Chapter 3
Cancer, Carcinogenesis, and Aging

Lodovico Balducci

Cancer is mainly a disease of aging. At present 50% of all cancers occur in the 12% of the population aged 65 and older [1]. By the year 2030, individuals over 65 years will represent 20% of the population of the United States and account for 70% of all cancers [1, 2]. The management of cancer in the older age group is going to become the most common practice of oncology.

The interactions of cancer and age are multiple and complex. They include carcinogenesis, tumor biology, as well as cancer prevention and treatment. We will explore these interactions after reviewing the extent of the problem.

Epidemiology of Cancer in the Aged

The incidence and prevalence of most cancers increase with age (Fig. 3.1). The association of cancer and age elicits a number of important questions: Is there a linear association between age and the incidence of cancer? Is the patient going to die or suffer from cancer? Does the presentation of cancer differ in older and in younger individuals? What are the consequences of cancer and its treatment for the older person? Epidemiology may provide important insights into these questions.

The Age Window

The incidence of most cancers increases steeply between ages 55 and 80, plateaus between 80 and 85, and declines thereafter. The prevalence of cancer, even occult cancer discovered only at autopsy, is negligible after age 95 [3]. This observation suggests a number of explanations including the possibility that the so-called longevity genes confer a protection against cancer or alternatively that an increasingly catabolic status prevents cancer growth after age 95.

L. Balducci (✉)
Senior Adult Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
e-mail: Lodovico.balducci@moffitt.org

Variations in the Incidence of Different Cancers in Older Individuals

Whereas the incidence of most cancers increases with age, the pattern of increase varies from one neoplasm to another. For example, the incidence of melanoma peaks at the age of 55 in men and plateaus thereafter; the incidence of breast cancer plateaus around the age of 80, whereas the incidences of cancer of the prostate and of the large bowel seem to increase without plateau even beyond the age of 80 [2]. These different incidence patterns suggest that a lesser number of carcinogenic stages are involved in the cancers whose incidence peaks earlier and also that some tissues, including the prostate and the colonic mucosa, become more susceptible to environmental carcinogens as the patient ages.

The case of lung cancer is of particular interest. In the last 20 years, the median age of lung cancer has changed from age 55 to age 71 [4]; the incidence of the disease has decreased for those younger than 50 years but has increased for individuals aged 65 and older, and the incidence of lung cancer in ex-smokers or non-smokers has increased. The likely explanation involves a decreased rate of cardiovascular deaths after smoking cessations, the development of a less aggressive type of lung cancer in ex-smokers, and a persistent susceptibility of the bronchial mucosa to environmental carcinogens in ex-smokers or non-smokers exposed to passive smoke. This hypothesis is supported in part by the change in lung cancer histology that includes higher incidence of adenocarcinoma and lower incidence of the most aggressive histologies, such as small cell and squamous cell.

Cancer Epidemics

Between 1950 and 1970, the incidence of non-Hodgkin lymphoma has increased by 80% among individuals aged 60 and over, and the incidence of malignant brain tumors (anaplastic carcinoma and glioblastoma multiforme) has increased sevenfold in those aged 70 and over [4]. These findings

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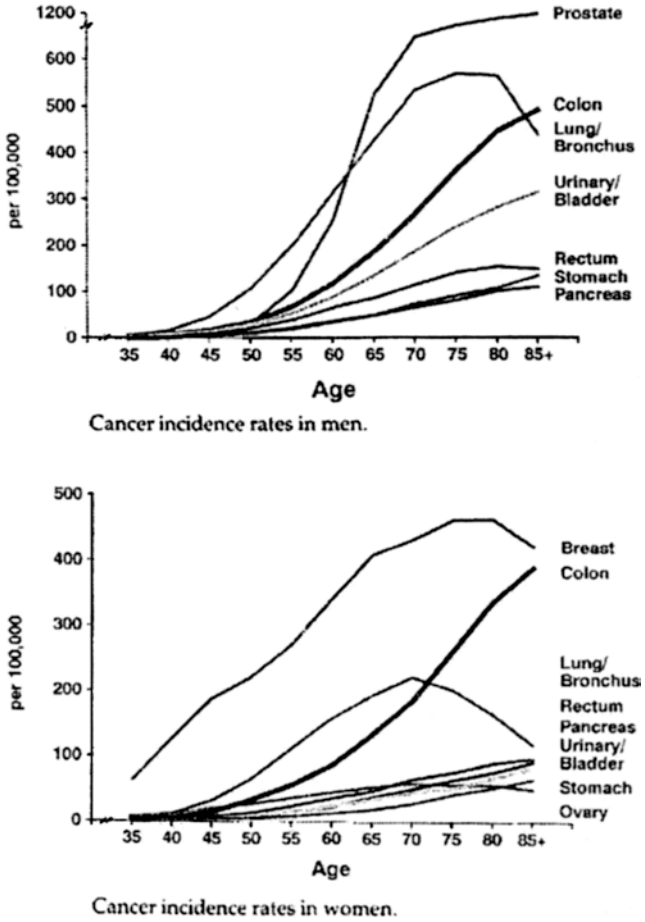

Figure 3.1 The incidence of cancer increases with age (from Yancik [2]. Reprinted with permission of John Wiley & Sons, Inc.).

suggest one of two possibilities. The first is that the improved life expectancy of the population has allowed the survival of individuals predisposed to develop these neoplasias. The second is that older individuals are natural monitoring systems for new environmental carcinogens. In other words, when exposed to new environmental carcinogens, older people are likely to develop cancer earlier than younger people. An epidemic of cancer in older individuals may herald an epidemic of cancer in the general population at a later time.

Who Are the Elderly with Cancer?

In studying the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data, Diab et al. determined that breast cancer did not shorten the survival of women aged 75–80 and was associated with an increased survival when it was diagnosed at the age of 80 and over [5]. These findings suggest that cancer is a prevalent disease among healthy elderly people. This suggestion is supported by the findings of Repetto et al. [6], indicating that older individuals with cancer were more likely than individuals of similar age without cancer to be independent and to have fewer comorbid conditions. The low prevalence of cancer among long term nursing home residents also supports this suggestion [7]. Obviously, cancer is a cause of mortality for older individuals and the prevention and treatment of cancer in the elderly can prolong life and preserve function.

Presentation of Cancer in the Older Person

A number of studies in the 1980s, on the basis of statewide tumor registries, indicated that some cancers present at a more advanced stage in older individuals [8]. These included cancer of the breast, of the colon, and of the bladder, whereas lung cancer was diagnosed at an early stage in older individuals. More recent studies of the issue are wanted. The increased use of early detection might have increased the diagnosis of breast and colon cancer. At least three explanations may account for the presentation of some cancer at a more advanced stage: increased aggressiveness of cancer with age (unlikely), lesser use of cancer screening and early detection by older individuals, and delayed recognition of cancer symptoms. It is well known that older individuals may harbor many comorbid conditions at the same time. Comorbidity may delay the diagnosis of cancer because early cancer symptoms may be mistakenly ascribed to preexisting conditions.

Multiple Malignancies

Approximately 20% of individuals aged 70 and over with cancer may carry a diagnosis of two or more malignancies [9]. It is not clear whether multiple malignancies may be attributed to increased susceptibility to cancer. In some cases, the use of diagnostic tests for monitoring the first malignancies may precipitate the diagnosis of a second one. For example, the association of non-Hodgkin's lymphoma and renal cell carcinoma may be explained through this mechanism. The frequent scanning of the abdomen to monitor the lymphoma may lead to early diagnosis of kidney cancer. In other cases, the treatment of a previous cancer may be responsible for the second one: for example adjuvant chemotherapy of breast cancer may increase the incidence of myelodysplasia and acute myelogenous leukemia in women aged 65 and older [10–13]. In the majority of cases, the association appears simply casual and because of the fact that age is a risk factor for multiple cancers.

Cancer Behavior and Age

Some cancers become more aggressive and others more indolent with age. For example, breast cancer in older women is

more likely to metastasize to bone and skin rather than to the viscera and the brain [14]. Likewise, older studies showed that the metastases from non-small cell lung cancer had a longer doubling time in older individuals [14]. Conversely, age is a poor prognostic factor for acute leukemia, lymphomas, and ovarian cancer. The potential mechanisms of these differences will be discussed in the biology of aging and cancer.

Consequences of Cancer and Its Treatment in the Older Person

Cancer has become the most common cause of death up to age 85 since 2000 [15]. Surprisingly, in the same period of time, the overall cancer-related mortality has decreased, but not as rapidly as mortality from cardiovascular disease.

A number of recent studies have also shown that age is a risk factor for the development of acute myelogenous leukemia [10–13] and of late congestive heart failure after chemotherapy [16–18]. A recent study based on the SEER data also suggested an association between chemotherapy and dementia [19]. Prolonged castration with LH-RH analogs for prostate cancer has been associated with increased incidence of osteoporosis and bone fractures and possibly also with increased incidence of diabetes and coronary artery disease [20, 21].

Are cancer and its treatment causes of disability? The answer to this important question is still wanted. Older studies suggested an inverse relationship between incidence and prevalence of disability and cancer, probably related to the fact that cancer was associated with an early death which prevented the emergence of chronic disabling conditions [22]. This situation might have changed, however, with the emergence of more effective cancer treatment that results in prolonged survival from many malignancies.

In conclusion, the epidemiology of cancer and age provides important information that allows the formulation of appropriate clinical and research questions (Table 3.1).

Table 3.1 The lessons from epidemiology

1. Cancer has become the main cause of mortality in the older aged person: it is likely, but yet unproven that cancer is a major cause of disability
2. Cancer affects predominantly older individuals in good health, for whom cancer is a cause of morbidity and mortality. Effective prevention and treatment of cancer may prolong the life and preserve the function of older individuals
3. Cancer may be diagnosed at a later time in older than in younger individuals, as a result of decreased use of cancer screening and neglect of the initial symptoms of cancer
4. Multiple malignancies are found in as many as 20% of cancer patients aged 70 and older. In the majority of cases, the association appears casual; in some cases it may be related to treatment of a previous cancer
5. The prognoses of some cancers change with age. The underlying biology of these changes is described in the section of cancer biology and aging

Biologic Interactions of Cancer and Age

Aging and Carcinogenesis

The association of cancer and age may be explained by three non-mutually exclusive mechanisms: duration of carcinogenesis, increased susceptibility of aging tissues to environmental carcinogens, and environmental changes that favor the development of cancer.

As carcinogenesis is a time-taking process, it is reasonable to expect that cancer will become more common with advanced age. Again, the example of lung cancer is compelling. Smoking cessation has been associated with a spate of lung cancer in older ex-smokers [4]. Apparently, smoking cessation resulted in reduced mortality from cardiovascular complications of smoking, and this allowed ex-smokers to live long enough to develop cancer.

The application of the same dose of a carcinogen to the skin of younger and older mice causes more cancers in the older than in the younger animal, suggesting that the older skin is in a condition of advanced carcinogenesis and consequently more susceptible to "late stage carcinogens." The lymphatic system, the liver, and the central nervous system of older animals also display increased susceptibility to environmental carcinogens [23].

For obvious reasons, these experiments cannot be performed in humans. Epidemiological observations suggest however that this may be the case in older humans as well. As already discussed in the epidemiology section, the incidence of prostate cancer, colonic cancer, and non-melanomatous skin cancer increases geometrically with age, and this finding suggests accelerated carcinogenesis. Likewise, one possible mechanism for the increased incidence of lymphoma and malignant brain tumors in older individuals includes enhanced susceptibility of the aged to environmental carcinogens [4]. In addition, age is a risk factor for acute myelogenous leukemia and myelodysplasia following adjuvant chemotherapy of breast cancer [11–13].

The contribution of the body environment to carcinogenesis is less clear. Chronic inflammation may cause the formation of carcinogens from the adipose tissue [24–26]. Adiponectin, a hormone produced by the adipose tissues, appears to stimulate the growth of colonic cancer in predisposed individuals [27]. Proliferative senescence of the stromal cells may facilitate tumor growth and metastases and possibly may influence carcinogenesis [28, 29]. Of special interest is the fact that the small molecules thalidomide and lenalidomide are able to reconstitute a normal hemopoiesis in some patients with myelodysplasia and to abrogate, for some time at least, the neoplastic clone involving the 5q-mutations [30]. As these agents act mainly at the level of the marrow microenvironment, their effectiveness suggests that the stroma has a role in carcinogenesis.

Aging and Tumor Growth

If one thinks of cancer as a plant, the growth of the plant depends on the seed (the tumor cell) and the soil (the tumor host). The importance of the tumor host was illustrated by a now classical experiment by Ershler et al. [31] These investigators injected the same doses of Lewis Lung Carcinoma and B16 melanoma into both older and younger mice [31]. The younger animals died earlier and with many more lung metastases than the older ones. As the seed in this case was exactly the same, only the diversity of the tumor bearers could explain the different outcome.

Age related differences in the neoplastic cells are well known. In older individuals, acute myelogenous leukemia (AML) presents a number of negative prognostic and predictive factors, including mutations in flt-3, wild type nucleophosmin, and multidrug-resistant 1 (MDR-1) [32]. In addition, AML in older individuals appears to be a disease of the pluripotent stem cells, which renders its eradication all but impossible. Breast cancer presents a more favorable proteomic and genomic profile in older than in younger patients. It has been known for a long time that the prevalence of hormone receptor positive breast cancer was higher among older women, whereas the prevalence of HER-2 positive or triple negative breast cancers was more common among the younger ones. More recently, a study from Duke University showed that a cluster of 24 genes purporting a particularly bad prognosis was more common in breast cancers occurring in women aged 35 and younger [33]. In breast cancer, the characteristics of the tumor bearer may also lead to a more indolent disease in older women. These include endocrine senescence and possibly immune senescence. Through mechanisms that have not been completely clarified, immune senescence may also be a favorable prognostic factor in the case of breast cancer [34].

Age is a poor prognostic factor in both follicular and large cell lymphoma. In the case of large-cell lymphoma, the prevalence of unfavorable genomic abnormalities does not seem to change with age, so that the seed does not seem different with age [35]. Increased concentration of IL6 in the circulation may explain in part the poorer prognosis in older individuals, because IL-6 is a lymphocytic growth factor. A recent study showed that the stromal pattern (stromal II), rich in new vessels, heralds a poor prognosis [36]. It is not clear whether this pattern becomes more common with age.

In conclusion, aging is associated with a different behavior and prognosis in a number of common neoplasms. These changes may be explained by fairly well defined genomic and proteomic changes in the tumor cell (seed effect) and less well defined but equally well established changes in the tumor host (soil effect). The exploration of soil effects in tumor growth appears as a promising research area in geriatric oncology.

Aging and Cancer Prevention

Aging has contrasting effects on cancer prevention [22]. On one side, the increasing prevalence of cancer in the older person makes the aged an ideal target of cancer prevention; on the other side, reduced life-expectancy, increased risk of treatment complications, and the less aggressive course of some tumors, such as breast cancer, may lessen the benefits of prevention in older individuals. We'll briefly describe two common forms of cancer prevention: chemoprevention and early detection.

Chemoprevention

Chemoprevention involves offsetting carcinogenesis with chemical substances. Older individuals appear as ideal targets for chemoprevention because of their condition of advanced tissue carcinogenesis and increased susceptibility to late stage carcinogens. A number of chemopreventative agents are available (Table 3.2), but none of them has widespread clinical use. The selective estrogen receptor modulators (SERM) tamoxifen and raloxifen prevent the occurrence of hormone-receptor positive breast cancer, but neither has been associated with a decreased risk of breast cancer mortality [37]. Both may exacerbate menopausal symptoms such as hot flashes and vaginal dryness and may cause deep vein thrombosis (more common in women 70 years and older who are overweight). Unlike tamoxifen, raloxifen does not cause endometrial cancer. Both substances prevent osteoporosis. Given the lack of demonstrable survival advantage and the substantial compromise of quality of life, the majority of practitioners do not recommend this form of cancer prevention.

Finasteride reduces the incidence of prostate cancer but it may increase the risk of aggressive prostate cancer [38]. Until this issue is properly addressed, the value of finasteride as a chemopreventative agent remains dubious. Furthermore, the treatment may cause gynecomastia and decreased libido. An ongoing trial explores the chemoprevention of prostate cancer with a dual 5alpha reductase inhibitor, dutasteride [39].

Retinoids may reduce the risk of smoking-related cancer of the upper digestive tract and airways, but the high incidence of serious complications prevents the general use of these agents [40].

Table 3.2 Chemopreventative substances

Selective estrogen receptors modulators (SERMs)	Breast cancer
Retinoids	Upper airways
Finasteride	Prostate
Non-steroidals (NAS)	Large bowel
Statins	Multiple cancers

A number of retrospective studies support a reduction in the incidence of colorectal cancer with aspirin and other nonsteroidal agents [41]. A small prospective study showed that Vioxx, no longer clinically available, reduced the number and the size of colonic polyps in patients with familial colonic polyposis. The clinical applications of these findings are problematic; in the absence of prospective studies, the dose and the treatment duration are unknown. The cancer-preventing ability of statins is controversial [42].

In conclusion, some human cancers may be prevented with chemoprevention, but the benefits of this cancer-preventing strategy are marginal at best.

Screening and Early Detection of Cancer

Early detection of cancer by screening asymptomatic individuals at risk has reduced cancer-related mortality from breast cancer among women aged 50–65, the mortality from cervical cancer for sexually active women, and the colon cancer-related mortality for people aged 50–80 [22]. The benefits of early detection may decline with age, given the patient's limited life expectancy and increased susceptibility to treatment complications. Is screening beneficial in older individuals? Data from randomized controlled studies are nonexistent and probably will never be obtained. Given the rapid development of new diagnostic techniques, randomized studies would become obsolete by the time they have been terminated. Retrospective analysis based on SEER data suggests that mammographic screening for breast cancer may be beneficial up to the age of 85, even in women with moderate degrees of comorbidity [43, 44]. Some form of screening for colorectal cancer appears reasonable in individuals with a life expectancy of 5 years and longer. Indiscriminate screening in older individuals is not advisable as it may have more complications than benefits [45]. In this respect, it is useful to remember that the United State Preventive Service Task Force (USPSTF) recently issued a recommendation against screening men aged 75 and older for prostate cancer because the risk of complications from unnecessary treatment appears to overwhelm the potential benefits of early detection [46].

Aging and Cancer Treatment

It has already been highlighted that aging involves a reduced life expectancy and reduced tolerance of stress, including cancer and cancer treatment. The risk/benefit ratio of preventive and therapeutic interventions may become smaller with age. The risk of therapeutic complications may mandate the enactment of measures that may ameliorate these complications, such as the administration of myelopoietic growth factors following cytotoxic chemotherapy or adjustment of the doses of chemotherapy to the glomerular filtration rate (GFR) [47].

In addition to prolongation of survival and preservation of quality of life, preservation of function is another major goal of cancer treatment in older individuals (which is often referred to as "active life expectancy") [48]. Functional dependence purports a decline in a person's life expectancy and quality of life, and substantially increases costs of management of the older aged person. Cancer treatment in older persons should therefore be undertaken with these considerations in mind.

Assessing the Geriatric Patient for Cancer Treatment

Clearly, elderly cancer patients may benefit from an array of treatment modalities. The practitioner is often faced with the vexing decision of whether to recommend a toxic treatment to patients with compromised functional status. While aging is universal, the rate of aging is highly individualized. For the purpose of clinical decisions, it is thus important to estimate each person's physiologic age rather than relying on chronological age alone. As the prevalence of age-related changes increases rapidly after the age of 70, it appears reasonable to estimate the physiologic age of individuals aged 70 and older [49–51]. In this estimate, it is important to remember that social support is instrumental to overcome some age-related limitations in a person's activities. For example, a reliable home caregiver may provide adequate access to care to a person unable to use transportation and to mitigate the complications of treatment.

The time honored methods to assess the physiologic age of an individual is a comprehensive geriatric assessment (CGA) that includes ability to perform activities of daily living and instrumental activities of daily living, comorbidity, presence of geriatric syndromes, nutrition, and social support [47, 52, 53]. Activities of daily living (ADL) include transferring, continence, feeding, grooming, dressing, and ability to use the bathroom alone. Instrumental activities of daily living (IADL) include use of transportation, ability to take medications, to provide to one's nutrition, to go shopping, using the telephone, and to manage one's finances. The geriatric syndromes are conditions that become more common with aging, although they are not specific of age, and include dementia, severe depression, delirium triggered by diseases and drugs that do not affect the central nervous system, spontaneous bone fractures, falls, dizziness, failure to thrive, and neglect and abuse.

The CGA provides an estimate of life expectancy on the basis of age, function, and co-morbidity. Using the CGA, 4 year mortality of patients of different ages (Fig. 3.2) can also

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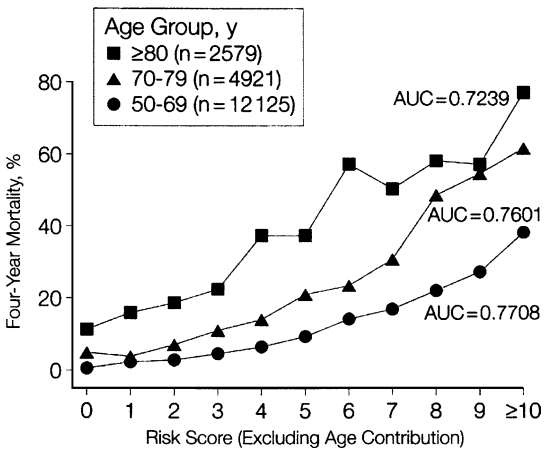

b **Four-Year Mortality Index for Older Adults**

1. Age _____	60-64: 1 point 65-69: 2 points 70-74: 3 points 75-79: 4 points 80-84: 5 points ≥85: 7 points
2. Sex (Male/Female)	Male: 2 points
3. a. Weight: _____ b. Height: _____ 703 x (weight in pounds/height in inches^2) BMI = _____	BMI >: 1 point
4. Has a doctor ever told you that you have diabetes or high blood sugar? (Y/N)	Diabetes: 1 point
5. Has a doctor told you that you have cancer or a malignant tumor, excluding minor skin cancers? (Y/N)	Cancer: 2 points
6. Do you have a chronic lung disease that limits your usual activities or makes you need oxygen at home? (Y/N)	Lung Disease: 2 points
7. Has a doctor told you that you have congestive heart failure? (Y/N)	Heart Failure: 2 points
8. Have you smoked cigarettes in the past week? (Y/N)	Smoke: 2 points
9. Because of a health or memory problem do you have any difficulty with bathing or showering? (Y/N)	Bathing: 2 points
10. Because of a health or memory problem, do you have any difficulty with managing your money – such as paying your bills and keeping track of expenses? (Y/N)	Finances: 2 points
11. Because of a health problem do you have any difficulty with walking several blocks? (Y/N)	Walking: 2 points
12. Because of a health problem do you have any Difficulty with pulling or pushing large Objects like a living room chair? (Y/N)	Push or Pull: 1 point
Total Points	_____

Figure 3.2 (**a**) The relationship between age, geriatric assessment, and 4-year mortality in a home dwelling population. (**b**) Mortality index: each element of the geriatric assessment receives a score. The total score provides an estimate of the 4-year mortality for individuals of different ages (from Lee et al. [49] Copyright © 2006 American Medical Association. All rights reserved).

be estimated [49]. The CGA also provides information on treatment tolerance on the basis of function and co-morbidity, as well as of family support and cognition (information of how treatment and cancer affect quality of life). According to recent studies, the CGA may also provide an estimate of the risk of chemotherapy-related complications [54]. An ongoing study, the Chemotherapy Risk Assessment Score in High Age Patients (CRASH) is aimed to assess the contribution of the various components of the CGA to an individual's risk of myelotoxicity and other complications.

The CGA also provides a profile of potentially reversible conditions, such as malnutrition, limited mobility, inadequate social support, and unrecognized geriatric syndromes, which may compromise treatment outcome.

Perhaps most importantly, the CGA translates the diversity of the elderly population into objective categories that may be used when planning clinical trials of cancer treatment in old persons.

Systemic Therapy

Hormonal Therapy

The major forms of hormonal cancer treatment are listed in Table 3.3. In the management of breast cancer, both adjuvant and metastatic, the aromatase inhibitors have proven more active than the SERMs and are now the management of choice. The main complications of these agents include severe arthralgias and osteoporosis [55]. The SERMs tamoxifen and toremifene may delay osteoporosis, but do cause endometrial cancer and deep vein thrombosis and the risk of these complications increases with age and in the presence of obesity. They may still represent valid options for the occasional patient for whom arthralgia causes severe impairment of movements. The role of the pure estrogen antagonist, Faslodex®, is not clear at present. This agent does not cause endometrial cancer and deep vein thrombosis. Progestin, estrogen in high doses,

Table 3.3 Common hormonal treatment of cancer

Tumor	Cancer
Breast	Aromatase inhibitors
	Selective Estrogen Receptor Modulators (SERMs)
	Pure estrogen antagonists (Faslodex)
	Progestins
	Estrogen in high doses
	Androgen
Prostate	Orchiectomy
	Estrogen
	LH-RH analogs
	Ketoconazol
	Abiraterone

and androgen are rarely used, although they may still have a role, especially in patients without visceral disease who have experienced a prolonged response to hormonal treatment.

Castration, surgical or chemical (LH-RH analogs, estrogen, ketoconazol, abiraterone), is the treatment of choice for metastatic prostate cancer and for locally advanced prostate cancer in combination with radiation therapy. The benefits of treating patients experiencing a chemical recurrence (elevated PSA) after prostatectomy or radiation have not been established, although this approach has become a common practice. Prolonged castration with LH-RH may cause increased risk of bone fractures, diabetes, and coronary artery disease [20, 21]. Intermittent medical castration may be as effective as continuous castration, and is associated with fewer complications [56]. Estrogens are now seldom used, because of the risk of deep vein thrombosis, but they had significant benefits over LH-RH analogs, including preservation of libido, as well as prevention of osteoporosis and hot flushes.

Ketoconazol blocks steroidogenesis throughout the body. Without a supplement of corticosteroids, it would cause renal insufficiency. It may also cause hepatitis. It is generally used after disease progression with LH-RH analogs. Abiraterone, currently in clinical trials, has two advantages over current treatment [57]. Unlike ketoconazol, it selectively blocks the production of sexual steroids in the testicles and the adrenal. Also, it seems to prevent steroidogenesis within the neoplastic tissue which is a major cause of resistance to current hormonal treatment. Androgen antagonists are mainly used in combination with castration; as single agents, they are less effective than castration. As single agents, they may represent the treatment of choice for patients who do not want to lose their libido.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy is still the mainstay systemic cancer treatment. Individuals over the age of 70 appear to benefit from cytotoxic chemotherapy in terms of cure, survival prolongation, and palliation. It is important to recognize, however, that the information related to patients aged 80 and older is very limited [58].

A number of complications of chemotherapy become more common with aging (Table 3.4). This is due in part to age-related alterations in pharmacokinetics and in part to decreased functional reserve of normal tissues. The most common pharmacokinetic change is reduction in GFR. Other changes of interest that are more difficult to assess include decreased intestinal absorption and hepatic metabolism, and decreased volume of distribution of hydrosoluble agents.

Myelotoxicity and febrile neutropenia may be prevented in more than 50% of older individuals with prophylactic myelopoietic growth factors (filgrastim, pegfilgrastim, and lenograstim). Prevention of malnutrition and anemia may also ameliorate the complications of chemotherapy to some extent.

Table 3.4 Age and complications of chemotherapy

A. Acute complications
Neutropenia and neutropenic infections
Mucositis
Cardiomyopathy
Neuropathy
B. Chronic complications
Myelodysplasia (MDS) and Acute Myelogenous Leukemia (AML)
Chronic cardiomyopathy and congestive heart failure
Neuropathy
Dementia

Cardiotoxicity may be prevented by avoidance of cardiotoxic anthracyclines, by combining anthracyclines with dexrazoxane, a drug that chelates the iron in the heart sarcomeres and prevents the release of free radicals responsible for the cardiac damage, or by substituting doxorubicin with pegylated liposomal doxorubicin that causes minimal cardiac damage. The use of anthracyclines has decreased dramatically in recent years and is largely restricted to the management of lymphomas and leukemias.

Mucositis is mainly a complication of methotrexate and intravenous fluorinated pyrimidines. There is no proven antidote to mucositis, but the utilization of the oral prodrug of fluorouracil, capecitabine, in lieu of intravenous fluorouracil may minimize this complication.

Peripheral neuropathy is a complication of alkaloids, platinum derivatives, and tubulin modulators (taxanes and epothilones), and may restrict considerably the independence of older individuals. The only prevention is early detection and dose-reduction. The substitution of cisplatin with carboplatin and of paclitaxel with docetaxel may minimize the risk of peripheral neuropathy.

The long term complications of chemotherapy in older individuals have been described only in the last 5 years [10–13, 16–19]. Age is a risk factor for anthracyclines induced myelodysplasia and acute leukemia. The reduced role of these drugs in the adjuvant treatment of breast cancer will minimize the risk of this complication; likewise, age is a risk factor for a chronic cardiomyopathy, incidence of which increased over the years since the chemotherapy was terminated, and has been described in patients treated for breast cancer, lymphoma, and small cell cancer of the lung. According to a SEER study, the incidence of dementia increases progressively in breast cancer patients treated with chemotherapy beginning 3 years from the termination of the treatment [19].

Unfortunately, there is no information concerning the most undesirable chronic complications of chemotherapy in older individuals, loss of independent living, and decreased active life-expectancy. Prospective studies of survivors are necessary to establish the risk and the prevention of this complication.

The NCCN has issued a number of guidelines for the safe management of older individuals with chemotherapy (Table 3.5) [47].

Table 3.5 NCCN guidelines for the management of older patients with chemotherapy

1. A geriatric assessment is necessary in all individuals aged 70 and older with cancer. This may provide an estimation of life expectancy and tolerance of treatment, and it may unearth conditions such as comorbidity or inadequate social support that may interfere with treatment
2. All patients aged 65 and older receiving moderately toxic chemotherapy should receive prophylactic filgrastim or peg-filgrastim
3. Hemoglobin should be maintained around 12 g/dl
4. In patients aged 65 and over, the dose of chemotherapy should be adjusted to the GFR
5. When possible the less toxic forms of chemotherapy should be utilized including capecitabine, pegylated liposomal doxorubicin, gemcitabine, vinorelbine, weekly taxanes, and pemetrexed

Targeted Therapy

An exhaustive review of the subject is beyond the scope of this chapter. We'll describe here commonly used products relevant to the management of older patients [59].

Imatinib is the quintessential form of targeted therapy. This small molecule is an inhibitor of the cytoplasmic tyrosine kinase, and has prolonged the survival of patients with chronic myelogenous leukemia, who now rarely need bone marrow transplantation. It is also effective against the tyrosine kinase encoded by c-Kit and for this reason, it is effective in gastro-intestinal stromal tumors (GIST). Complications are rare and reversible, and include myelosuppression and fluid retention.

Rituximab is a monoclonal antibody with CD20 specificity that has improved the survival in virtually all B-cell malignancies. Besides rare allergic reactions, the incidence of complications is minimal, although it has been reported that long term use may lead to demyelinating disorders.

Alentuzumab is also a monoclonal antibody with CD52 specificity that is very effective in some of the most therapy-refractory B-cell malignancies such as chronic lymphocytic leukemia with 17p (-) mutation. This agent has considerable myelotoxicity and should be used with prophylactic antimicrobial coverage.

Trastuzumab has revolutionized the history of the 25% of breast cancers that over-express HER2neu. It is a monoclonal antibody with specificity for Epidermal growth factor 2 (EGFR2). In combination with chemotherapy in the adjuvant setting, it almost doubles the number of patients who are free of disease 5 years from mastectomy. Trastuzumab causes myocardial freezing by interfering with myocardial trophism. Age is a risk factor for this complication that is generally reversible upon discontinuance of the treatment.

Bevacizumab is a monoclonal antibody directed against the endothelial growth factor, which inhibits tumor angiogenesis and decreases intratumoral pressure, thus allowing better chemotherapy diffusion. As a single agent, bevacizumab is active only in renal cell carcinoma, but it enhances the effects of chemotherapy in cancer of the colon, of the lung, and of the breast. Bevacizumab is associated with hypertension, bleeding, and deep vein thrombosis. It should not be used within 4 weeks of surgery, because it interferes with healing. Rarely, after abdominal surgery, bevacizumab has caused visceral perforation. All complications of bevacizumab are more common in the aged.

Receptor bound tyrosine kinase is critical to the signal transduction. This enzyme is the target of a number of agents, both monoclonal antibodies and small molecules. A common complication of all these agents is a maculopapular rash, that is more common and severe in the elderly, in whom necrolytic epidermolysis occasionally may be fatal.

Conclusions

Age is a risk factor for cancer because carcinogenesis is a lengthy process, older tissues are more susceptible to environmental carcinogens, and changes in the body environment favor cancer growth. Changes in cancer behavior are seen in some common malignancies. These are partly because of a change in the neoplastic cell and of changes in the tumor host. Although the elderly appear as ideal targets for chemoprevention, the benefits of this form of prevention have not been conclusively demonstrated. Screening and early detection of breast and colon cancer may be beneficial in older individuals with a life expectancy of at least 5 years. Systemic cancer treatment is effective in older patients. Although the complications become more common with age, most of the time they may be minimized with appropriate interventions.

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