study protocol with a prespecified search process, inclusion and exclusion criteria, and the hypotheses to be tested is critical to both. In both situations, an exhaustive search for relevant studies should be conducted with careful data collection based on dual independent data extraction and entry. Primary and secondary outcomes of interest should be specified in advance and the results from individual studies systematically analyzed providing summary estimates of the treatment effect. Pooled analyses of aggregate patient data are

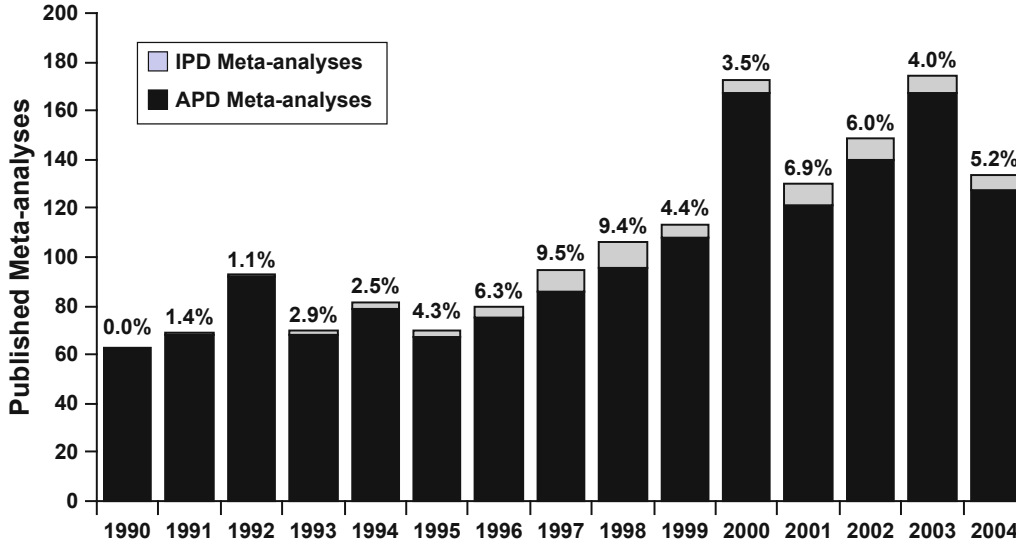

Fig. 1 Published aggregate and individual patient data meta-analyses (Lyman and Kuderer 2005)

conceptually the same as for individual patient data including estimating study-specific treatment effects, assessing heterogeneity, estimating a summary effect size, and evaluation of heterogeneity. Such meta-analyses employ essentially the same summary and statistical measures. While secondary analyses may explore the reasons for any heterogeneity, the exploration of patient-level characteristics is best undertaken with individual patient-level data. The use of averages or proportions of patient characteristics in aggregate analyses of trials may lead to the common ecological bias, underestimating the influence of such characteristics (Bossuyt et al. 2003). Such analyses are often not prespecified in individual trials which are generally underpowered to address subgroup evaluations and, therefore, should be considered as exploratory or hypothesis generating. Publication bias represents an important limitation of any review, and retrieval of data from all relevant studies should be the goal in order to avoid publication bias. An acknowledged limitation of individual patient data meta-analyses is the need to exclude studies for which data are not available due to proprietary interest or other concerns.

Summary estimates from aggregate meta-analyses have been shown to be similar to the least squares estimate of effect from individual patient data computed from a two-way fixed-effects model where the effects in the model are those due to treatment and due to different studies (Olkin and Sampson 1998). If the same studies are used for both approaches, there appears to be limited difference in the summary effect estimates between study aggregate and individual patient meta-analyses. Table 2 summarizes potential advantages of individual patient data meta-analyses (Lyman and Kuderer 2005). However, many of the specific processes providing

Table 2 Potential advantages of individual patient data meta-analyses (Lyman and Kuderer 2005)

1. Ability to use common definitions, coding, and cut-points
2. Address questions not addressed in original publication
3. Assess adequacy of randomization
4. Permits data checking
5. Permits data updating
6. Permits checking of analyses
7. Allows adjustment for the same variables across studies
8. Permits ready use of time-to-event data for estimating survival
9. Ability to address long-term outcomes
10. Facilitates exploration of heterogeneity at the patient level and subgroup analyses of patient level data

Table 3 Comparison of individual patient data (IPD) and aggregate patient data (APD) meta-analyses (Lyman and Kuderer 2005)

Steps in meta-analysis		IPD	APD
Explicit and relevant clinical question		√	√
Exhaustive search	All published studies	√	√
	All presented studies	√	√
	All completed studies	√	±
Screening: Inclusion/exclusion criteria		√	√
Data acquisition (extraction/transfer)	Aggregate data	√	√
	Individual patient data	√	–
Data checking	Source data	±	–
	Submitted data	√	√
	Published/ presented	√	√
Data updating		√	±
Missing studies/data		±	±
Uniform outcomes		√	–
Tests for heterogeneity		√	√
Estimating summary effect measures	Binomial data	√	√
	Time-to-event data	√	±
Exploring heterogeneity subgroup analyses	Study level	√	√
	Patient level	√	–

systematic reviews with an advantage over narrative reviews are shared by both types of analyses (Table 3). Aggregate study meta-analyses can be used to determine whether proceeding with more resource-dependent individual meta-analysis is worthwhile (Tudur et al. 2001). Efforts to obtain updated data and assess the quality of source data in individual patient data meta-analyses require considerable collaboration of the original investigators, institutions, organizations, or companies. Individual patient data meta-analyses rarely provide access to the source data such as patients, medical records, laboratory results, etc., to assure that data collection was properly conducted, that randomization was appropriate, and the same data items were actually collected. Differences in estimated outcomes are rare when comparing checked data to unchecked data (Burdett and Stewart 2002). At the same time, publication bias due to studies unwilling to collaborate may limit the validity of the analysis. Unpublished studies may be the result of low observed treatment effect either leading the investigators not to pursue publication or editorial bias against negative study results or may reflect the poor quality of the study. It is critical to avoid combining patients across studies as if they came from a single very large clinical trial. Several studies have demonstrated that when the same studies and outcome measures are utilized, effect size estimates are similar for both types of meta-analysis (Olkin and Sampson 1998; Steinberg et al. 1997). Updated data obtained after completion of the study may be influenced by crossover between arms, unblinding, and retrieval bias. Proper Institutional Review Board review, informed consent, and data privacy compliance are essential for analyses beyond those planned in the original study.

Survival Outcomes

When reporting an RCT with survival type data, the most appropriate summary statistics are the log hazard ratio and its variance, which are particularly designed for comparing two survival curves. The hazard ratio is a global summary of the difference between two survival functions and represents the reduction in the risk of death with treatment compared to controls over the entire period of follow-up. In a meta-analysis of such studies, the overall log hazard ratio is a weighted average of the log hazard ratios of each study where the weights are inversely proportional to the variance of the log hazard ratio for each trial. While the log hazard ratio and its variance are often directly reported in the trial results, there are also indirect methods for estimating the log hazard ratio and its variance either from summary trial results or the published survival curves. While survival curve estimates tend to underestimate the treatment effect provided directly from the papers, a number of methods may accurately

reproduce summary survival estimates statistically similar to that derived from individual patient data (Earle et al. 2000). If the time to an event and censoring are ignored, the log hazard function becomes simply the log relative risk.

A Summary of Systematic Reviews and Meta-analyses in Geriatric Oncology

A comprehensive systematic search of the English language literature published between 1990 and 2016 was undertaken for published systematic reviews or meta-analyses related to geriatric oncology including studies related to prevention, diagnosis, staging, treatment, supportive care, survivorship, or end-of-life. The search algorithm, inclusion and exclusion criteria, and data items for extraction were defined *a priori*. Titles, abstracts, and full text manuscripts were reviewed when needed. The initial search identified 1088 potentially eligible records of which 703 were not limited to elderly patients, 89 were not cancer studies, and 236 were deemed not be a systematic review or meta-analysis (Fig. 2). Hand search of citations identified one additional study. A total of 61 systematic reviews or meta-analyses were in geriatric oncology published since 1990 were identified in the peer-reviewed literature with more than half published over the past 5 years (Fig. 3). Systematic reviews were reported in 39 studies (64%), meta-analyses in 43 (70%), and both were reported in 23 (40%) studies. Published systematic reviews and meta-analyses in geriatric oncology were conducted across geographic regions including Europe (Whiting et al. 2003), US (Steinberg et al. 1997), Canada (Tierney et al. 2000), Asia (Bland and Altman 1994), and South America (Richardson et al. 1995) (Fig. 4). Most publications (N = 44) addressed a specific cancer type while 17 included studies across cancer sites. Many studies were designed to evaluate multiple outcomes including survivorship or end-of-life issues (40), cancer treatment (Moher et al. 1999), geriatric assessment (Olkin and Sampson 1998), treatment related toxicity, or supportive care (Lijmer et al. 1999). At the same time, the primary outcome reported in trials included in the systematic reviews included overall survival (39), progression-free (including disease- or relapse-free survival) (Sylvester et al. 2000), response or recurrence (Olkin and Sampson 1998), treatment-related toxicity (Horton et al. 2010), and geriatric assessment or frailty (Tierney et al. 2000). While studies including younger patients were not included, others reported results for different elderly

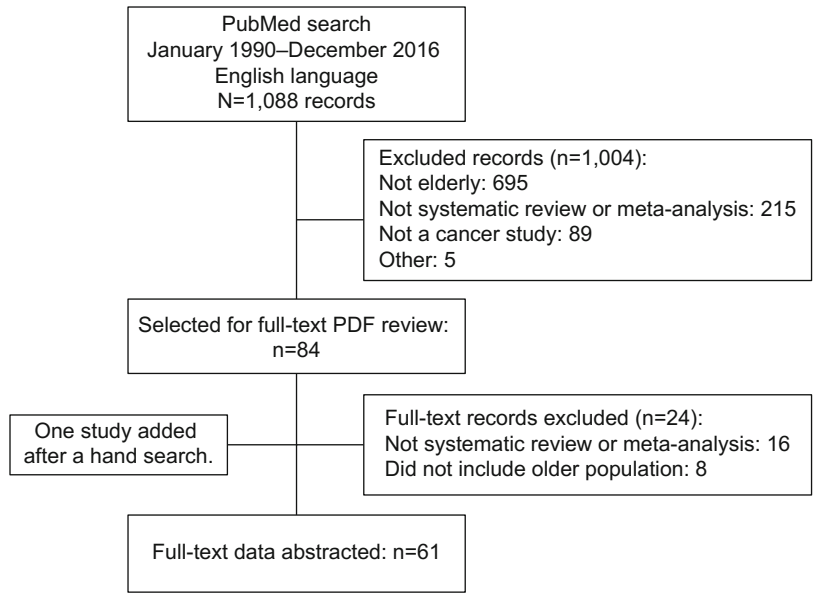

Fig. 2 PRISMA diagram: Flow of publications selected for data abstraction

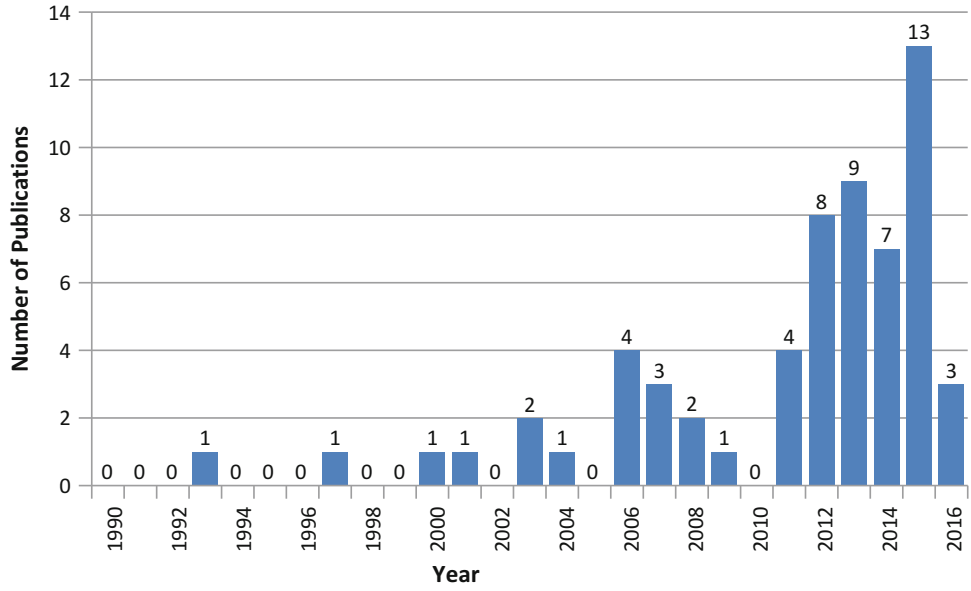

Fig. 3 Recent systematic review and meta-analyses publications, by year

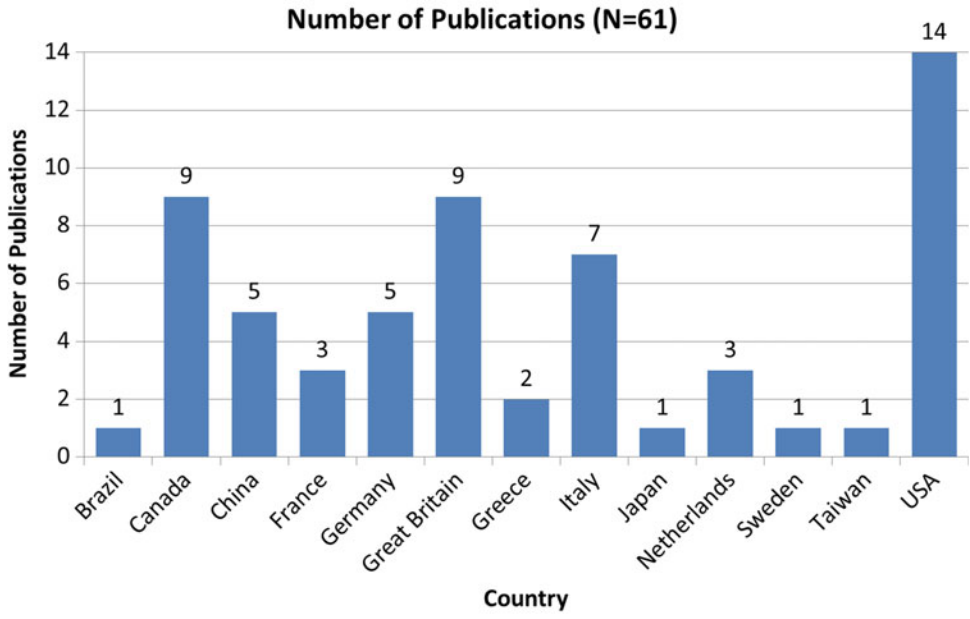

Fig. 4 Recent systematic review and meta-analyses publications, by country

cohorts. The age thresholds reported in the eligible studies included ≥60 (Buscemi et al. 2006), ≥65 (Whiting et al. 2003), ≥70 (Vandenbroucke et al. 2007), and ≥75 years (Fig. 5). Published systematic reviews and meta-analyses related to geriatric oncology included only RCTs (N = 37) or only non-RCTs (N = 9) while 16 permitted both types of studies. Depending on the topic of interest, the size of the evidence reviews identified differed considerably with the majority including 10 or fewer

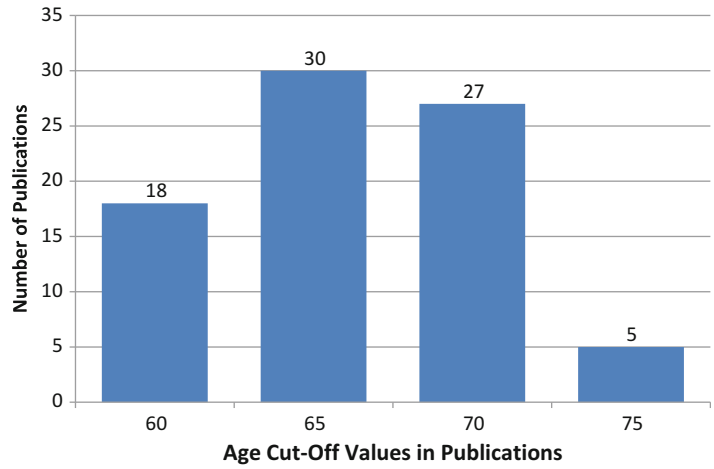

Fig. 5 Recent systematic review and meta-analyses publications, age cut-off values in publications

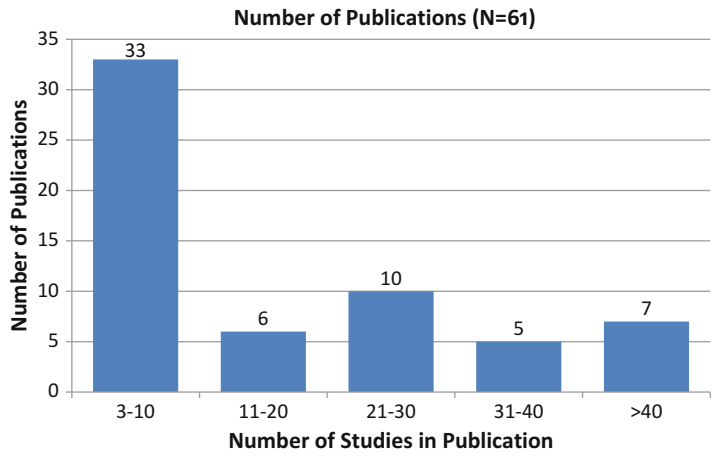

Fig. 6 Recent systematic review and meta-analyses publications, by number of included studies

studies (N = 33) while 16 included 11–30 studies and 12 included more than 30 studies (Fig. 6). Likewise, the number of subjects in the included trials of each systematic review ranged from 153 to over 15,000 whereas most reported fewer than 3000 subjects and 6 studies did not present the total numbers of subjects included. While 15 reviews looked at a range or multiple cancer types, 46 focused on patients with specific cancer types, most commonly non-small cell lung cancer (N = 9), colorectal cancer (N = 8), breast cancer (N = 7), multiple myeloma (N = 5), and lymphoma (N = 4) along with acute myeloid leukemia, chronic myelogenous leukemia, glioblastoma, ovarian cancer, and genitourinary and upper gastrointestinal malignancies. Of note, 19 studies (31%) utilized a limited subset or convenience sample of studies often based on access to individual patient data. These are included but may not represent true comprehensive systematic reviews.

Summary of Major Recommendations/ Guidelines for Quality Appraisal or Reporting of Systematic Reviews and Meta-analyses

As summarized earlier, systematic reviews and meta-analyses are formal, defined research methods for gathering, appraising, and summarizing evidence relating to specific defined clinical questions. The methods applied to systematic reviews and meta-analyses of geriatric oncology studies do not differ from those in other areas of

clinical medicine although the focus of the review may be, e.g., comprehensive geriatric assessment. The criteria for reporting and appraising results of systematic reviews have been detailed by several organizations, professional societies, and major medical journals (Moher et al. 1999, 2009; Bossuyt et al. 2003, 2004; Burdett and Stewart 2002; Steinberg et al. 1997; Earle et al. 2000; Bown and Sutton 2010; Buscemi et al. 2006; Elamin et al. 2009; Fleming et al. 2014; Horton et al. 2010; Kho et al. 2008; CEBM 2007; Shea et al. 2007; Sylvester et al. 2000; Vandenbroucke et al. 2007; Viswanathan et al. 2008; von Elm et al. 2007; Whiting et al. 2003, 2006, 2011; Willis and Quigley 2011; Zeng et al. 2015). The Institute of Medicine established standards for systematic reviews entitled "Finding What Works in Healthcare." (Eden et al. 2011) An excellent general source of information and tools for enhancing the quality and transparency of health research is found at the Equator Network (http://www.equator-network.org/). This site provides links to the PRISMA Statement, Checklist, and Protocol along with extended versions of PRISMA for (a) incorporating Network Meta-analyses, (b) Individual Patient Data Meta-analyses, and (c) reporting on health equity, and reporting in journal and conference abstracts along other resources. A PRISMA diagram is generally regarded as essential for displaying numbers and reasons for study exclusion along with the number of studies considered eligible for data extraction and analysis. The quality review should include the search strategy, study eligibility and selection, data extraction, outcome measures, data quality measures, and efforts to minimize bias. Appraisal of study quality and standards of reporting of diagnostic studies should consider the available QUADAS (Quality of Assessment of Studies of Diagnostic Accuracy for inclusion in Systematic reviews) and STARD (Standard for Reporting of Diagnostic Accuracy) (Whiting et al. 2003). Also available are links to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) for reporting meta-analyses of such studies (Stroup et al. 2000). These initiatives outline the most important features to consider in assessing studies of diagnostic accuracy and the methods employed to reduce systematic error or bias in such studies.

Discussion

The rising incidence of cancer with age is paralleled by an increase in the number of major medical comorbid conditions that often complicate the disease and its treatment. Historically, cancer clinical trials have provided limited information on the management of older patients with cancer due to imposed eligibility restrictions on age and/or comorbidities. Geriatric Oncology has emerged as a clinical and scientific discipline within oncology directed at issues related to clinical management and specific research questions relevant to the elderly patient with cancer. Increasingly, systematic reviews and meta-analyses of randomized and nonrandomized trials related to cancer in the elderly have appeared addressing a range of fields including prevention and screening, diagnosis and staging, functional assessment including comprehensive geriatric assessment, cancer treatment, supportive care, and survivorship and end-of-life. Systematic reviews should specify a specific question and establish the target patient population and setting as well as the exposure prognostic factor or intervention of interest, and specify relevant comparison(s) and clinically important outcomes. A rigorous explicit and transparent process of identifying, appraising, and selecting or excluding the relevant evidence should be conducted. The results of a systematic review may then be summarized descriptively or as a formal meta-analysis. In this chapter, we have presented the general principles and specific steps recommended in the planning, conduct, analysis, and reporting of high quality systematic reviews and meta-analyses. We have presented and summarized reported systematic reviews and meta-analyses related to Geriatric Oncology published over the past two decades. Currently available tools for the conduct, analysis, quality appraisal, and reporting of systematic reviews and meta-analyses are provided and reviewed designed to enhance the quality and understanding of systematic evidence reviews and meta-analyses. Such rigorous and systematic evidence summaries and analyses are likely to continue to increase in number and quality as the field of Geriatric Oncology continues to mature.

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Research Methods: Quality of Life and Patient-Reported Outcome Research in Geriatric Oncology

68

Ulrich Wedding

Contents

Abstract

Both clinical care for and clinical research in older patients with cancer need to define endpoints of treatment. Clinical research in geriatric oncology aims to improve the care for older adults with cancer. When asking older adults with cancer what they consider most important as aim of their treatment, some will focus more on lengths and others more on quality of life. Whereas it is easy to measure length of survival, it is more difficult to measure quality of life. As variety of quality of life assessment instruments is available, some of them are addressing health-related quality of life in general; some are developed in a disease-specific background, such as cancer; and others focus on special types of cancer or special kinds of cancer treatment. In the context of older adults

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with cancer, geriatric assessment is established to address areas of resources and limitations. Those items of geriatric assessment reported by the patient or demonstrated in performance test should be considered as patient-reported outcomes as well. Results of geriatric assessment and of health-related quality of life are closely related in older adults with cancer.

Introduction

Traditionally, the tumor was the main – if not exclusive – target of treatment in oncology, the removal of the tumor via surgery and the elimination or shrinkage via radiation or via chemotherapy. In the consequence, either cure (often reported as 5 years survival rates) or remission rates (complete or partial) were the focus of reports of success of oncological trials. However, cure is in any case temporary, as all lives end with the death and remissions seen in X-rays, CT or MRT scan, or ultrasound might not be of any meaningful benefit for the patient either, when they do not result in improved length and/or quality of life. This is especially true in the context of older adults with cancer, as their remaining average life expectancy is lower and the potential gain of years in life via cure less, compared to younger once. Therefore, the field of geriatric oncology is a paradigm to focus on patient-reported outcomes and quality of life.

What Are Patient-Reported Outcomes?

Patient-reported outcomes (PROs) are any reports coming directly from patients about a disease, health, or treatment without interpretation by a clinician or anyone else (Kyte et al. 2016). They include a range of outcomes, such as health-related quality of life (HRQoL), symptoms, functional status, and well-being (Acquadro et al. 2003). In the context of geriatric oncology, some items assessed within the geriatric assessment are patient-reported outcomes; others are physician-reported or performance-based.

Endpoints in Clinical Research in Geriatric Oncology

When the remaining length of survival becomes less achievable, as old itself, age-related and other health-related conditions limit the chance to gain more length of life, and the quality of life becomes more important. In cancer care, cancer treatment often affects quality of life in a negative way substantially. The best way to avoid these treatment-associated negative effects on quality of life would be not to treat a patient. However, that would result in the omission of the positive effects on length of life and quality of life as well. Therefore, treatment decision in geriatric oncology is always a balancing between positive and negative effects. This is summarized in Fig. 1.

Phase 3 clinical trials aim to improve clinical care in a way to establish new standards of care. When setting up phase 3 clinical trials, the most important question is: Will the results be able to set a new standard of care, if the primary endpoint is achieved? Therefore, there is no need to make a difference between endpoints in clinical care and in clinical research. Endpoints in clinical research, at least in big phase 3 trials, should be those the patient is most interested in to achieve.

The Task Force Elderly of the European Organization for Research and Treatment of Cancer (EORTC), the International Society of Geriatric Oncology (SIOG), and the Cancer-Alliance for Clinical Trials in Oncology published a recommendation on appropriate trial design and on selection of appropriate endpoints for clinical trials in older adults with cancer (Wildiers et al. 2013). Combined endpoints or composite endpoints, including efficacy and patient-reported outcomes, seem to be most appropriate for clinical trials in older adults with cancer. However, they are more difficult to plan and less established so far, and the number of patients might be higher than in trials just looking on a single endpoint. The advantage of combined endpoints or composite endpoints overweighs the disadvantage as these endpoints fit much better in the real world of the patients.

In randomized controlled trials, clinical research demonstrates group differences,

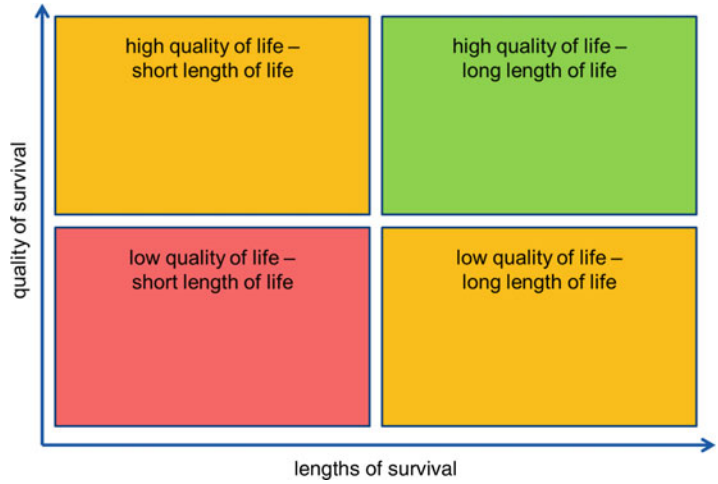

Fig. 1 Goal in treatment

comparing a group receiving standard treatment to a group receiving experimental treatment. In clinical care and in patients, the main comparison to judge the situation is, e.g., quality of life, before and after treatment. In clinical care, a much more individualized approach is possible to define each patient's most important aim of treatment. However, even in clinical care, a standardized approach is recommended in addition not to miss important areas of concern of the patient. Physicians and patients tend to consider different areas as important for the patient (Atkinson et al. 2012). In addition, cancer patients tend to underreport their symptoms to the physician (Nekolaichuk et al. 1999). The reasons may be diverse, e.g., reporting of symptoms related to the disease or the treatment might result in a physician's decision to withdraw treatment. However, the patient might be interested to carry on with the treatment, as it is part of his hope for further survival.

Instruments to Assess Patient-Reported Outcomes

Most instruments to measure PROs are developed in the field of health-related quality of life. A newer area within cancer treatment is patient-reported experience of toxicity of treatment, as patient-reported outcome. Health-related quality of life is a broad concept which can be defined as the patient's subjective perception of the impact of his/her disease and its treatment(s) on his/her daily life; physical, psychological, and social functioning; and well-being.

Health-Related Quality of Life Instruments

A broad variety of instruments to assess patient-reported outcomes exists. Some are general instruments, like the EUROQUAL or the SF-36; others are disease-specific, focusing, e.g., on cancer patients. In this chapter, we will focus on the description of disease-specific tools.

Within the disease-specific tools, often a general tool exists, which can be used in combination with tools for specific types of cancer, e.g., breast cancer or pancreatic cancer; specific types of treatment, e.g., high-dose chemotherapy; specific treatment situation, e.g., palliative care; specific symptoms, e.g., cachexia; or specific age groups, e.g., elderly.

In a systematic review, Fitzsimmons points out that within health outcome assessment, there has been less focus on the older person with cancer and provides a theoretical framework for the further focus (Fitzsimmons 2004). Later she together with others provided a systematic review on the use of quality of life instruments in older adults with cancer and concludes that the development, validation, and use of HRQOL instruments often ignore the specific needs of older people. This

review highlights the need for a HRQOL instrument specifically designed to capture the issues and concerns most relevant to older cancer patients (Fitzsimmons et al. 2009).

The European Perspective

In 1993, Aaronson et al. published the quality of life questionnaire (QLQ) of the European Organization for Research and Treatment of Cancer (EORTC) (Aaronson et al. 1993). The questionnaire contains 30 questions, covering 15 different areas, global health status/quality of life; 5 different functional roles, such as physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning; and 9 areas that cover different symptoms, such as fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

Within the European Medicines Agency (EMA), the Committee for Medicinal Products for Human Use (CHMP) and its Oncology Working Party (ONCWP) provide a new guidance with recommendations for the incorporation of PROs and HRQoL in the clinical development of anticancer medicines and advice on appropriate design, conduct, and analysis of PRO studies. The guidance was published in April 2016 and came into effect in November 2016. The guidance has a special focus on elderly patients, mentioning their special needs and on patients I a non-curative (palliative) treatment setting (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205159.pdf).

The paper focuses mainly on the licensing process; however, it provides interesting insides, e.g., the use of time-dependent endpoints of patient-reported outcome measures, such as the time till deterioration of symptoms, e.g., pain (Gravanis et al. 2013). The EMA paper mentions the EORTC-QLQs and the FACT as possible instruments to assess PROs. They consider the PRO-CTCAE (see below) as not yet validated enough to recommend them for use. Regarding elderly patients, they point out: "In elderly patients, concomitant diseases are more frequent, affecting psychological status and general performance. It is important to consider that HRQL is affected by comorbidities, multiple medications (polypharmacy), functional status, ability to carry out activities of daily living, mental status (depression, cognitive functioning) and social support."

Members of a task force of the International Society for Quality of Life Research (ISOQOL) provided comments to the EMA-PRO guidance and point out steps for further development (Kyte et al. 2016).

The North American Perspective

Nearly in parallel in North America, the Functional Assessment of Cancer Therapy-General (FACT-G) was developed (Cella et al. 1993). It covers physical, social/family, emotional, and functional well-being of patients receiving cancer treatment. In addition, 21 cancer-specific measurement tools, 27 cancer-specific symptom indexes, 12 treatment-specific measures, 18 symptom-specific measures, 13 non-cancer measures, and 4 pediatric measures are available (Camuso et al. 2016).

The EORTC QLQ-ELD14

As written above, Fitzsimmons et al. pointed out the need of special quality of life instruments for older adults with cancer (Fitzsimmons et al. 2009). Johnson et al. performed phases 1 to 3 of the development of an elderly cancer patients specific quality of life module, initially called ELD15, after removal of one question, ELD14 (Johnson et al. 2010). This ELD14 module was tested in phase 4, and the results were published by Wheelwright et al. (Wheelwright et al. 2013). The following items are included and add relevant PROs in addition to the global EORTC-QLQ-C30 questionnaire: mobility (three questions), joint stiffness (one question), family support (one question), worries about others (two questions), future worries (three questions), maintaining purpose (two questions), and burden of illness (two questions).

Creation of New Quality of Life Instruments

If one considers the existing quality of life measurements as not suitable to catch the patient's

voice, a structured process exists to how to approach the development of a new quality of life questionnaire.

The stepwise process, as suggested by the EORTC Quality of Life Group, is described in details in a handbook (http://groups.eortc.be/qol/sites/default/files/archives/guidelines_for_developing_questionnaire-_final.pdf). The authors describe four phases/steps: Phase 1, generation of quality of life issues; Phase 2, construction of the item list; Phase 3, pretesting; and Phase 4, field-testing. The process is exemplary described by Johnson et al. in their report on the development of the EORTC QLQ-ELD14 (Johnson et al. 2010). In each step, it is important to involve the patients in the process (Camuso et al. 2016).

Patient-Reported Outcome and Toxicity

Traditionally, the toxicity of cancer treatment is reported within the Common Terminology Criteria for Adverse Events (CTCAE), a part of the Cancer Therapy Evaluation Program (CTEP) which coordinates the clinical therapeutics development program of the Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute (NCI) of the USA.

Traditionally in clinical trials and in clinical practice, data on toxicity are not directly reported by the patient in the database, but it takes a long way from experience of symptoms, being asked for the symptoms with in a visit in clinic, interpretation of symptoms, writing them to the chart, and extracting them from the chart to a database by a data manager. Multiple steps between the patient and the database make it a process contains many possibilities to miss important parts of the symptoms the patients experience (Basch et al. 2014). In addition, Maio et al. analyzed the difference, when toxicity was reported by physicians and by the patients separately (Di Maio et al. 2015).

Therefore, a couple of years ago, an approach was suggested to let patients rate the toxicity they experience from chemotherapy or other cancer treatments they experience themselves, the so-called PRO-CTCAE (Reeve et al. 2014). With a structured process included different approaches of assessment of PROs and a formulized consensus process, they identified that following 12 items as important: fatigue, insomnia, pain, anorexia (appetite loss), dyspnea, cognitive problems, anxiety (includes worry), nausea, depression (includes sadness), sensory neuropathy, constipation, and diarrhea. These symptoms should belong to a core set of symptoms which should be included in all trials in cancer measuring PROs. Important criteria for the selection were:

- Rank ordered within the top 10 symptoms based on prevalence, severity, and/or importance ratings in at least two data sources
- Present across diverse cancer populations
- Attributable to either disease or to anticancer treatment
- Sensitive to change
- Measurable from the patient perspective

Further studies demonstrated that the preferred recall period for the PRO-CTCAE is the past 7 days (Mendoza et al. 2017). A comprehensive educational review is provided by Kluetz (Kluetz et al. 2016). A limitation of this approach is the focus on adverse event based on cancer treatment, which is of great important for drug approval, compared to a broader approach, where the overall situation, the cancer itself, and the treatment are considered all together, which reflects the situation of the patient in clinical practice better.

Patient-Reported Outcome/Health-Related Quality of Life and Geriatric Assessment

The content and meaning of a geriatric assessment within the care for older adults with cancer are reported in details at other chapters within this book (see ► Chap. 25, "Comprehensive Geriatric Assessment (CGA) for Cancer Patients"). Fitzsimmons points out that the focus on HRQoL only does not cover all areas that are important for older adults with cancer

Table 1 Items of geriatric assessment and their association with HRQoL (Wedding et al. 2007a)

Area	GA scale	HRQoL scale	Effect	Author
Functional status	ADL	EORTC-QLQ-C30	Dependence ADL – Reduced global HRQoL	Esbensen et al. 2004
	ADL	EORTC-QLQ-C30	Dependence ADL – Reduced global HRQoL	Thome et al. 2004
	IADL	EORTC-QLQ-C30	Dependence IADL – Reduced global HRQoL	Wedding et al. 2007b
Mobility/falls	6-minute walk test	Sf-36	Impaired mobility – Reduced HRQoL	Saad et al. 2006
Cognition	MMSE	EORTC-QLQ-C30	No association	Iconomou et al. 2004
Depression	BDI	EORTC-QLQ-C30	Depression – Reduced HRQoL	Wedding et al. 2008
Comorbidity	CIRS-G	EORTC-QLQ-C30	Comorbidity – Reduced HRQoL	Wedding et al. 2007c

GA geriatric assessment, *ADL* activities of daily living, *IADL* instrumental activities of daily living, *MMSE* mini-mental status examination, *BDI* beck depression inventory, *CIRS-G* cumulative illness rating scale geriatric version, *HRQoL* health-related quality of life

Table 2 Comparison of assessment: geriatric assessment vs. health-related quality of life assessment

Area	GA	HRQoL
Structured way to collect data in areas often missed by history taking and physical examination	√	√
Limitations in these areas occur more often in elderly patients	√	√
These areas are important for the patients, e.g., regarding their quality of life	√	√
Validated diagnostic tools exist	√	√
Regular follow-up is recommended	√	√
Diagnostic and therapeutic parts are performed by a multi-professional and multidisciplinary team	√	No
Validated therapeutic interventions exist	√	No
Improves quality of life	√	√

GA geriatric assessment, *HRQoL* health-related quality of life

(Fitzsimmons 2004). When asking older adults what is an important aim for them, they mention the maintenance of their ability to care for themselves and to stay independent as very important. Maintenance of independence or ability to care for oneself is not an established endpoint in clinical trials but part of geriatric assessment.

With a review on quality of life in older adults with cancer, Wedding et al. could point out that most items of geriatric assessment were closely associated with health-related quality of life (Wedding et al. 2007a) (see Table 1). In another table, we compared geriatric assessment and quality of life assessment for their use in clinical cancer research and care (see Table 2).

First trials including geriatric assessment and HRQoL come up. They could demonstrate

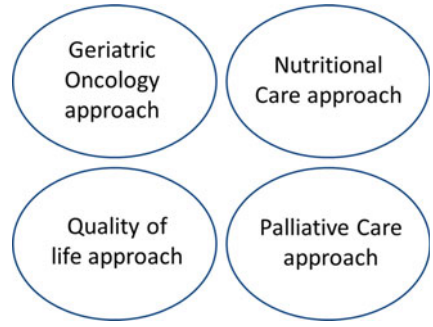

Fig. 2 Overlap between different approaches toward the patient

that limitations in geriatric assessment prior to treatment are associated with poor recovery of HRQoL in the course of treatment, e.g., in patients older than 65 years receiving radiotherapy

Table 3 Pro and contra arguments for the use of QoL measurement in older adults with cancer

Pro	Contra
QoL is one of two major endpoints patients are interested in	Filling in a QoL questionnaire does not contribute to QoL
QoL becomes more important when length of life becomes more limited	In an elderly cancer patient many assessment tools are already used
QoL summarizes a lot of different items	Even in a cognitive fit elderly population, the average time they are able to concentrate is less than 1 hour
Validated instrument exist	QoL measurement is mostly based on cognitive competence and excludes increasing number of elderly patients
QoL measurement improves QoL outcome	Results of geriatric assessment are closely related to QoL
	Interventions to results of geriatric assessment are more or less defined and interventions to poor quality of life not
	Many items of QLQs do not measure QoL but symptoms

for cancer of the lung or head and neck (VanderWalde et al. 2017).

Different approaches to the patient cover identical or similar areas, e.g., quality of life instruments contain a considerable number of symptoms, which are assessed within a palliative care approach as well, and geriatric assessment contains assessment of nutrition, which is covered in nutritional assessment as well. Future activities should address the overlap between the different approaches (Fig. 2). All areas belong to a holistic approach to the patient and cover the non-tumor-directed care/supportive care (Hui et al.). Table 3 provides pro and contra arguments for quality of life assessment compared to geriatric assessment as patient-reported outcome in the care for older adults with cancer.

Improving PRO by Using PROM

Finally, the focus on patient-reported outcome is to improve patient-reported outcomes. Thus the question arises: Does the use of patient-reported outcome measurement improve patient-reported outcome?

Velikova et al. randomized 286 patients treated by 28 different oncologists between three arms, one with no intervention (control group), one with measurement of EORTC-QLQ-C30 and the HADS questionnaire (attention control group), and one with the measurement of the questionnaire and recommendations of interventions regarding the results (intervention group). The effect was measured with the FACT questionnaire. Whereas quality of life deteriorated in 31% and improved in 14% of patients of the control group, the figures were 7% and 32% for the attention control group and 14% and 40% for the intervention group (Velikova et al. 2004). Thus even the reporting of quality of life data improves quality of life outcomes. A study in which cancer patients treated as outpatients self-reported their symptoms electronically and got advise when to contact their clinicians demonstrated improved symptom outcome compared to a control group (Berry et al. 2014a, b). This approach was further developed at the Sloan Memorial Cancer Center, where patients were asked to self-report their symptoms computed based on a weekly base; received a reminder via e-mail, when they missed it; and got a printed version for their routinely visit in the clinic and a contact to a nurse, when severe symptoms occurred. Compared to a control group, quality of life improved (Basch et al. 2016). Strasser et al. could demonstrate that such approaches are applicable on a multicenter setting as well (Strasser et al. 2016).

PRO-cision Medicine

In medicine in general and in oncology especially, the term personalized medicine or precision medicine is used to describe the selection of tumor-specific treatment based on characteristics of the tumor, especially when analyzing molecular targets. Nathan Cherny et al. pointed out that this is a rather small concept of personalized medicine and

further elements should be included, such as the social context, etc. (Cherny et al. 2014). The term PRO-cision Medicine, used by Jensen and Snyder, supports this approach (Jensen and Snyder 2016).

Conclusion

Patients are interested to live longer and better. With decreasing options regarding length of life, quality of life becomes more important. Better life in the context of medicine, oncology, and geriatric oncology should be addressed in an in-depth talk to the patient and his/her relatives. A use of tools can help to focus on topics important for the patients (PROs). Most areas of geriatric assessment are important regarding QoL.

Cross-References

► Comprehensive Geriatric Assessment (CGA) for Cancer Patients

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Research Methods: Outcomes and Survivorship Research in Geriatric Oncology

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Abstract

As the population is aging, and cancer treatment is advancing, the life span of significant proportion of older cancer survivors is increasing. In order to maintain wellbeing and functional independency of older cancer survivors, it is critical to appreciate the intersection of aging, cancer and cancer treatments, and its impact on older cancer patients' functional status. While the main focus of treatment of older cancer patients after the diagnosis is on the cancer, this should be broadened as active cancer treatment subsides and their transition to survivorship starts. While the best models of care for older cancer survivors are emerging, it is essential for the primary care providers and/or oncologists to be aware of unique challenges facing older cancer survivors. In this chapter, we will review challenges that are more common among older cancer survivors. We will assess the existing literature in this regard and explore the opportunities for further research in each section.

Keywords

Cancer survivorship · Functional activity · Cognitive impairment · Emotional wellbeing · Geriatric oncology

Introduction

With the advances in cancer treatment, the USA is facing an increasing number of cancer survivors. The number of cancer survivors in 2014 was estimated to be 14.5 million, and the number is expected to increase to 19 million by 2024. With the population aging, it is highly likely that the significant portion of cancer survivors will be age 65 or older (Desantis et al. 2014). Moreover, given the early diagnosis of cancer and advances in cancer treatment, the likelihood of long-term cancer survivors (those living beyond 5 years after cancer diagnosis) will increase (Siegel et al. 2014). As a result, it is critical to provide better care to older cancer survivors to fully assess the medical and physiological challenges pertinent to them. The models of care for older cancer survivors are still evolving. There is a difference in the attitudes of primary care providers and oncologists in the provision of care for cancer survivors. More than 1/3 of primary care providers prefer to provide care for cancer survivors in collaboration with the oncologists; however, only 1/6 oncologists agreed with this model. More than 50% of primary care providers felt confident in providing such care; however, only 23% of oncologists agreed with such statement (Potosky et al. 2011). As expected, the confident primary care providers had more intensity of care for cancer survivors (Klabunde et al. 2013).

It is critical for primary care providers and oncologists to be aware of the intersection between aging, cancer, cancer treatment, and their impact on cancer survivors' frailty status in order to provide more comprehensive care.

Interaction Between Aging, Cancer, Cancer Treatment, and Their Impact on Frailty

With a broad definition, frailty is "a state of decreased (or total lack of) reserve and resistance to physical and emotional stressors, due to continuous decline in various organ functions" (Rockwood 2005). While the correlation is not 100%, in general, patients tend to become more frail as they age (Schuurmans et al. 2004). Those with cancer tend to be more frail compared to noncancer patients (Mohile et al. 2009; Flood et al. 2006), and cancer treatment itself may lead to frailty.

Measuring Frailty of Older Cancer Survivors

Traditionally, geriatricians perform comprehensive geriatric assessment (CGA) in order to assess aging-related deficits of older cancer patients and survivors (Caplan et al. 2004; Vidán et al. 2005). CGA is a multidimensional assessment. While its specific domains and instruments vary among investigators, most agree that CGA

should include functional domain with assessment of Activities of Daily Living, Instrumental Activities of Daily living, comorbid conditions, cognition, nutritional status, and emotional well-being. Based on CGA, investigators have been able to develop models to predict chemotherapy toxicity (Hurria et al. 2011; Extermann et al. 2012). CGA has also been shown to be correlated with complications and outcome after cancer surgery (Kristjansson et al. 2010a, b) and to influence cancer treatment decision-making (Caillet et al. 2011; Chaïbi et al. 2011).

Older Cancer Survivors' Outcomes and Research

In the following sections, we will review the available literature on outcomes of older cancer survivors and potentials for future research and investigations.

Functional Decline

Disability among cancer survivors appears to be most pronounced in the area of physical functioning, with nearly one in six (16.8%) working-age cancer survivors reporting an inability to work and another 7.4% limited in their ability to work (Hewitt et al. 2003). Nearly one half of cancer survivors are aged 65 and older. They may have preexisting chronic diseases and functional limitations at the time of their cancer diagnosis. Functional dependence is associated with decreased survival (Reuben et al. 1992). In older women who are breast cancer survivors, though the ability to perform normal activities were most affected during the period 2 years after diagnosis, even more than 5 years after cancer diagnosis, survivors had 30–50% increased odds of reporting an inability to do activities requiring mobility and strength (Sweeney et al. 2006).

The assessment of function needs to include Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADLs) in addition to performance status (PS). ADLs and IADLs bear a poor correlation with performance status (Extermann et al. 1998). While about 80% of older adults with cancer have an ECOG performance status of 0 or 1 at the time of diagnosis, more than 50% of these patients require assistance with instrumental activities of daily living such as driving, shopping, and managing finances (Schubert et al. 2008). These assessments are listed in Table 1.

In addition, asking about recent falls is important in the assessment of functional status. Older cancer survivors may be predisposed to falls because of the sequelae associated with cancer and its treatments (Huang et al. 2014). Falls are associated with lower health-related quality of life scores as well as with a significant prospective decline in these scores in older cancer survivors (Pandya et al. 2016).

Cancer-Related Functional Compromise

1. Fatigue is one of the most common symptoms of cancer and it can manifest as weakness and exercise intolerance (Gilliam and St. Clair 2011). Depending on the site, the tumors may

Table 1 Some commonly used functional assessment tools

	Performance status (PS) scales					
	Eastern Cooperative Oncology Group (ECOG)	Karnofsky (KPS) (Schag et al. 1984)	Activities of daily living	Instrumental activities of daily living	Gait speed (Studenski et al. 2011)	Timed get up and go (Shumway-Cook et al. 2000)
Scores	5 to 0	0–100	0–6	0–8	In meters/second	In seconds
Type of tool	Self-report	Self-report	Self-report	Self-report	Performance based	Performance based

directly impact physical functioning capability. Involvement of the spinal cord by cancer is seen in 5–10% of all patients with cancer (Chamberlain 2015). Neoplastic myelopathies are not infrequent. Spinal tumors may cause spinal cord compression and vascular compromise resulting in neurologic compromise. They may also alter the architecture of the spinal column, resulting in spinal instability (Ruppert 2017).

2. Adjuvant chemotherapy for breast cancer has been associated with deterioration of fine motor skill. Compared with a population-based reference group, cyclophosphamide methotrexate 5-fluorouracil chemotherapy-exposed breast cancer survivors demonstrated motor slowing while drawing an Archimedes spiral, on average 20 years after completion of primary treatment (Hoogendam et al. 2015). Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting side effect that can lead to long-term morbidity. Approximately, one third of patients receiving chemotherapy with taxanes, Vinca alkaloids, platinum compounds, or proteasome inhibitors develop this toxic side effect (Podratz et al. 2016). Chemotherapy-induced neuropathies cannot be treated, and protective strategies have not been found to be effective. Neurotoxicity is usually dependent on cumulative dose. Severity of neuropathy increases with duration of treatment and progression stops once drug treatment is completed. The platinum compounds are an exception where sensory loss may progress for several months after cessation of treatment, called "coasting" (Windebank and Grisold 2008). Neurotoxicity from chemotherapy has shown declines as large as 50% in performance-based measures, persisting over 2 years, and with patient reported recurrent falls, cane use, and mobility-related disability (Hile et al. 2010). CIPN, primarily motor, is associated with falls and functional impairments (Gewandter et al. 2013).
3. Surgery is a major stressor to functional status, and functional decline is commonly noted after surgery. Memorial Sloan Kettering Cancer Study has shown that 51% of adults 75 years and older who underwent cancer surgery required skilled care at discharge (Alexander et al. 2016). Studies have shown that postoperative functional setbacks tend to persist in older patients (Lawrence et al. 2004). A significant proportion of older patients undergoing major surgery experienced functional decline at 1 month (45.3%), 3 months (30.1%), and 1 year (28.3%) (Kwon et al. 2012). This same study found that, though a higher preoperative functional status was related to a quicker recovery, no subgroups returned to baseline functional status.
4. Data on long-term functional compromise in older cancer patients treated with hormone therapy (HT) or radiation therapy is scant. There are, however, some studies that show their impact on health-related quality of life. Patients with low-risk prostate cancer who received external beam radiation therapy (EBRT) are significantly more likely to experience a decrease in more than one functional domain (urinary, sexual, bowel, or hormonal) at 1 year when compared with those on active surveillance – 60% versus 28% (Banerji et al. 2017). Bowel function significantly worsened with the addition of HT to EBRT (Brassell et al. 2013).

Oncologic management of spinal tumors varies according to the stability of the spine, neurologic status, and presence of pain. Treatment options include surgical intervention, radiation therapy, chemotherapy, and hormonal manipulation. When combined with this management, rehabilitation can serve to relieve symptoms, improve quality of life, and enhance function (Ruppert 2017). In patients with neuropathy, restorative approaches have not been well established. Symptomatic and other management are necessary to maintain and improve quality of life (Windebank and Grisold 2008). Enhancing fitness and functional capacity prior to surgery can accelerate postsurgery recovery. Presurgical exercise may benefit cancer patients through positive effects on function and physical capacity (Singh et al. 2013). Patient mobilization on postoperative day 0 provides better outcomes than later mobilization

Table 2 Tests to assess cognition

	Mini-Mental status examination (Kang et al. 1997)	Montreal cognitive assessment (Nasreddine et al. 2005)	Mini-Cog (Borson et al. 2000)
Year of creation	1975	1996	2000
Time to administer	7–8 min	10–12 min	3 min
Scoring	Maximum score of 30 Cut-off score of 24	Maximum score of 30 Cut-off score 26	Maximum score of 5 Cut-off score of 3
Domains assessed	Attention, visuospatial, memory, language	Attention, visuospatial, memory, executive, language	Executive, memory
Advantages/ disadvantages	Affected by educational level, language, and cultural barriers	Greater sensitivity to detect mild levels of cognitive impairment	Not influenced by education level or language abilities Fast and simple

with lower length of stay, need for opioids, and enhanced recovery (Ibrahim et al. 2013). In reducing fatigue among older cancer survivors, various interventions have been tested. A secondary analysis on patients age 60 or older, who completed cancer treatment between 2 and 24 months prior to enrollment into the study, showed that yoga might be helpful in reducing fatigue (Sprod et al. 2015). Another study on older prostate cancer survivors showed that Qigong intervention (meditative focus on breath, sitting exercises, and standing movements) experienced an improvement in their fatigue level (Campo et al. 2014). The majority of studies on cancer survivors have been focused on breast and prostate cancer survivors. As a result, American College of Sports Medicine encourages investigators to explore the impact of physical exercises in other cancer survivors and to assess the dose-response effect of the interventions (Panel 2010).

Cognitive Decline

Both cancer and cancer therapies can negatively affect cognition, and older adults with preexisting cognitive impairment may be more susceptible to cognitive decline with therapy than younger patients (Magnuson et al. 2016). A recent study in lymphoma patients showed that cognitive disturbance may be a significant survivorship issue. These patients had a higher frequency of impairment on both objective and subjective cognitive measures and these were in turn associated with other psychosocial factors such as fatigue, anxiety, and pain (Krolak et al. 2016). The common tests to assess cognition are listed in Table 2.

Cognitive screening tests commonly used in Oncogeriatrics are often not sensitive enough to detect subtle disorders. Hence, more detailed cognitive assessment batteries of neuropsychological tests may be necessary. Trained neuropsychologists are needed for formal neuropsychological testing. The data obtained are compared to normal population valuesand can be adjusted for the patient's baseline intelligence and previous educational level. It is composed of different tests, the exact constituents of which tend to vary between individual neuropsychologists and depending on the specific population or clinical question to be addressed. Typically, it will take 1–3 h to perform (Woodford and George 2007).

Cancer-Related Cognitive Deficits

1. The impact of cancer itself on cognitive functions, known as the "*cancer brain"* concept, could also play a role through increased inflammation, dysregulation of cytokines, or oxidative stresses (Lange et al. 2014). About 60–90% patients with intracranial tumors face cognitive impairments along with some emotional and behavioral changes (Dhandapani et al. 2016). In the intracranial tumors, the duration and location of the mass, brain edema, and associated neuroinflammation contribute to cognitive dysfunction.

2. Chemotherapy-related cognitive impairment (CRCI), or the "*chemobrain*" phenomenon, refers to the chemotherapy-induced impairment of memory, executive function, or information processing speed (Lange et al. 2014). CRCI has been reported in up to 12–75% of patients with cancer and is associated with cancer type, treatment, duration of follow-up, type of study design, and definition of cognitive impairment (Loh et al. 2016). It has been extensively described in breast cancer patients. Survivors of breast cancer treated with adjuvant CMF chemotherapy more than 20 years ago perform worse, on average, than random population controls on neuropsychological tests (Koppelmans et al. 2012). The epsilon 4 allele of APOE may be a potential genetic marker for increased vulnerability to chemotherapy-induced cognitive decline (Ahles et al. 2003).
3. Hormonal therapy could be associated with increased risk of cognitive changes as well. Different studies have shown possible immediate to longer term cognitive sequelae with the use of selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). Thousands of breast cancer patients have been enrolled on trials evaluating the efficacy of endocrine therapy, but there is a relative paucity of data addressing cognitive changes with these agents (Agrawal et al. 2010). There is a strong argument that androgen-ablation therapy is linked to subtle but significant cognitive declines in men with prostate cancer. Androgen deprivation therapy (ADT) patients are more vulnerable to experiencing specific cognitive and neurobehavioral symptoms than non-ADT patients, but these cognitive symptoms may not easily be detected using neuropsychological tests (Wu et al. 2016). Between 47% and 69% of men on ADT declined in at least one cognitive area, most commonly in visuospatial abilities and executive functioning (Nelson et al. 2008). Prostate cancer patients who received ADT performed significantly worse on visuomotor tasks compared to non-cancer control groups (Mcginty et al. 2014).
4. There are two main entities of postoperative cognitive decline: delirium and postoperative cognitive dysfunction (POCD). Both have multifactorial pathogenesis but differ in numerous other ways, with delirium being well defined and acute in onset and postoperative cognitive dysfunction being subtler and with longer duration (Krenk and Rasmussen 2011). POCD has been documented after cardiac and noncardiac surgery (Evered et al. 2011). Apart from the nature of the surgical procedure, advanced age is the most important risk factor for POCD. In patients older than 60 years, a POCD rate of 10% is detected 3 months after surgery (Coburn et al. 2010). The anesthetic technique is not a determinant of POCD, the risk appears to be similar after both general and regional anesthesia (Sauer et al. 2009). On the other hand, patients with intracranial tumors have substantial cognitive dysfunction with deficits in different domains based on tumor size and location, and this tends to show significant improvement beyond 6 months following surgery, especially among tumors which are extra-axial, benign, and non-irradiated (Dhandapani et al. 2016; Hendrix et al. 2016).
5. Cognitive deficits are common in people who have received cranial irradiation and have a serious impact on daily functioning and quality of life. Standard treatment of primary and metastatic brain tumors includes high-dose megavoltage-range radiation to the cranial vault. About half of patients survive >6 months. However, 50–90% of survivors exhibit disabling cognitive dysfunction (Makale et al. 2016). Low-grade glioma patients who received radiotherapy, followed long term (6–28 years), showed a progressive decline in attentional functioning, even those who received fraction doses that are regarded as safe (</=2 Gy) (Douw et al. 2009). Prophylactic cranial irradiation (PCI) in locally advanced NSCLC patients was associated with decline in tested and self-reported cognitive functioning both at 6 and 12 months post radiation (Gondi et al. 2013).

There is supportive evidence that memantine may help prevent cognitive deficits for adults with brain metastases receiving cranial irradiation and that donepezil may have a role in treating cognitive deficits in adults with primary or metastatic brain tumors who have been treated with cranial irradiation (Day et al. 2014). Sparing "radiosensitive" areas such as hippocampi could have a modest but measurable impact with regard to cognitive preservation, an effect that can possibly be enhanced when used in conjunction with memantine and/or donepezil (Dhermain and Barani 2016). There is no strong evidence to support any nonpharmacological interventions (medical or cognitive/behavioral) in the prevention or amelioration of cognitive deficits (Treanor et al. 2016.)

Older Cancer Survivors and Endocrine Abnormalities

Cancer is a major risk factor for both generalized and local bone loss. Bone loss assessed by bone mineral density (BMD) testing is substantially higher in cancer patients than in the general population, independent of cancer type (Drake 2013). Aging in both men and women is associated with increased rates of osteoporosis and fractures due to decline in sex steroids, primarily estrogen, and testosterone that occur in both sexes with aging; however, cancer survivors are at higher risk for osteoporosis and subsequent fractures compared with the general population. Breast cancer therapies can lead to bone loss and increased fracture risk. Although tamoxifen is associated with a decreased risk of osteoporosis if used in postmenopausal women, it may lead to an increase in the incidence of osteoporosis in premenopausal women (Shahrokni et al. 2016). Men who undergo long-term androgen deprivation for prostate cancer are at increased fracture risk due to severe suppression of testosterone levels. Men with prostate cancer were found to have a 1.9-fold relative risk of fracture with this risk being higher for those on androgen deprivation therapy (Tuck 2017). Bone health is a particular concern because androgen deprivation therapy causes a high annual rate of bone loss and this, combined with the preexisting high prevalence of osteoporosis in men with prostate cancer, results in a dramatic increase in fracture rates (Tuck 2017). Early bone loss can be seen in patients who have undergone bone marrow transplantation, and patients with multiple myeloma develop characteristic focal osteolytic lesions, generalized bone loss, and a fracture rate as high as 16-fold when compared to the general population (Drake 2013). Additionally, patients with gastric cancer who have had a gastrectomy are at an increased risk of developing osteoporosis thought to be secondary to the loss of gastric acidification necessary for optimal intestinal calcium absorption (Virik and Wilson 2016).

Epidemiologic studies have shown an increased risk of cancer as well as a higher mortality rate in patients with type 2 diabetes. Type 2 diabetes, obesity, and the metabolic syndrome are associated with an increased risk of cancer development. Although this correlation is not fully understood, proposed mechanisms include insulin resistance, hyperinsulinemia, and inflammatory cytokines. A meta-analysis of 221 datasets found that a 5 kg/m^2 increase in BMI was associated with an increased risk of developing esophageal, thyroid, colon, and renal carcinoma and multiple myeloma in men and women, in addition to hepatocellular and rectal cancer, and malignant melanoma in men, and endometrial, gallbladder, postmenopausal breast, and pancreatic cancer and leukemia in women (Zelenko and Gallagher 2014). Two known causes of the metabolic syndrome are testosterone deficiency and estrogen deficiency (Shahrokni et al. 2016). Patients with testicular cancer and hematological malignancies are considered to be at increased risk for the metabolic syndrome (de Haas 2010). Patients with prostate cancer receiving androgen-deprivation therapy had a higher prevalence of metabolic syndrome (55%) than patients treated with prostatectomy, radiotherapy, or both (22%) and healthy controls (20%) (Micucci et al. 2016). Metabolic syndrome can also represent a long-term complication after cancer treatment that

affects life expectancy and quality of life (Micucci et al. 2016). The presence of metabolic syndrome in cancer survivors is associated with signs of early atherosclerosis and may represent the connection between cancer treatment and its severe late effects like cardiovascular disease (Micucci et al. 2016).

Physical activity helps patients maintain a healthy weight and is beneficial for bone health. Physical activity has been shown to improve muscular strength and endurance, and improve fatigue (Campo et al. 2014). According to consensus, physical activity is safe during and after cancer treatment but "relationships related to specific cancer diagnoses, treatments, and underlying cardiometabolic mechanisms associated with survival has not been thoroughly examined in randomized controlled trials" (Tuck 2017). Clinicians should consider individual differences among cancer survivors and tailor physical activity programs to meet the individual needs of the patient.

The Psychosocial Aspects of Cancer Survivorship

Surviving cancer can be as much of a psychological battle as it is a physical one. Thirty-five to 38% of patients have significant emotional distress related to their cancer diagnosis (Faller et al. 2013), and at least 11.6% and 17.9% of long-term cancer survivors have depression and significant levels of anxiety, respectively (Shahrokni et al. 2016). Even years after a cancer is diagnosed and treated, a variety of practical, spiritual, and emotional challenges can be present. Cancer-related distress can include a wide continuum of emotions related to, among others, symptoms of depression, anxiety, and adjustment disorder. In the cancer population, distress is often reported to be above 30% (Jacobsen et al. 2005). Symptoms of anxiety and depression may also occur independently and progress quite differently after a cancer diagnosis (Paice et al. 2016). A meta-analysis showed that exercise training can reduce depressive symptoms of cancer survivors; however, the most showed benefit was for patients aging 47–62 (Brown et al. 2010). The studies on other types of interventions on reducing anxiety, depression, and adjustment disorder among older cancer survivors are very limited.

Post-cancer pain syndromes can be viewed as part of a cluster of symptoms, including fatigue, anxiety, depression, and sleep disturbance (Aaronson et al. 2014). Patients with neurologic cancers often report high levels of depression, fatigue, distress, and existential concerns, often exacerbated by aggressive treatment regimens and poor prognosis. These patients typically report lower quality of life, irrespective of the time since diagnosis or treatment (Bultz et al. 2013).

Estimates of the prevalence of pain in cancer survivors vary widely and have been reported to be as high as 40% (Paice et al. 2016). Risk factors for chronic pain in survivors include the type and invasiveness of the tumor, the treatment regimen used, the time since cancer treatment, and the efficacy of initial pain therapy. Management may include nonopioid medication options such as antidepressants, antiepileptic drugs, and topical agents. Interventional modalities may be considered, including nerve blocks, trigger point injections, spinal cord stimulators, or implanted intrathecal pumps.

Cardiotoxicity

In general, older cancer patients with preexisting cardiac conditions are more likely to develop cancer-treatment-related cardiotoxicity in the short term and long term (Schmitz et al. 2012). For example, the incidence of cardiotoxicity among breast cancer patients is 3–35% (Yeh and Bickford 2009), and the mortality risk due to cardiotoxicity may at times surpass the risk of mortality due to breast cancer (Patnaik et al. 2011). The cardiotoxicity of chemotherapy agents differs. For example, even low doses of anthracyclines, drugs commonly used in breast cancer patients, can cause cardiotoxicity in patients with preexisting cardiac disease (Ryberg et al. 2008). A systematic review showed that incidence of clinical and subclinical cardiotoxicity in patients who received anthracyclines

was 5.4 and 6.25 higher compared to those who did not receive anthracycline (Smith et al. 2010). These patients were also five times more likely to die because of cardiac disease than those who did not receive anthracycline. One study showed that for every 10 year increase in age, the risk of developing congestive heart failure in these patients is doubled (Pinder et al. 2007).

Among prostate cancer patients on ADT, the risk of cardiotoxicity is higher than those who are not on ADT (O'Farrell et al. 2015; Taylor et al. 2009). Once again, increasing age is associated with increasing likelihood of toxicity as each year increase in age, increased the risk of toxicity by 3% (Saigal et al. 2007). It is expected that 5.5% of patients on ADT following prostatectomy die within 5 years due cardiac causes, compared to 2% of patients who only underwent prostatectomy (Tsai et al. 2007).

Among other agents causing cardiac toxicity, 5-fluouracil (5-FU), a commonly used agent for a variety of cancers, should also be noted. Patients receiving 5-FU may experience cardiotoxicity with the incidence rate ranging from 1.2% to 18%. The toxicity usually occurs while the patient is receiving the treatment (Saif et al. 2009). Capecitabine, an oral derivative of 5-FU, is also responsible for causing ischemia in as high as 9% of patients (Curigliano et al. 2010). Similar to 5-FU, the cardiotoxicity from capecitabine is also short term.

The Future of Cancer Survivorship Research for Older Patients

Despite advances in exploring and improving physical and psychosocial problems of older cancer survivors, many questions have remained unanswered. These questions are in four broad levels of the patient, the healthcare provider, the caregiver, and the society. In the patient level, models based on geriatric assessment have been developed that can predict chemotherapy toxicity (Hurria et al. 2011; Extermann et al. 2012). There has been effort to utilize geriatric assessment in predicting surgical outcomes of older cancer patients (Kristjansson et al., 2010a). Moreover, efforts have been made to predict short- and long-term mortality of older cancer patients (Freyer et al. 2005). However, there is a significant gap between short-term outcomes (e.g., chemotherapy toxicity) and long-term outcomes (e.g., mortality). Are patients who are predicted to die after a certain amount of time, die suddenly? Or do they experience a gradual functional decline and then die? What role can the healthcare system and the society play to avoid gradual decline? Studies have shown that patients with more comorbid conditions are at higher risk for adverse short- and long-term outcomes (Patnaik et al. 2011). What is the interaction between comorbid conditions, cancer, and outcomes? Do more intensive follow-up and management of older cancer survivors and their comorbid conditions improve outcomes of these patients? While the survivorship guidelines have been developed for cancer survivors regardless of their age, there is a need for specific recommendations regarding the issues pertinent to older cancer survivors (e.g., bone health). As mentioned in the introduction, with the aging population and advances in cancer treatment, it is expected that more older cancer patients be diagnosed and treated properly and transition to the survivorship and many younger patients experience years of cancer free period and transition to become older cancer survivors. In order to provide more intense care and monitoring for these patients, the traditional healthcare system may reach its capacity soon. Can advances in the information technology in other fields be used in caring for older cancer survivors? Are older cancer survivors receptive to such interventions and assessments? Does it improve outcomes such as maintaining functional activity of older cancer survivors? Does it shift the care from more expensive emergency room visits and hospital admissions to more proactive outpatient clinics? Regardless of method of assessment (in person, over the phone, or using wireless technology) which healthcare provider should be responsible for responding to the findings? Outpatient primary care provider, oncologist, or a special older cancer survivorship clinic? What is the role of the caregiver and how we can empower the caregiver? Majority of older patients are receiving informal

care either through their spouses and/or their children. In the era with emphasis on caregiver empowerment, how could the caregivers, who might be old themselves, be educated, trained, and empowered to care for the older cancer survivor? How can supportive services be directed to those in need?

Methodological Challenges

Studies on older cancer patients' survivorship may pose methodological challenges unique to this population. It has been proposed that there could be an interaction between age, cancer, and cancer treatment on frailty (Shahrokni et al. 2016). As a result, in order to assess the impact of any of these three factors (age, cancer, cancer treatment), a control group with similar characteristics in the other two factors is needed. For example, if the question is to assess the impact of 5-year hormonal treatment on frailty of breast cancer survivors older than age 75 who have undergone lumpectomy and radiation, the optimal control group would be breast cancer survivors older than age 75 who have undergone lumpectomy and radiation but did not receive hormonal treatment. In addition, it is also important to assess, address, and control for timing of cancer diagnosis and treatment in relationship. In the example above, there might be differences between frailty levels of patients in the control group who had surgery a year ago compared to 6 years ago. As wellbeing and fitness of older cancer survivors may have direct correlation with their socioeconomic status, studies of older cancer survivors need to consider assessing factors such as socioeconomic status (e.g., income, insurance status, primary language, living condition, social support). Healthy selection bias is always a major challenge in any observational or interventional study (Hernán et al. 2004). One way of solving such problems is to use datasets that are collected as routine care via electronic medical records. This will significantly decrease the possibility of healthy selection bias. This also may solve a problem of accruing patients into clinical trials. Recruitment to clinical trials can be challenging, leading to 1 in 10 cancer trials registered on ClinicalTrials.gov between 2005 and 2011 being closed prematurely due to poor accrual and other trials taking longer than anticipated to complete recruitment. This is a major problem for oncologists, not only from a scientific perspective but also due to the implications of failing to meet recruitment targets (Moorcraft et al. 2016). Few adult cancer patients are treated on clinical trials; however, patients previously enrolled in these trials are an important source of information about treatment-related late effects. Retrospective recruitment has substantial limitations. In the future, mechanisms should be established for prospective long-term follow-up to identify and understand the frequency and type of late effects associated with cancer treatments (Ganz et al. 2009).

Conclusion

The advances in cancer treatment will lead to substantial increase in the number of older cancer survivors in the next decade. Collaborative clinical, research, and policy efforts need be made in order to preserve functional independency and maintain wellbeing of older cancer survivors.

Cross-References

- ▶ Comprehensive Geriatric Assessment (CGA) for Cancer Patients
- ▶ Exercise and the Older Cancer Survivor
- ▶ Frailty in Cancer Patients
- ▶ Geriatric Interventions in Oncology
- ▶ Geriatric Screening in Cancer Patients
- ▶ Healthcare Informatics and Technology in Managing the Older Cancer Patient
- ▶ Integrating Geriatric Oncology in Public Health Planning
- ▶ Organizing the Clinical Integration of Geriatrics and Oncology
- ▶ Pain Management in Older Cancer Patients
- ▶ Population Trends in Aging and Cancer
- ▶ Predictive Tools for Older Cancer Patient Management

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