IAN OLVER
*EDITOR*

# The MASCC Textbook of Cancer Supportive Care and Survivorship

*Second Edition*


Springer

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# Preface

Supportive care in cancer encompasses both the management of the symptoms of cancer and the side effects of treatment throughout all stages of surviving cancer. It covers the physical, psychosocial and spiritual needs of those with cancer and recognises that the relatives and carers often need similar support.

The Multinational Association of Supportive Care in Cancer has a mantra that supportive care makes excellent cancer care possible. We are very grateful to all of our volunteer authors who share this belief.

This second edition of the MASCC textbook has been completely revised, demonstrating how much changes in 6 years. The advent of targeted small molecules and immunotherapies comes with a raft of new side-effects to understand and either attempt to prevent or treat. The challenges faced by cancer survivors and the rehabilitation of cancer survivors are now better defined.

New topics start with the opening chapter, which Fred Ashbury wrote with me, and now emphasises the disparities in support care which are often based on geographic location, socioeconomic status and cultural differences between people. The first edition of this textbook included a chapter on cancer fatigue, but we have now added a chapter on sleep and cancer, with Ann Berger as the first author.

The haematological section now incorporates a chapter on anaemia written by Matti Aapro to highlight the new MASCC anaemia guidelines. The chapter on eye toxicities has had a range of new authors contributing to the update. Dermatological toxicities have become more prominent with many new dermatological side effects of targeted and immunotherapies necessitating major additions to that chapter. Many other chapters have included the new side effects of immunotherapies. I have also rewritten and updated the section on extravasation injury.

Some symptoms are now less emphasised and so there is not a separate chapter on superior vena caval syndrome but it is covered in the cardiovascular section. The opposite is the case with survivorship issues which now warrants its own chapter in addition to extending the chapters on psychosocial and spiritual issues.

This is a comprehensive text with 42 well-referenced chapters, which will be helpful to oncologists, nurses and allied health practitioners as well as those caring for patients in primary care. It is also a great resource for students and trainees coming into the oncology field.

Adelaide, SA, Australia Ian Olver

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# Part I

# Introduction

# 1 Cancer Symptoms, Treatment Side Effects and Disparities in Supportive Care

Fredrick D. Ashbury and Ian Olver

## Introduction

Supportive care is about managing the symptoms of cancer and the side effects of its treatment across the spectrum of the patients' cancer experiences from diagnosis through treatment to the issues faced by survivors and embracing palliative care. This is the emphasis of the Multinational Association of Supportive Care in Cancer [1] which emphasizes that supportive care makes excellent cancer care possible.

The second edition of this textbook adds new authors and new toxicities and expands the coverage of some symptoms where much progress has been made since the previous edition. Systemic treatments are progressing from predominantly cytotoxic chemotherapy to immunotherapies and small molecules targeted at the products of mutated genes. Many of the chapters are grouped into toxicities within organ systems, as previously, but with these newer therapies, there are newer toxicities arising, for example, due to autoimmune destruction of tissues. There is a wealth of new skin reactions which require management. Organ toxicities can occur from targeted therapies in their own right and may exacerbate the cumulative organ damage from prior cytotoxics. A good example is the increase in cardiotoxicity seen with trastuzumab when given after anthracyclines [2]. These novel agents are also producing toxicities seen in patients receiving traditional chemotherapies, but their expressions can be different and therefore their management can also be different.

New chapters include the social issue of financial toxicity which has been increasingly recognized as patients face the burden of having to pay for some high-cost therapies or have their income reduced when their employment status changes due to the impact of cancer and its treatment [3]. Other new chapters simply recognize that there has been great progress in understanding and managing common symptoms like fatigue and general symptoms such as sleep disturbance. There is more space in this second edition devoted to psychosocial and spiritual wellbeing as it is increasingly clear how much impact these have on quality of life during and following treatment as survivorship issues.

The challenge of managing cancer and its follow-up is to distinguish symptoms of cancer and its recurrence and the side effects of its treatment from other common conditions. The major characteristic of a cancer symptom is persistence.

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Symptoms due to other causes such as infections or trauma tend to resolve over time, whereas left untreated cancer symptoms will progressively worsen. It is important in patients with cancer not to ascribe all symptoms to the cancer and its treatment. We remind medical students that patients with cancer can also develop acute appendicitis, which must not be missed.

The symptoms can relate to the organ in which the cancer arises or from its metastases, and so knowing the patterns of spread of various cancers is important. However, distant effects of cancer unrelated to secondary spread, so-called paraneoplastic syndromes, are caused remotely by hormones and cytokines produced by the cancer and often are diagnoses of exclusion. Side effects, such as nausea and vomiting, can occur within hours of administration of therapy. Toxicities due to cumulative organ damage such as cardiotoxicity or neuropathy take months to develop. Late toxicities such as second cancers often take years to develop.

We now embrace a more holistic concept of the aims of cancer treatment which are directed to control cancers but also to improve the quality of life during treatment and beyond as patients survive. Psychological wellbeing is important to this, and being able to predict anxiety and depression allows its management before it seriously compromises quality of life. Likewise, existential issues faced by patients require recognition so that appropriate support can be given to promote spiritual wellbeing which has an impact on quality of life independent of other factors.

Palliative care clinicians are experts in symptom control, and this expertise can be utilized by oncologists to manage difficult cancer-related symptoms. The concept of parallel care with palliative care clinicians having input into symptom control during the anticancer treatment phase can improve supportive care. Eventually, as the benefit of anticancer treatments lessens and the specific expertise in recognizing and treating their toxicities which has been contributed by the oncologist is not required, the palliative care physician takes the major role in symptom control at the end of life.

Unfortunately, just as there are disparities in the availability and delivery of cancer treatments, so this applies to supportive care. This is such an important global problem which needs addressing that we have highlighted it in this opening chapter.

Despite the improvements in cancer treatment and symptom control over the past few decades, many cancer patients have limited or no access to these treatments and/or supportive care, particularly those of lower socio-economic status, persons who reside in lower- and middle-income countries and those who live in rural/remote areas. Escalating costs of cancer treatment coupled with increasing cancer incidence and prevalence will exacerbate the burden of cancer and place even greater pressure on these disparities. Global cancer incidence is projected to increase significantly to more than 19 million people by 2025 [4], and there will be more than 45 million cancer survivors. In terms of geographic distribution, over half of the people who are diagnosed with cancer and nearly two-thirds of cancer deaths occur in lower-income countries.

We will focus specifically on the challenges of providing efficient and effective supportive care, with an emphasis on disparities in care access and delivery. In oncology, supportive care is the prevention and management of the adverse effects of cancer and its treatment. MASCC defines supportive care as management of the symptoms of cancer and side effects of treatment across the entire continuum of cancer care, including prevention, screening, diagnosis, treatment, post-treatment rehabilitation/survivorship and end-of-life care (MASCC). Supportive care is patient-centred and includes support for the physical, psychological, social, instrumental and spiritual sequelae of cancer and its treatment. By disparities in care, we accept the definition offered by Braveman [5], which states certain social groups (e.g. racial/ethnic minorities, poor) who routinely experience social disadvantage or discrimination also systematically experience inferior health or increased risk to develop health problems compared to other social groups who are more socially advantaged (e.g. the dominant racial/ethnic groups, wealthy). As Ahmed and Shahid [6] write, “Health disparities not only result in avoidable death, disease, disability, anguish, and discomfort, but are also harmful for the health system…”. The concept of health disparities in cancer control and supportive care

**Table 1.1** Side effects of common cancer treatment modalities

| Side effect | Surgery | Chemotherapy | Radiation therapy |
|---|---|---|---|
| Fatigue | √ | √ | √ |
| Anxiety | √ | √ | √ |
| Depression | √ | √ | √ |
| Pain | √ | √ | √ |
| CVD risk | | √ | √ |
| Pulmonary changes | √ | √ | √ |
| Cognitive changes | √ | √ | √ |
| Lymphoedema | √ | | √ |
| Immune risk | | √ | √ |
| Sexuality | √ | √ | √ |
| Nausea | | √ | √ |
| Vomiting | | √ | √ |
| Weight changes | √ | √ | √ |

can be extended to include disparities between wealthy nations and lower- and middle-income countries [7].

As context, the most common cancer treatment modalities (surgery, radiation and chemotherapy) result in many different side effects adversely affecting the patient's experience [8–12]. These side effects are highlighted in Table 1.1.

Moreover, the advances of research that have generated new immunotherapies and targeted treatments based on genomic science have resulted in novel agents that, despite early predictions, when used alone or in combinatorial strategies, are producing toxicities that require innovative approaches for successful management [13]. Skin and organ toxicities, which are quite problematic as a result of targeted therapies, are a significant research focus. Both practitioners and cancer patients require education about these novel agents, their associated toxicities and appropriate management strategies and tools. The need for supportive care is key when the survival advantage of cancer treatment is weighed against the side effects of treatment, financial toxicities, and their impact on the person's quality of life.

## Disparities in Supportive Cancer Care

Disparities in access to and the availability of cancer supportive care exist on many levels and include (1) the ability to finance the costs of cancer treatment and supportive care for societies and individuals—these financial pressures are further demonstrated between higher-, middle- and lower-income countries; (2) the availability of skilled oncology professionals; (3) limited or lack of implementation of evidence-based guidelines and policies; (4) rural/remote population distribution; and (5) racial and ethnic disparities.

The high cost of cancer drugs (treatment and supportive care) is a global issue, but the challenges at the societal level are even greater for lower- and middle-income countries. Furthermore, treatment of more advanced cancers often requires radiation therapy, including palliative radiation treatment. These services are typically only available in locations where there is sufficient patient volume to warrant the costs associated with establishing a radiation treatment centre and where cancer treatment has sufficient priority over other health expenditures such as managing infectious diseases or survival priorities such as food security. A recent study by de Lima Lopes [14] has calculated the cost of cancer care as a percentage of gross national income (GNI) in US dollars. The United States spends approximately 1.02% of GNI on cancer care, while Japan is 0.6% and the United Kingdom is 0.51%. In contrast, countries in South America spend on average 0.12% of GNI on cancer care, China spends about 0.11%, and India spends approximately 0.05%. Keefe and colleagues [15] point out that health-care financing structures in the Asia Pacific and Middle East differ consid-

erably. Many lower- and middle-income nations remain "out-of-pocket markets", as CINV drugs and other supportive care therapies are not typically reimbursed. While the use of generic drugs can help defray costs, as can improved access programmes, new targeted treatments will not come off patent for several years before lower-cost generics will be possible. Alternatively, government implementation of price controls may be a solution, but this strategy requires "political will".

These "societal burdens" of the high cost of cancer drugs are persistent at the individual level. Socio-economic status (SES) is a measure of one's "social class", indicated by a person's wealth, occupation, educational attainment and income. Persons of higher SES have more resources, while those of lower SES have fewer resources. In addition, low SES individuals often have poor lifestyle behaviours that increase their risk of chronic diseases including cancer, are less likely to participate in cancer screening programmes and lack sufficient health insurance coverage [16]. Moreover, low SES individuals cannot keep pace financially with the escalating costs of health care and therefore experience poorer outcomes [17].

In all nations there are serious limitations in the number of trained professional resources to incorporate supportive care into routine care delivery, including psychiatrists, psychologists, psychotherapists, spiritual care workers, social workers and integrative care professionals. According to Locke and Winship [18], the representation of mental health professionals and social workers in rural areas of the United States is even more dismal. In low-income countries such as Kenya, there is a dearth of skilled oncology professionals to provide oncology care, including supportive care, and the same can be said of middle-income countries such as Brazil [19]. Failure to provide appropriate supportive care during treatment has been shown to impact patient adherence to the treatment plan and therefore jeopardizes achievement of optimal outcomes [20, 21]. Every physician should receive training to recognize disparities and the associated biases that undermine the patient-provider relationship and communication [22]. Nevertheless, current labour-intensive strategies to deliver care cannot be successful in the longer term. Fresh approaches that can be scaled are urgently needed to ensure patients with cancer have access to trained supportive care workers not only to maintain appropriate management of the physical, emotional, psychosocial and spiritual toxicities of the therapies they receive.

Health services studies of rural/remote patients with breast cancer have reported significantly higher rates of mastectomy even though other treatment options such as lumpectomy and radiotherapy, which have similar efficacy, are less available in these areas [23, 24]. In addition, regulatory policies impact the delivery of supportive care agents globally, as is the experience of the distribution of and access to pain control medications. Physicians in many countries, especially low-income countries (but not only), are under tremendous scrutiny for whom, when and how pain medications are prescribed [25]. Furthermore, some differences in supportive care practice occur whether or not evidence-based guidelines and policies are implemented. Where guidelines and policies do exist, these can be different from institution to institution. The purpose of guidelines in supportive care (as well as all health care) is to improve access to delivery and quality of care cancer patients receive. To facilitate implementation of supportive care guidelines in cancer will require consensus among oncology professional associations of what constitutes appropriate supportive care, priorities for supportive care delivery and strategies and tools to facilitate adoption and implementation. Because effective supportive care guidelines already exist and are endorsed by national and international bodies such as the Multinational Association of Supportive Care in Cancer, these should be reviewed by oncology professional associations in nations where they are lacking supportive care guidelines and subsequently adapted and translated within the context of local resources and circumstances. Additional investment will also be necessary to ensure the appropriate skills and capacities are in place for successful dissemination and implementation of international supportive care guidelines [26].

Cancer patients in rural/remote regions in all nations experience specific challenges in access to treatment and supportive care. Research shows that rural/remote residents often present with later-stage cancer diagnoses compared to urban residents [27], for several key reasons: (1) the lack of availability of or challenges accessing primary care and formal screening programmes (e.g. distance required to travel for primary care consults or to participate in screening); (2) absence of programmes that provide routine cancer screening; (3) loss of wages from leaving work to attend primary care consults, cancer screening, treatment, rehabilitation and end-of-life care; (4) lack of adequate health insurance or financial resources; (5) lack of understanding of the health risks and benefits of screening and early detection; and (6) being more likely to engage in unhealthy behaviours that increase risk of cancer, including smoking, poor diet, physical inactivity and not using sunscreen [28, 29]. The case example below illustrates some of the challenges of access to cancer care, including supportive care.

> Jane S: Jane is a 57-year-old patient who lives in a community of 625 residents. She traveled 70 kilometers to her family physician with complaints of abdominal pain and painful passing of bloody stool. A physical examination revealed a mass at the anus and the family physician referred her for a surgical consult with a general surgeon in the community hospital 300 kilometers away. The appointment was scheduled 40 days later due to availability of the surgeon. In the interim, the patient was prescribed a diet rich in fibre and low in fat along with stool softeners to ease her bowel movements to mitigate pain. The general surgeon confirmed the mass and advised the patient he suspects she has anal cancer. The surgeon's next step is a referral to a specialist cancer surgeon as he believed this path would optimize her chances for a successful outcome. The appointment with the specialist cancer surgeon was arranged and scheduled for ten days later. Jane was told she should prepare to stay overnight or longer if that surgeon needed to have any tests performed. The specialist cancer surgeon is located in a teaching hospital a further 300 kilometers away. Once again, Jane was advised to continue with stool softeners and the diet recommended by her family physician. Jane subsequently had to travel 600 kilometers from her home to make her appointment with the specialist cancer surgeon who ordered a CT scan and blood work for the next day. The specialist cancer surgeon determined she needed surgery and was now required to stay in town an extra few days. The surgery was performed, including lymph node resection. A biopsy confirmed adenocarcinoma and two positive lymph nodes. Over the next year, the patient had subsequent treatments of radiation therapy and chemotherapy. In total, she travelled more than 9,000 kilometers for consults, visits and treatments and interacted with more than two dozen providers.

The case example illustrates a number of challenges faced by rural/remote residents with respect to participation in cancer care, including supportive care. These challenges are geography, physical burden, practical and financial considerations and social and psychological factors.

Rural/remote areas generally lack locally available, accessible health services, including general practice, screening, diagnostic and specialty (e.g. oncology) services, including palliative care. The absence of these health services requires rural/remote residents to travel to receive care. A person who is suspected to have cancer will need to travel for diagnostic investigations, which may mean more than one trip, consultations, subsequent treatment and follow-up care. The travel challenges to access health services by rural/remote residents throughout Ontario have been demonstrated in large health services research projects conducted by the Institute for Clinical Evaluative Sciences [30]. If one has to travel for cancer treatment, it is generally necessary to find accommodation closer to where the treatment is provided. That is, the distance to travel to receive treatment can make it impossible for many rural/remote residents to participate. Practical concerns such as the time and effort it takes to secure accommodation near to where the treatment is offered, the costs of the accommodation, being away from loved ones and other social support networks and whether or not accommodation is available in the first place play important roles in the decision to receive treatment far from one's home. In addition to being described as "inconvenient" and "impractical", the physical stress on the person to travel longer distances (e.g. increased fatigue) reduces the likelihood of participation in cancer treatment offered through an urban centre [31]. The physical burden on

family members or caregivers may also be significant, as they may participate in assisting with transportation or visitation during treatment. Even if entry to diagnostic and treatment services is possible, often residents of rural/remote areas experience challenges accessing treatment-related ancillary services (e.g. oncology nurses), supportive care, palliative care and survivorship care resources (e.g. lymphoedema support) when treatment is completed.

Residents in rural/remote locations generally have lower incomes than those who live in urban areas. Travel and accommodation cost money, and with less disposable income, people may decide to forego treatment in a cancer programme offered farther away, even if that treatment programme provides better services and greater likelihood of successful outcomes. Furthermore, because many rural/remote residents are self-employed [31–33], persons in these areas may experience reduced or no income for the period of time they are not working as a result of attending appointments for tests, treatment, or consultations [34], a situation that jeopardizes their ability to receive the right treatment and supportive care when needed. For cancer patients who live on farms, for example, they can face challenges associated with the "cycle" of farming activities. For example, in the middle of harvest seasons all "hands on deck" will be needed to ensure the harvest is successful. Conversely, if there is a drought, individuals working on farms need to work to mitigate the negative financial consequences the drought will cause. These practical situations can prevent people from seeking health services in a timely way or participating in care according to schedules defined by cancer treatment pathways/plans.

Rural/remote residents are more likely to lack access to current knowledge and education about the services and care options available. As such, they rely heavily on local services for advice. Rural health services, including primary care physicians and surgeons, as shown in US studies, typically offer treatment options that motivate residents to remain closer to home to meet their personal needs but which may not always be the optimal choice for the most positive outcome. Furthermore, while the adoption of technologies to access the Internet has increased substantially over the last few years, generally residents in rural/remote locations report much less use than their urban counterparts due to poorer availability of broadband services [34]. In fact, Befort and her associates found that rural/remote residents are less likely to trust the Internet, government or print media as a health information source, compared to urban residents. They are, however, more likely to have confidence in their healthcare providers as a cancer information source. Douthit and colleagues reported that cultural and financial challenges, a paucity of services, inadequate or insufficient public transportation, limited or no broadband access and a lack of trained personnel conspired to mitigate rural residents' access to appropriate health care and resulted in poorer health outcomes [35].

Psychological factors, including fear of the unknown, anxiety over treatment and its associated side effects, anxiety over how the diagnosis will affect finances and concerns about the impact of a cancer diagnosis and its treatment on relationships with family members and friends, have been shown to influence participation in cancer care. These needs tend to be somewhat more pronounced among rural/remote residents compared to urban residents, according to a review by Butow and colleagues [36]. Furthermore, there is some research showing that rural/remote residents may hold culturally embedded views towards cancer treatment, and these views may affect their willingness to go for treatment. Rural residents are more likely to perceive that cancer treatment holds significantly more negative consequences than positive outcomes [37]. Befort and colleagues have reported that rural/remote residents hold a "fatalistic view" of cancer. For example, rural residents, compared to urban residents, are more likely to report that "everything causes cancer". This fatalistic view translates into expectations among rural residents that a cancer diagnosis is a "death sentence", and since there is little someone can do about it that does not cause her or him serious side effects and a negative quality of life (pain, nausea and vomiting), why bother with treatment?

Several studies have also documented racial and ethnic disparities in cancer care [38, 39]. African Americans, for example, have a higher incidence of and poorer outcomes from the more common cancers compared to white Americans [40]. Black American women experience more prolonged access to definitive cancer surgery [41]. Similarly, indigenous populations tend to have poorer access to cancer services, including screening, treatment and supportive care [42]. Australia's aboriginal population tends to have higher rates of and mortality from cancer compared to the general population [43]. In New Zealand, recent research has shown that Māori and Pacific women experience significantly more barriers to breast cancer care [44]. In developing countries access to high-quality cancer care is generally a problem but much more so for minority populations in these countries [23]. Ethnic and racial differences in cancer care are exacerbated by income and educational disparities, cultural differences in attitudes towards health and health care and regional and institutional differences in available services and programmes. Nevertheless, it is imperative that these differences are addressed in order for every cancer patient, regardless of her/his background, to have equitable access to appropriate cancer care.

## Implementing Supportive Care: Opportunities and Benefits

The successful dissemination and adoption of supportive care policies and practices to mitigate these disparities can be thought of within the context of diffusing an innovation. The Agency for Healthcare Research and Quality [45] defines an innovation as an idea, practice or object that a person, group or institution perceives as being new or different from standard or existing practice. In response to the innovation, the individual will make a conscious decision to adopt or reject it. Whether an innovation is actually adopted, implemented and ultimately embraced is dependent, in part, on specific characteristics of the innovation (e.g. the perceived relative advantage of the innovation compared to what is currently being used). Adoption of a new behaviour can involve a behaviour that currently does not exist or one that is a variant of an existing behaviour (e.g. use of a revised clinical practice guideline). In the latter case, replacing an existing behaviour can be particularly challenging, if the new behaviour and its benefits are not acknowledged to be superior, if the new behaviour is compatible or not with belief systems, if new skills to learn the behaviour are needed and these skills are difficult to acquire and/or implement, if there are financial or logistical impediments to implement the new behaviour, if the new behaviour can be easily tested to validate it can be done and the desired outcome can be achieved and/or if the implementation of the new behaviour is not recognized by one's peers as appropriate. Unfortunately, there remains a tendency for minimal personnel and fiscal resources to be devoted to the diffusion/adoption process related to an innovation as compared to the resources that were devoted to the actual discovery of the innovation and its subsequent demonstration of value.

Rather than devoting adequate resources to support the thoughtful planning and implementation of a specific diffusion/adoption strategy, all too often there seems to be an implicit belief that the "osmotic potential" of the innovation is of such a magnitude that it can overcome whatever barriers may exist to the innovation's adoption. In other instances, there is no apparent priority or planning given to the diffusion/adoption process once the important and all-consuming goal of discovery of the innovation has been realized.

Innovation adoption will require change management strategies and tactics to be successful [46]. As such, change management will be necessary to mitigate disparities in the successful dissemination, adoption and delivery of supportive care and will involve several key components:

- Understanding how the change will impact the health system's existing resources, including employees and broader stakeholders
- Defining the roles that leadership and key stakeholders should have in advancing change
- Integrating the programme (e.g. supportive care) within existing services, including

education, training, communications and health service delivery processes. This integration is vital as it will determine the various interactions needed to secure organizational buy-in and commitment to the change

For adoption and uptake of supportive cancer care evidence-based guidelines and practice to be successful, medical societies, government, third-party payers, providers and patients will need to adopt and promote a single vision. This vision needs to emphasize a "burning platform" for the need to eliminate disparities in access to and participation in effective cancer and supportive care. The burning platform should build upon shared values of equity in care and care providers' beliefs in the value of providing excellent cancer care, including supportive care. Real examples of successful patient and provider experiences delivering supportive care with positive outcomes should be shared to create resonance. It is also imperative to have a change management plan that is guided by data on stakeholders' beliefs, perceptions, knowledge and experiences with supportive cancer care. These data will act as context for the strategies required to facilitate education, training and practice change and mitigate against resistance. There needs to be a plan to ensure all providers understand policies and processes; otherwise knowledge of supportive care will remain underutilized in practice at the unit, organizational and policy-making levels [47]. Some successful strategies also include creating a "community", in which there are peer-to-peer conversations that enhance "belonging" and encourage participation and buy-in. Getting commitment to the novel approach will also be necessary, and incremental steps in this regard may be necessary. Let people "practise" and provide feedback on performance in a nonthreatening and encouraging environment. Acknowledge successes publicly and reinforce these successes to encourage that the new "behaviour" becomes routine. Identify local "change agents" or "leaders" who can further disseminate the desired programme. Local change agents should be people recognized by their peers to be credible and possess knowledge of the programme and the science behind the programme. Local workshops that draw in external experts as needed can also stimulate interest and uptake. Finally, activities that boost understanding and reinforce adoption of the programme will be necessary to safeguard sustainability.

To reduce disparities between wealthier nations and lower- and middle-income countries, innovation sharing or "spreading the wealth" of evidence-based supportive care programmes will be needed. Sharing does not have to include financial resources, rather it can include educational exchanges, sharing expertise, providing supportive care programme designs and processes and "train the trainer" initiatives. On a local level, initiatives could be supported to establish and build relationships to create regional supportive care associations. These "associations" can help build knowledge and capacity through educational exchanges and personnel transfers. External experts can share knowledge to facilitate training, acceptance and adoption, perhaps by working through existing post-secondary institutions, hospitals, professional associations, foundations, non-governmental organizations and government health departments [7]. International, regional and local partnerships can be created between programmes, institutions and international societies such as the Multinational Association of Supportive Care in Cancer can share resources and help create national and local associations.

Increasingly, digital health technologies have opened up access to cancer information, information exchange between providers and patients through e-portals and the exchange of health-care data through wearable devices and home-monitoring technologies. Importantly, telehealth and telemedicine opportunities can reduce travel, improve information access and facilitate patient-provider communication [48, 49]. These technologies can help scale existing resources in supportive care and mitigate financial pressures on health systems to train, recruit and compensate clinicians and staff to deliver care.

Workforce strategies are also needed in wealthy and lower- and middle-income countries to ensure that trained oncology professionals and

proper capacity are in place to mitigate the challenges of the increasing burden of cancer. Cancer Council Australia [50] has recommended that cancer programmes must identify local staffing needs and increase capacity to facilitate care closer to home (e.g. trained oncology nurses, social workers), which can be integrated with outreach by oncologists and telehealth/telemedicine programmes. This approach includes formal linkages to larger cancer programmes with the necessary resources and expertise to provide care to rural/remote people.

## Concluding Remarks

Following a cancer diagnosis, supportive care is a real and persistent need through treatment, rehabilitation, survivorship and end of life. Physical, psychological and spiritual "symptoms" will result from the cancer as well as toxicities associated with different treatments.

Disparities in cancer control and supportive care exist within all countries. These disparities are more pronounced between wealthy and middle- and lower-income countries and for rural/remote residents in these countries. There are, nevertheless, real opportunities to improve the effective delivery of supportive care. Successful collaborations are required at the international level between leading cancer control agencies and organizations, governments, not-for-profit agencies, professional associations and industry. It will also require "political will" within all societies to commit the resources needed to ensure cancer patients have access to the right treatments and appropriate support throughout the cancer journey. Supportive care might be an "innovation" for some, and as such, the relative advantage of structured, coordinated and integrated supportive care programmes over existing approaches that may be more "opportunistic" than systematic will need to be communicated and reinforced. Supportive care must become part of the "natural order" of the belief system of oncology care delivery, and as such, it is imperative to position supportive care as an expectation not a desire. Socio-economic status, geography, race and ethnicity or other social factors must be removed as barriers for cancer control and supportive care to be successful.

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# Part II

# General

# Cancer Pain

2

Mellar P. Davis

## Introduction

Pain is one of the more important symptoms to occur at the presentation of a malignancy. One third of individuals with cancer will have pain at diagnosis, and it will be a major problem in 60–70% of those with advanced cancer. Of those with cancer-related pain, nearly half will have severe pain which interferes with daily activity [1, 2]. The classification of cancer pain is often thought to be distinctly different than non-cancer pain. Cancer pain has been subdivided into cancer pain syndromes, and the use of opioids and general management is now considered distinctly different from non-cancer pain. This concept is particularly illustrated by the Center for Disease Control (CDC) that recently published pain management guidelines for non-cancer pain which excludes cancer pain [3, 4]. However, pain mechanisms are not distinctly different whether pain is due to cancer or to non-cancer causes. This is true for neuropathic and nociceptive pain. The CDC guidelines are motivated by the rising number of opioid-related deaths and were motivated by safe opioid prescribing practices. However, patients with cancer share the same risks of long-term toxicity and mortality associated with long-term opioid therapy since many of the opioid deaths are not due to overdoses [5].

The pain experienced by individuals with cancer is not always related to cancer. Patients with cancer are older, usually in their 60s or 70s, and frequently have arthritis, neuropathic pain from diabetes or herpetic infections, and pain from injuries or surgery unrelated to cancer. Treatment with surgery, radiation, chemotherapy, and targeted agents can induce injury and pain which accumulate as patients survive their cancer [2, 6].

Pain associated with cancer is not an isolated sensory experience. Pain influences physical function, personality, mood, and social relationships and is shaped by beliefs. In turn, personality, mood, social support, and spirituality influence pain. Cicely Saunders adopted the term "total pain" to describe this bidirectional relationship [7, 8]. Persistent helplessness and hopelessness and a loss of a sense of self are a root cause for pain intensity which will not respond to opioids but need to be addressed within an interdisciplinary approach to pain management. The focus on pharmacology alone or a biomedical approach based on pain intensity is inadequate to meet the needs of those with cancer and non-cancer pain [9, 10].

Efforts to relieve pain are welcomed by patients. Most patients accept some pain and most often focus on improved function as a

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primary goal. Patients want effective measures taken to relieve their pain but place a greater value on good clinicians who are willing to work as a team, who are willing to listen to their story, who effectively communicate with them in a timely fashion, and who demonstrate compassion and empathy [11]. Patients place as much value on how physicians care for them as to what physicians do to relieve their pain and suffering.

There are tremendous interindividual differences in analgesic responses despite the use of the same analgesic therapy and same dose. Large high-quality analgesic trials demonstrate modest benefits for opioids and adjuvant analgesics overall. The number needed to treat to get a 30–50% reduction in pain intensity is 3 on average or more. Overall modest benefits by prospective studies include patients with differences in drug metabolism (pharmacokinetics) and differences in mu receptor expressions (spliced variance of the mu receptor) among other factors which influence responses [12, 13].

There are also different responses to analgesics related to differences in pain phenotype and mechanisms between patients despite the label of "cancer pain" [14–16]. Certain pain phenotypes may be more responsive to analgesics than others, and certain pain mechanisms may respond to only certain classes of analgesics [17, 18].

As patients live longer with cancer and as cancer has become a chronic illness, cancer pain has gone from being largely acute or subacute pain to persistent pain lasting months to years [19, 20]. When pain changes from acute pain to persistent or chronic pain, there are changes in the brain connectivity pattern (default mode networks) as seen with functional MRI studies. Chronic pain deactivates endogenous opioid systems within the CNS and activates areas which lead to negative affect, anxiety, and increased pain unpleasantness. Pain becomes less localized and more widespread [21–25]. The normal linear opioid dose response seen with acute pain is lost when pain becomes chronic. As pain becomes chronic, it becomes less responsive to opioids [26, 27]. Opioid therapy over time and with increasing doses may accentuate the negative mood associated with pain and increase the unpleasantness of pain [28–30].

## Central Nervous System Pain Modulation

First-order sensory A-delta and unmyelinated C fibers have cell bodies in dorsal root ganglia and synapse within the superficial laminae (I–V) of the spinal cord dorsal horn. Second-order afferents ascend in the contralateral spinothalamic tract to the brain stem (pons, medulla) and thalamus. Third-order sensory fibers synapse in multiple locations including the periaqueductal gray, limbic system including hypothalamus and amygdala, prefrontal cortex, insular cortex, cingulate gyrus, and primary and secondary sensory cortex [31]. There is a "bottom-up" modulation of pain within the dorsal horn. Inhibitory interneurons within lamina II use gamma-aminobutyric acid (GABA) as a transmitter to down-modulate nociceptive traffic. Inhibitory and excitatory interneurons "gate" nociceptive traffic within the medulla, mesencephalon, and thalamus up to the final "interpretation" of pain by the cerebral cortex. Medial thalamic nuclei along with the prefrontal cortex, insular cortex, cingulate gyrus, and limbic system provide the affective-motivational experience of pain, while lateral structures such as the primary and secondary sensory cortex provide the sensory-discriminatory perception of pain [32–35].

"Top-down" pain modulation starts from descending pain pathways originating from the anterior cingulate cortex, prefrontal cortex, and insular cortex. This pathway dampens or enhances the activity of descending nociceptive signals [36, 37]. From the anterior cingulate and prefrontal cortex pathways descend through several brain stem nuclei. The nucleus reticularis dorsalis (NRD) within the medulla (which is responsible for conditioned pain modulation) receives input from these sites [38–40]. The NRD connects to the superficial dorsal horn via the dorsolateral funiculus. A second pathway descends to the periaqueductal gray and rostral ventromedial medulla (PAG/RVM) which reaches the superficial dorsal horn by way of the dorsal funiculus. The descending inhibitory activity causes postsynaptic inhibition of second-order afferent neurons [41–45]. Norepinephrine

is the major descending inhibitory neurotransmitter which binds to alpha-2 adrenoceptors. Serotonin facilitates descending pain via certain serotonin (5HT3) receptors. Serotonin can also dampen pain via 5HT2a and 5HT7 receptors [37, 46]. Norepinephrine acts on adrenoceptors found on GABA and glycinergic inhibitory interneurons. These neurons are tonically activated by continuous exposure to norepinephrine released from the locus coeruleus and PAG [47]. The underlying mechanism to NSAID analgesia may not be through inhibition of prostaglandin production but by way of release of norepinephrine and activation of alpha adrenoceptors [48, 49].

Within the PAG/RVM, opioids cause a firing of "off" cells which inhibit nociceptive within the superficial dorsal horn. Secondly opioids indirectly inhibit the firing of "on" cells which facilitate pain [46, 50, 51]. Opioid analgesia is now thought to be due to a large degree to its effects on the PAG/RVM. Adjuvant analgesics such as the serotonin-norepinephrine reuptake inhibitors (SNRIs) support pain modulatory circuits through the brainstem by increasing spinal norepinephrine [52, 53]. Placebo responses which occur in 1/3 of the population also utilize this "top-down" modulating pathway [54].

Not only is the PAG/RVM recipient of prefrontal and cingulate gyrus input but also receives input from the amygdala. The amygdala is a pain modulatory center which influences cognitive function. The amygdala is involved in tasks such as decision-making, and assessment of the risk and reward versus pain and punishment versus avoidance [55]. The central nucleus of the amygdala is activated with inflammation and enhances pain responses. Neuroplastic changes within the amygdala are one of the mechanisms which transforms acute to chronic pain [56–58].

## Chronic Pain

Two models have been proposed to explain chronic pain. One model envisions continued end-organ dysfunction based on tissue injury. Pain intensity therefore would reflect the degree of structural damage. The second model involves altered nervous system processing (neuroplasticity) in which central sensitization causes persistent pain despite healing of the original injury or stable disease [59–61]. Determining the balance between peripheral and central influences on pain and ascertaining which are due to a pathological versus emotional cognitive changes will influence decisions regarding treatment [62]. Neuropathic changes alter the functional connectivity within the pain matrix. As distinct from acute pain, chronic pain is a functional connectivity disorder within multiple supraspinal sites which govern the pain experience. This leads to a different experience of chronic pain compared with acute pain [63]. Multiple factors such as catastrophizing, economic status, social support, and past experiences govern the severity and disability of chronic pain [64]. Cancer pain may be severe because of the financial toxicity of treatment, loss of social support, demoralization, catastrophizing, and suffering from a loss of a sense of oneself, all of which are relatively opioid refractory. Illness, injury, inflammation, and personality may upset the balance between descending pain inhibition and facilitation. Individuals with a dysfunctional endogenous pain inhibition are more likely to develop chronic pain [65–68]. It is when the endogenous descending inhibitory system becomes overwhelmed or impaired that cancer pain is experienced [69]. Habituation to repeated pain episodes is an important protective mechanism to the chronification of pain. This has been shown to be mediated in part by the rostral anterior cingulate cortex which is the same site which modulates anxiety and depression. The lack of habituation has been seen with patients who experience chronic pain [70, 71].

Central neuropathic changes may be associated with a chronic pain from cancer. And late detection of cancer may be related to the ability to activate downward inhibition in the spinal cord. Decreased thalamic blood flow contralateral to the site of pain that has been demonstrated in patients with cancer hypoperfusion may reflect a decrease in neural activity or deafferentation [72]. A mouse species develops spontaneous pancreatic cancer. These mice do not develop pain until late stages of their cancer like humans.

However, when given an opioid antagonist in the early stages, robust visceral pain occurs which normally is not observed. In this model activation of central endogenous opioid systems during the development of cancer masks cancer pain and delays the diagnosis [73].

## Peripheral Mechanisms to Chronic Pain

One reason for the relatively modest benefits of opioids in cancer pain is that cancer pain has multiple complex molecular mechanisms. Cancer-induced bone invasion sends afferent signals to the spinal cord causing a hyperexcitable state within the dorsal horn partly due to activation of glia (a mechanism common with neuropathic pain). This is a shared mechanism that is relatively opioid resistant [74]. Metastatic bone pain is a neuropathic, ischemic, and inflammatory mechanism, the sum of which contributes to the experience of pain. The ischemic state of a tumor activates ACID-SENSING ION CHANNELS, while inflammatory responses activate cyclooxygenase and release multiple cytokines and chemokines as well as interleukins. Tumor cells directly destroy sensory nerves by infiltration or compression or cause remodeling which leads to hyperinnervation or denervation. Bone metastases extend through the cortex and compress and/or stretch periosteal nerve endings [75].

Within the bone, osteoclasts are activated by a tumor-derived RECEPTOR ACTIVATOR OF NUCLEAR FACTOR KAPPA-B LIGAND (RANKL) which binds to RANK receptors. RANKL is not only produced by a local tumor but also by stromal cells, surrounding T cells and osteoblasts [76, 77]. Osteoclastic activation not only leads to bone destruction and mechanical pain but also increases to local tissue acidosis and activation of multiple ion channels (ACID-SENSING ION CHANNELS, TRANSIENT RECEPTOR POTENTIAL VANILLOID-1) which stimulates sensory nerves within the bone. Local release of TRANSFORMING GROWTH FACTOR-BETA and INSULIN-LIKE GROWTH FACTOR-1 stimulates more tumor growth [78]. Osteoprotegerin, denosumab (an antibody which neutralizes RANKL), and bisphosphonates inhibit osteoclast activation and reduce skeletal-related events as well as pain [79, 80].

Infiltration of tumor by inflammatory cells including macrophages, mast cells, neutrophils, and T lymphocytes causes a release of a multitude mediators which causes pain and hypersensitivity (growth factors, cytokine, bradykinin, ATP, chemokines, prostaglandins, endothelins) [81]. As a result, it is unlikely that a single agent such as an NSAID which targets a single mediator will have a major impact on cancer pain [75, 82]. The use of multiple agents which have complementary targets is more likely to be successful in reducing pain [75, 82].

Cancers cause a remodeling of sensory and sympathetic nerves, causing growth and sprouting that leads to neuroma-like structures which spontaneously fire resulting in unprovoked pain which is responsible for complex regional pain syndromes in cancer [83, 84]. Neuroma formation is caused by Nerve Growth Factor arising from tumor metastases. Nerve growth factor stimulates sensory nerves and increases the expression of multiple transmitters, receptors, and channels leading to hypersensitivity and neuropathic pain. Anti-nerve growth factor antibodies are a potential pathway to palliate cancer pain [75].

Peripheral afferent input to the superficial dorsal horn occurs from growing cancer metastases. Neuroplastic changes from continuous input changes the spinal cord resulting in a greater proportion of wide dynamic range neurons activated. Wide dynamic range neurons become hyperexcitable to mechanical, thermal, and electrical stimuli and project largely to areas in the brain that influence the affective component of pain (limbic system). Persistent activity of these neurons can lead to anxiety, depression, and sleep disorders [85]. Gabapentinoids and low-dose ketamine dampen white dynamic range neuron responses which may be the mechanism responsible for improved sleep and mood seen with these agents [86–88].

## Cancer Pain Classification

The Edmonton Classification System for Cancer Pain (ECS-CP) has been used to characterize pain complexity based on five prognostic fea-

tures: pain mechanisms (neuropathic or nociceptive), presence or absence of incident pain, psychological distress, addictive behavior, and cognitive dysfunction. Each of these features has been found to predict for high pain complexity and difficulty in achieving adequate analgesia [89]. In a study of 1070 adult patients with advanced cancer recruited from 17 sites in Norway, the United Kingdom, Austria, Germany, Switzerland, Italy, Canada, and Australia, 670 (64%) were assessed by a clinician as having cancer pain: nociceptive pain ($n$ = 534; 79.7%), neuropathic pain ($n$ = 113; 16.9%), incident pain ($n$ = 408; 60.9%), psychological distress ($n$ = 212; 31.6%), addictive behavior ($n$ = 30; 4.5%), and normal cognition ($n$ = 616; 91.9%) [90]. Successful documentation of the ECS-CP is a challenge and requires simplification and intensive education fully adopt the system. Physician compliance can be a challenge [91].

## Pain Assessment

A systematic and comprehensive pain assessment as standard of care is critical for good cancer pain management. Assessment should include the patient's "total pain" which includes the spiritual and psychosocial background and concerns patients have. Past medical history should include previous analgesic responses and activities of daily living, history of sexual abuse as a child (a risk factor for drug misuse), and a personal or family history of drug abuse. Active depression and anxiety disorders reduce responses to analgesics. Patients often have multiple pains, and each should be classified and characterized. A standard assessment tool like the Brief Pain Inventory characterizes pain and its impact on cognition, function, mood, sleep, and appetite. In follow-up, a numerical rating scale (NRS), categorical scale (CRS), or visual analog scale (VAS) is used to determine pain responses. A VAS is the least favored scale and should be used cautiously. Most patients will have a scale preference with high intrapatient consistency in choice of scales with follow-up. Numerical rating scales are generally preferred by the majority of patients [92]. The personalized symptom goals for pain have been reported to be $\leq$3 on a NRS for most patients. Personalized goals allow clinicians to tailor treatment to patient-specific outcomes while adjusting for individual differences in scale interpretation and factors associated with symptom response [93]. Alternatively, pain assessment using the PQRST mnemonic can be used as a guide to pain assessment (pain severity, quality, location or region, radiating characteristics or referral pattern, provoking and relieving factors and temporal pattern). Unfortunately, clinical practice guidelines about pain registration and assessment are poorly implemented in oncology outpatient clinics [94].

Once obtaining a history and physical assessment, the presumed etiology is often clear particularly if previous radiographs are reviewed. The inferred pathophysiology is categorized into a pain syndrome which can be established in the majority. Further radiographic procedures should be guided by a thorough and complete pain assessment [95, 96]. Radiographs are not substitutions for a good pain history and thorough physical examination.

Additional pain outcomes to pain management include physical function, activities of daily living, and role within the family. Mood and coping may be impaired by pain and alternatively depression, anxiety, and catastrophizing impair analgesic responses. Pain impairs sleep, and impaired sleep produces hyperalgesia [97, 98]. It is important that clinicians not become narrowed in their focus and limit the definition of response to pain intensity alone. Secondary outcomes may be more important to patients than reduction in pain intensity. In fact, pain severity is influenced by a multitude of factors, by pain beliefs, catastrophizing, or pain interference over and above any effects of pain intensity. Individuals with greater pain interference, pain catastrophizing, and a number of pain-related beliefs have more severe pain intensity than those without these factors [99]. These will need to be addressed in order to improve pain responses to analgesics.

## Treatment of Cancer Pain

One way to treat cancer pain is to treat the cancer. Surgery, radiation therapy, chemotherapy, and targeted agents can reduce the cancer burden and

reduce pain. However, it may take time. Response to radiation may take 2 weeks after radiation is completed which means analgesics will be needed in the interim [100]. In this setting the dosing strategy may be to use short-acting opioids as needed rather than exposing patients to sustained release opioids. Certain cancers such as lymphoma, multiple myeloma, breast cancer, ovarian cancer, testicular cancer, and small-cell lung cancer will respond quickly to chemotherapy; chemotherapy should not be delayed until "pain is under control." Surgery and/or radiation therapy for bone metastases is more likely to be successful in managing breakthrough incident pain than the use of a rapid-acting fentanyl. Even re-irradiation for symptom control can be successful but not for all cancers [101–103]. Stereotactic radiation limits the amount of normal tissue exposed to re-irradiation and can be delivered in only a few fractions which reduces the patient's travel time and the burden of therapy [104]. However, a recent study of stereotactic body radiation for recurrent head and neck cancer led to significant toxicities and had adverse effects which have to be weighed against in pain [105]. Balloon kyphoplasty and vertebroplasty can successfully reduce pain related to cancer-associated vertebral fractures [106, 107]. Cryotherapy can be considered in areas previously radiated [108]. Combining cryotherapy with radiation may improve pain control over single-modality therapy [109]. Microwave ablation and cementoplasty have also successfully palliated bone metastases [110]. Ethanol injections into bone metastases and radiofrequency ablation have also been used [111]. Rhenium, samarium, and strontium isotopes can reduce pain from bone metastases in the majority often within days. Rhenium is associated with less myelosuppression [112].

## Pharmacological Management of Cancer Pain

Patients with advanced cancer are usually older and have multiple comorbidities which will influence the choice of analgesics. Patients with significant heart failure or advanced liver disease should not receive NSAIDs. Individuals with Child-Pugh class C cirrhosis should be treated preferably with morphine or hydromorphone since both opioids are glucuronidated which is relatively spared in advanced liver disease. Oxycodone, fentanyl, and tramadol depend on mixed function oxidases for clearance, and the half-life of these drugs is significantly prolonged in advanced liver disease. Individuals with unstable renal function should be considered for methadone or buprenorphine [113–117]. Individuals with COPD are at increased risk for sleep disorders; altered breathing on opioid therapy may not only produce symptoms such as fatigue and daytime sleepiness but also increase cardiovascular events particularly at night [118–120]. Patients with major and organ dysfunction in general should be treated with short-acting opioids and perhaps initially start on an "as needed" basis rather than being placed on long-acting opioids around the clock. Comorbid illnesses both increase the bioavailability of opioids and prolong the opioid half-life.

Opioids have a bidirectional effect on anxiety and depression. Depression reduces analgesic responses and pain thresholds. Opioids in the past have been used to treat depression [121]. Low-dose transdermal buprenorphine reduces suicide ideation [122, 123]. Patients can somatize their depression and "successfully" respond to opioid therapy. On the other hand, recent studies found that long-term opioid therapy can precipitate depression in individuals who do not have a history of depression [28, 124]. Therefore, depression should be treated simultaneously with pain management. Physicians should not assume that the patient's mood disorder is caused by pain and rely on opioid therapy to treat the patient's mood.

Physicians should assess patient expectations and goals for pain management. This also includes patient concerns, fears, and barriers to opioid therapy. Patient and family education about opioid therapy, risks, and benefits goes a long way in reducing barriers. Establishing individual goals to opioid therapy produces a sense of hope. Tailoring goals to reasonable expectations will improve satisfaction with therapy and the reality of what can be accomplished.

## Opioid Dosing Strategies

The World Health Organization (WHO) analgesic stepladder now is over 30 years old. In general, most patients respond when pain management is directed by the analgesic ladder [125, 126]. The WHO bases analgesic choices ± adjuvant analgesics on pain severity alone. In recent years the WHO analgesic ladder has been modified to a two-step ladder where low doses of potent opioids replace "weak" opioids in step two [127]. There are multiple choices for frontline potent opioids. Morphine, oxycodone, transdermal fentanyl, and buprenorphine are equally affected in reducing pain over a 4-week period. Nonresponders range from 10% to 15%. Each opioid analgesic does require titration to pain control. The need to switch from one opioid to another ranges between 12% and 22%. Discontinuation of treatment ranges from 15% to 27%. Adverse drug reactions are similar except for central nervous system toxicity which may be higher with morphine [128]. The WHO analgesic stepladder does not provide directions as to which opioid to use or how to dose the opioid to temporal changes in pain. The focus is entirely on intensity as the major outcome and not function or pain interference. The WHO analgesic stepladder was developed for cancer pain and should not be used for non-cancer pain [129]. Additional important principles to opioid therapy include using opioids preferably by mouth, using opioids around the clock, and individualizing therapy to the patient and clinical context.

Potent mu agonists are recommended over "agonist/antagonists" and "partial agonists." However, there is little evidence to substantiate this recommendation, and there are no randomized trials in cancer which give evidence to such a recommendation. Recent studies suggest that these opioids have a distinctly different pharmacology than potent opioids. Buprenorphine, nalbuphine, and butorphanol analgesia involve activation of six transmembrane and seven transmembrane mu receptors, whereas morphine and methadone are dependent on seven transmembrane receptors alone [130, 131]. In a recent systematic review nalbuphine demonstrated similar analgesia as morphine in managing acute pain but had significantly fewer side effects (nausea, respiratory depression, and pruritus) [132].

The opioid dosing interval should be based on the opioid half-life, and dose titration should be based upon study state. Short-acting opioids around the clock (every 4 h) should not have doses changed for 20–24 h. Oral sustained-release opioids should not be changed until 48 h, and transdermal fentanyl should not be changed before 72 h. Methadone is complicated and has a complex pharmacology with wide individual differences in drug half-life. In general methadone doses should not be changed for 5–7 days [133]. For pain, in between a breakthrough, a short-acting opioid should be available. Reasonable starting doses include short-acting morphine 5 mg every 4 h, oxycodone 5 mg every 4 h, and hydromorphone 1 mg every 4 h. Sustained-release morphine 15 mg every 12 h and sustained-release oxycodone 10 mg every 12 h are reasonable starting doses. Fentanyl at 12 μg/h has been used in opioid-naive individuals. Methadone starting doses are 2.5 mg every 8–12 h. In the frail elderly, lower doses should be used (morphine 2.5 mg, oxycodone 2.5 mg). For patients who continue to have pain at steady state, rescue doses for non-incident pain should be added, and the total dose of opioid increased by 25–50%. This does not apply to methadone. Short-acting potent opioids are used with methadone for breakthrough [133]. If pain persists before reaching steady state, then the breakthrough dose can be increased by 50–100%. For severe uncontrolled pain, frequent small doses of a potent opioid (morphine 1 mg, fentanyl 20 mcg, hydromorphone 0.2 mg) are given subcutaneous (SC) or intravenous (IV) every 1–5 min until pain control by clinician based bedside titration. Once pain is significantly reduced (10–6 on a NRS), a continuous infusion of 1/3 to 1/4 of the effective dose is given hourly by continuous infusion, or the effective dose is given every 4 h as a bolus dose. Patient-controlled analgesia (PCA) administration after clinician titration can be used with appropriate close follow-up every 2 h initially [134, 135].

Rescue doses of short-acting opioids are used during titration and for incident or spontaneous breakthrough pain once the underlying chronic pain is well controlled. Standard rescue doses are 10–15% of the total daily opioid dose. Most patients will have breakthrough pain, and so a rescue dose should be added to the around-the-clock opioid [136]. Breakthrough pain is divided into spontaneous and incident pain; incident pain is divided into voluntary and involuntary. End-of-dose failure is the result of suboptimal around-the-clock opioid doses and is no longer classified as a breakthrough pain [137]. The proper management of end-of-dose pain is to increase the around-the-clock dose. Rapid-acting fentanyl (SL, buccal, and intranasal) has been developed for breakthrough pain. Rapid-acting fentanyl products do result in more rapid analgesia relative to short-acting morphine and oxycodone [138]. The number needed to treat to benefit one patient with rapid-acting fentanyl products relative to oral immediate release morphine or oxycodone is 10. These products are expensive and long-term safety may be a concern [139, 140]. The National Institute for Health and Clinical Excellent (NICE) guidelines for opioid therapy in palliative care recommend using short-acting oral potent opioids first and rapid-acting fentanyl products as second-line opioid therapy for breakthrough pain poorly responsive to oral short-acting opioids [141].

## Acute Opioid Toxicity

During the titration phase of opioid therapy, it is vitally important that patients be reassessed on a regular basis and families educated about potentially emerging opioid toxicities. Drowsiness, constipation, and dry mouth occur in more than half of patients. Adverse drug-related toxicities judged as moderate or severe by patients are occur in half of patients on opioid therapy. Dry mouth, early satiety, nausea, vomiting, and constipation occur similarly between potent opioids [128]. In a recent study, neurotoxicity was more frequent with morphine (13%) than with oxycodone, buprenorphine, or fentanyl [128]. Severe myoclonus occurs in approximately 5% of morphine-treated patients and was not seen with oxycodone. Severe confusion is found to be less frequent with fentanyl (6%) than with morphine (15%) [128].

Laxatives should be used to prevent opioid-induced constipation. Polyethylene glycol is safe and effective [142]. Senna, bisacodyl, lactulose, and sorbitol have been used. A reasonable approach is to start with polyethylene glycol and, if there is no response, add a stimulating laxative like senna. Oral sustained-release naloxone has been licensed for patients with non-cancer pain who have opioid-induced constipation [143]. For those who have constipation not responding to oral laxatives, enemas (mineral oil or cottonseed oil), or a peripheral restricted opioid receptor antagonist, like methylnaltrexone, may produce laxation [144]. Lubiprostone is also now licensed for opioid-induced constipation and could be tried when laxatives fail [145]. The narcotic bowel syndrome is characterized by the paradoxical abdominal pain associated with continuous or increasing dosages of opioids and may be associated with constipation. It appears to be a visceral hyperalgesic response to opioids and will not respond to opioid antagonists. Patients only have relief when opioids are withdrawn.

Opioids can cause nausea at the beginning of therapy in opioid-naive individuals. Tolerance to this side effect can occur rapidly. Mu receptors within the area postrema are emetogenic, but receptors within the central pattern generator are antiemetic [146]. There are few trials to guide therapy in regards to nausea. Metoclopramide is a reasonable choice as an antiemetic due to its prokinetic effects [147].

## Opioid Rotation

If the patient experiences intolerable side effects but pain is controlled, then opioid dose reduction by 30% is the most reasonable approach to management. However, if patients are having significant opioid-related side effects and pain is poorly controlled, then opioid rotation is one of several approaches that can be tried to reduce side effects and improve pain control. It is also important to realize that opioids can cause paradoxical pain,

that is, as opioids are titrated pain increases which will improves with opioid dose reduction [148]. Alternatives to opioid rotation include aggressive management of side effects, route change to spinal analgesia, or opioid dose reduction with the addition of an adjuvant analgesic.

Opioid rotation is successful because opioids are relatively or partially non-cross tolerant analgesics. This likely reflects the fact that each opioid can stabilize the mu receptor in a unique confirmation which changes downstream signaling. Each opioid ligand interacts with a different set of mu receptor subtypes. In addition, metabolites of the opioid may be responsible for side effects, and changing routes (i.e., spinal analgesia) directs opioids to spinal and supraspinal mu receptor sites and reduces the level of metabolites thus increasing the therapeutic index of the opioid [149].

It is tempting to do several changes at once particularly when patients are in severe pain. Changing drug and route and adding an adjuvant analgesic confuses patients and does not allow physicians to gauge what seems to have worked to reduce the pain intensity. At the end of the day, one will not know what worked or even worse what made the patient worse. It is better to change drug and route or add an adjuvant analgesic and assess response rather than doing several changes at one time.

There are important steps to choosing an opioid for rotation. Select an opioid based on a patient's prior experience, regional opioid availability, cost, and organ function and comorbidities. Use equianalgesic tables (see Table 2.1) for a guide to rotation, realizing that equianalgesic tables are not opioid conversion tables. Many equianalgesic tables were constructed based on single doses in opioid-naive individuals, in individuals without comorbidities, and in individuals who are not on polypharmacy. Most patients for whom rotations are performed are older, are opioid tolerant, have significant comorbidities, have organ dysfunction, and are on polypharmacy [150–152]. When rotating opioids for side effects, reduce the equianalgesic dose by 25–50%; when rotating for uncontrolled pain, maintain doses near equianalgesic doses. Thereafter doses should be adjusted based on the clinical situation (comorbidities, organ function, polypharmacy). Equianalgesic tables are notoriously inaccurate at high opioid doses. Further dose reductions should be done in this situation. Methadone is an exception because of its unique pharmacology. Methadone dose reductions should be 75–90% and should not be started at greater than 30–40 mg/day regardless of the previous opioid dose [150–152].

**Table 2.1** Equianalgesic table

| Opioid | Oral | Parenteral |
|---|---|---|
| Morphine | 30 mg | 10 mg |
| Oxycodone | 20 mg | – |
| Hydromorphone | 6 mg | 2–3 mg |
| Oxymorphone | 10 mg | 1 mg |
| Fentanyl | – | 0.25 mg |
| Buprenorphine | 0.6 (SL) | 0.3 mg |
| Tapentadol | 100 mg | – |
| Tramadol | 300 mg | – |

## Long-Term Opioid Toxicity

Chronic toxicity from opioids is different from acute toxicity. Tolerance can develop to many of the acute toxicity-related opioids, and opioid rotation is frequently helpful. Opioid rotation is not known to reduce long-term toxicity. Opioids are associated with increased cardiovascular events to the same extent as NSAIDs [153, 154]. Methadone prolongs the QTc interval and is associated with torsades de pointes [155]. Opioids cause urinary retention in 4–18% of treated individuals. Opioids reduce detrusor muscle tone and force during urinary contraction which may be reversed by the peripheral restricted antagonist, methylnaltrexone [156, 157]. Opioids are associated with an increased risk of falls and fractures in the elderly. This is mainly due to reduced alertness and dizziness [158]. The risk is dose dependent. Weak opioids such as tramadol are also associated with a falls risk. Opioids are strongly associated with wound dehiscence after abdominal and pelvic surgery [159]. Opioids increase keratinization but prevent neutrophil and macrophage recruitment to the wound delaying bacterial clearance, reducing wound angiogenesis, and impairing myofibroblast recruitment to the wound [160, 161]. Opioids are associated

with an increased risk for pneumonia in the elderly and in those with COPD. Opioids increase mortality from pneumonia [162, 163]. Opioids produce a central hypogonadism leading to reduced libido, sexual dysfunction, depression, fatigue, and sarcopenia as well as osteoporosis [164–166]. Chronic opioids reduce working memory and verbal fluency. Cognitive changes have been particular to those with cancer on long-term opioids [167, 168]. Most individuals on opioids will have sleep-disordered breathing (central sleep apnea and/or obstructive sleep apnea) due to the effect of opioids on pre-Bötzinger neurons which generate the respiratory cycle with inspiration and opioid-related interference with upper pharyngeal dilators during inspiration [169, 170]. Nocturnal hypoxemia from sleep-disordered breathing increases the risk for arrhythmia and sudden death. This is likely the reason for the increased mortality found when long-term opioids are used for chronic non-cancer pain and COPD [5, 171].

Because of these significant long-term side effects of which many are related to dose, early opioid rotation should be done in those not responding to opioid titration, and opioid sparing should be attempted with early use of adjuvant analgesics. Radiation, surgery, and other non-pharmacologic approaches (such as a celiac block, cognitive behavior therapy, etc.) should not be reserved until the patient's pain has failed to respond to several opioids or the patient is on high opioid doses (200 mg morphine equivalents per day). Cancer survivors should be weaned off opioids as a standard procedure.

## Adjuvant Analgesics

### Acetaminophen

The mechanism of acetaminophen analgesia remains obscure. One mechanism proposed is fatty acid amide hydrolase-dependent metabolism of acetaminophen into a metabolite which indirectly involves cannabinoid CB(1) receptors by this metabolite followed by endocannabinoid-dependent reinforcement of the serotonergic bulbospinal pathways and spinal pain-suppressing serotonergic receptors [172]. Doses should be limited to 4 g/day in the healthy, 3 g in the elderly frail, and 2 g in those with liver disease and should be avoided in those who are abusing alcohol. Hepatotoxicity is associated with reduced glutathione and is reversed by acetylcysteine [173]. NSAIDs are more effective than acetaminophen for most painful conditions [174]. There is very little evidence from systematic reviews that NSAIDs or acetaminophen adds to opioid analgesia for various painful disorders [175]. Because of the differences in mechanisms of action between NSAIDs and acetaminophen, the combination appears to be superior relative to each analgesic alone [176, 177].

### Nonsteroidal Anti-inflammatory Drugs

NSAIDs are classified as such due to the ability to inhibit cyclooxygenase (COX) 1 and 2. Analgesia though is unrelated to the degree of cyclooxygenase inhibition. Analgesia may be related to central actions mediated by endogenous opioid peptides or blockade of the release of serotonin (5-hydroxytryptamine; 5-HT or inhibition of excitatory amino acids of *N*-methyl-D-aspartate receptor activation [178]. Both COX 1 and 2 inhibitors produce renal toxicity, cause fluid retention, and impair diuretic therapy, resulting in resistance to antihypertensives. Neither COX 1 nor 2 inhibitors should be prescribed for those with significant heart failure or renal dysfunction. Both should be avoided in the elderly and the lowest effective dose should be used. COX 2 inhibitors have relatively less gastrointestinal toxicity and risk of bleeding due to platelet dysfunction, but both COX 1 and 2 inhibitors are associated with increased cardiovascular events and thrombosis. Both inhibitors should be avoided in severe liver disease [179–182]. Commonly used NSAIDs and dose are ibuprofen 400–600 mg every 6–8 h, naproxen 250–500 mg every 8 h, and celecoxib 100–200 mg twice daily.

## Glucocorticoids

Glucocorticoids have been used as adjuvant analgesics to reduce headache from brain metastases, bowel obstruction, and tumor-related compressive neuropathy. In a systematic review, the evidence for the efficacy of corticosteroids for pain control in cancer patients is weak. Significant pain relief was noted in some studies, albeit only for a short period. On a numerical scale of 0-10, the mean difference in pain was -0.84 (95%CI -1.38 to -0.30) with low quality evidence [183]. Corticosteroids given in modest doses are well tolerated for up to 7 days. Corticosteroids have serious toxicities and result in higher mortality when administered in high doses over 8 weeks [184]. Corticosteroids improve cancer-related anorexia and fatigue [185, 186]. Corticosteroids can alter mood and cause insomnia, cognitive dysfunction, and psychosis. Though corticosteroids increase appetite, this class of drug accelerates myopathy and causes lower extremity muscle weakness and sarcopenia. Initial doses should be moderately high (dexamethasone 8 mg once in the morning or at 8 AM and at noon) and rapidly tapered to the lowest effective dose [187].

## Tricyclic Antidepressants

Tricyclic antidepressants have multiple mechanisms by which pain is reduced. One mechanism involves increased spinal norepinephrine levels. Tricyclics reduce neuroinflammation and long-term potentiation as another mechanism [188]. Analgesia occurs at lower doses than those required for depression. The secondary amine tricyclic antidepressants (nortriptyline and desipramine) are preferred because secondary amines are less anticholinergic than amitriptyline. Tricyclic antidepressants should be avoided in those with heart failure, and in those who have a cardiac conduction defects or arrhythmia. This class of antidepressant should also be avoided in prostatic enlargement associated with slow urination and narrow-angle glaucoma. Initial nortriptyline and desipramine doses are 10–25 mg at night with a slow titration at 5–7 day intervals [189].

## Serotonin-Norepinephrine Reuptake Inhibitors

Duloxetine and venlafaxine are better tolerated than tricyclic antidepressants, and even though this class of drugs is not as effective as tricyclic antidepressants based on numbers needed to treat, it is a preferred class because in general SNRIs are better tolerated. Milnacipran, mirtazapine, and desvenlafaxine may also be considered members of this class of drugs [190–193]. Although tricyclic antidepressants, gabapentinoids, and duloxetine all increase spinal norepinephrine levels, duloxetine uniquely improves conditioned pain modulation [52]. Duloxetine is the only adjuvant analgesic which has been shown to reduce neuropathic pain from chemotherapy [194, 195]. Venlafaxine has been reported to reduce acute neuropathic pain from oxaliplatin and taxanes, but a recent trial was negative [196–199]. Venlafaxine reduces hot flashes related to estrogen deficiency [200, 201]. Both SNRIs can cause nausea and insomnia and should be taken in the morning. Duloxetine doses need to be reduced in the face of renal and hepatic failure. Both are metabolized by mixed-function oxidases and so subject to drug interactions. Starting venlafaxine doses are 37.5 mg and titrated to 225 mg/day. Duloxetine starting doses are 30 mg titrated to 60 mg in the morning 1 week later.

## Gabapentinoids

Gabapentinoids (gabapentin and pregabalin) prevent the surface expression of the alpha2-delta subunit of the calcium channel but also dampen neuroinflammation and increase spinal norepinephrine levels [202]. Gabapentin is absorbed in the small bowel by a neutral amino acid transporter which is saturable. Thus, a disproportionate lesser amount of gabapentin is absorbed at higher doses [203]. Pregabalin is also absorbed by diffusion and thus not limited to a transporter mechanism for bioavailability. Both gabapentinoids are dependent of glomerular filtration for clearance; doses will need to be reduced with renal dysfunction. There are few drug interactions since they do not depend on mixed

function oxidases for clearance. Initial gabapentin doses are 300 mg at night, 300 mg twice daily the next day, and then 300 mg three times daily. Therapeutic doses are 1800 mg/day though higher doses (3600–4200 mg/day) have been found to be effective [204]. Single high doses of gabapentin (600–1200 mg) and pregabalin (250–300 mg) can reduce severe acute pain and reduce postoperative opioid requirements [205]. Gabapentin has other symptom benefits which include reduced pruritus related to renal failure and treatment of anxiety, insomnia, nausea, hiccough, and cough unresponsive to usual measures. Side effects to gabapentinoids include sedation, confusion, edema, dizziness, gait disturbances, and myoclonus. Gabapentin and pregabalin can be abused [206].

## Cannabinoids

Cannabinoids are popular as analgesics, but the benefits in cancer pain are limited. The combination of tetrahydrocannabinol plus cannabidiol reduces pain at low doses. However two recent trials of the combination by GW Pharm have been negative for the primary endpoint of the trial. There appears to be an analgesic ceiling at 20 mg per day. Tetrahydrocannabinol 10–20 mg/day is equivalent to 60–120 mg of codeine daily [207].

### Conclusion

To manage cancer pain well, one needs, as a minimum, a thorough assessment of the pain and patient and a good understanding of opioid pharmacology. Adjuvant analgesics are extremely beneficial when added to opioids to improve pain, limit opioid dose titration, and reduce opioid side effects. Physicians are often overreliant on opioids alone. Cancer pain should be managed using an interdisciplinary team of multiple specialties to effectively reduce the patient's "total pain."

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# Cancer-Related Fatigue

3

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## Introduction and Significance

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms experienced by cancer patients [1, 2] and often is more distressing than pain, nausea, or vomiting [3]. CRF may be dose-limiting, may compromise the timing and frequency of treatments [2], and may also affect treatment adherence and survival [4]. Despite its frequency and negative impact, CRF remains underreported, underdiagnosed, and undertreated [1].

## Prevalence Rates

Approximately 70–100% of cancer patients experience CRF at some time during diagnosis and treatment [1]. Prevalence rates vary from 25% to 99% [5, 6] depending on the type of treatment, dose and route of administration, type and stage of cancer, and the method and timing used to assess CRF [7]. In patients receiving chemotherapy (CT), 80–90% report CRF, and its prevalence rates and patterns over time may vary with the specific CT agent, its route of administration, and the frequency and density of treatment cycles. Less is known about CRF's prevalence rates and patterns prediagnosis [2] and in patients receiving oral or targeted CT agents [7]. Few researchers have examined fatigue in surgically treated or hospitalized cancer patients. One group reported an increase in fatigue in cancer patients that was associated with a longer period of hospitalization [8].

During radiation therapy (RT), CRF is an almost universal occurrence with 70–100% of patients experiencing a gradually increasing cumulative pattern of CRF over time that peaks and plateaus usually at 4–6 weeks after treatment initiation and gradually declines thereafter. Patients need to be forewarned about the possibility of experiencing this type of CRF pattern, as they may feel that their disease is getting worse instead of better and may fear that their treatment is not working [1, 7]. Increased CRF may be reported when different therapies such as RT and CT are used in combination [9].

In patients treated with biologic-response modifiers or biotherapy, such as interleukin-2 and interferon-α, CRF may be dose-limiting [7]. A prevalence rate of 70% is reported in patients receiving interferon therapy [10]. Fatigue in can-

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cer patients receiving hormonal therapy has not been well studied [10, 11]. Increased levels of CRF are reported by patients with advanced malignancies [12, 13] and in those who have other illnesses or comorbidities [14]. In patients with metastatic disease, for example, fatigue prevalence rates may exceed 75% [1, 7].

## Definition(s)

Many definitions for CRF exist in the literature [7]. One commonly used definition proposed by the National Comprehensive Cancer Network (NCCN) states: CRF is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1].

There is an emerging consensus for clinicians and researchers to develop a "case definition" for CRF in order to make it easier to compare results across studies [7, 15]. At present, many researchers use a "cut score" of ≥4 on a 0–10 numeric rating scale (NRS) during the past week, where "0" = no fatigue and "10" = worst fatigue, to distinguish between those who do and do not have fatigue and define fatigue severity as mild (0–3), moderate (4–6), or severe (7–10) [1, 16–19].

In 1998, the first attempt to develop a case definition included a set of diagnostic criteria for the syndrome of CRF [20]. Developers planned to include these criteria in the US version of the World Health Organization's International Classification of Diseases-10 Clinical Modification (WHO ICD-10-CM), but the criteria were never submitted to the Centers for Disease Control and Prevention (CDC) (D. Pickett, personal communication, December 8, 2008). At an international CRF consensus conference in 2009 [21], it was acknowledged that these criteria were based on clinical experience rather than research [7] and were intended to identify patients with fatigue who were receiving chemotherapy every 2 weeks. In retrospect, it seems these criteria may have "set the bar too high," as many patients who otherwise reported fatigue did not fit these criteria.

At that same CRF consensus conference, participants concluded that there were probably different phenotypes [22] or manifestations for CRF, across the cancer illness and treatment trajectories (i.e., active treatment, survivorship, and palliative end-of-life care) and that more research was required to determine if this was the case [7]. This conclusion was reached, in part, because symptoms of CRF such as weakness tend to be more common in palliative care patients with advanced or incurable malignancies [12], who also may be experiencing anorexia, weight loss, and the loss of muscle mass. Reports of weakness are less common in descriptions of CRF in earlier-stage patients, such as women undergoing treatment for breast cancer or men receiving hormonal ablation therapy for prostate cancer [7, 23].

## Underlying Mechanisms

Cancer type and stage, as well as the type or intensity of oncology treatment, may differentially impact the biology and phenotype of CRF [2]. Because these treatments work through distinct pathways and generate different CRF phenotypes, they likely cause fatigue through different mechanisms. Evidence for this is seen by the fact that while radiotherapy triggers an increased inflammatory response, chemotherapy tends to suppress the inflammatory response [24]. These distinctions also help illustrate why clear characterization of CRF is important for further etiological investigations.

Despite the prevalence of CRF, little is known about CRF's underlying mechanisms. Overall proposed etiologic mechanisms of CRF from recent reviews implicate immune system dysregulation, impaired nerve conduction, neuroendocrine and neurotransmitter dysregulation, and energy depletion [25–27]. The proposed models to explain mechanisms of CRF are derived from the concept that CRF is either central or peripheral in origin. Central mechanisms proposed include disruptions in basal ganglia and frontal lobe function, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and enhanced pro-inflammatory cytokine release affecting neuronal metabolism [24, 28–30].

It is believed that changes in inflammatory mediators in fatigued cancer patients may lead to 5HT receptor and serotonin dysregulation, leading to a cycle of neurotransmitter and cytokine disturbances [31]. Moreover, pro-inflammatory cytokines are believed to be initiators of fatigue, where they can act directly on the brain to affect neural metabolism [32]. A recent report highlights the influence of circadian rhythm changes and sleep disturbances in mediating the effects of inflammation in cellular energy availability and non-adaptive energy expenditure that can contribute to CRF [33]. This mounting evidence suggests that inflammation-induced reduction in cellular energy can explain the underlying mechanisms of cancer-related neurotoxic symptoms including CRF [34]. Cytokines are believed to impact the brain via four main pathways: (a) activation of the vagus and other afferent nerves with consequent signaling to the brain, (b) secretion by circumventricular organs, (c) active and passive transport across the blood–brain barrier (BBB), or (d) active secretion by BBB cells [35]. The basic elements of the frontostriatal network, including the basal ganglia and frontal cortex, have been found to be the targets of these inflammatory mediators as well as the site where significant alterations in activity and function have been observed in chronic inflammatory conditions that are plagued by fatigue [36–38].

Peripherally, impaired muscle cell membrane activity, peripheral nerve conduction, and other neuromuscular abnormalities are thought to contribute to CRF [39, 40]. It is proposed that systemic inflammation causes significant changes in cellular metabolism including an increase in resting energy expenditure which can compromise membrane integrity disrupting cellular homeostasis causing a net loss in muscle mass resulting in muscle wasting and generalized weakness [41]. The accumulation theory hypothesizes that waste product collection outpaces the body's ability to dispose them, whereas the exhaustion theory proposes that essential substances integral to muscle activity are not available or have been depleted [42, 43]. Lastly, mitochondrial genetic [44] and enzymatic dysregulation [45] have also been associated with CRF, with the proposed downstream pathobiologies being ATP depletion and impairment of mitochondrial bioenergetics, resulting in reduced cellular-energy availability due to cancer treatment-induced genetic instability and cellular damage. Associations between fatigue and specific genetic polymorphisms related to regulatory pathways of immune and neurotransmitter systems have been explored, but not adequately in CRF [46]. While the potential for involvement of these diverse mechanisms has been demonstrated, no biomarker has been consistently associated with CRF in large sample studies [25, 26, 29, 47, 48].

## Assessment

Several clinical practice guidelines for CRF are currently available [49–51]. Most guidelines recommend a two-step assessment process comprised of screening, followed by a more in-depth assessment process dependent on the CRF level.

## Screening

Most guidelines state that all patients should be screened for the presence or absence of CRF at their first visit and at each subsequent visit. If CRF is present, the guidelines recommend that a simple 0–10 numeric rating scale (NRS) be used to assess CRF intensity (0 = no fatigue; 10 = worst fatigue you can imagine). Patients can be asked directly: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?" Mild fatigue is indicated by a 1–3 score, moderate fatigue by a 4–6 score, and severe fatigue by a 7–10 score [52]. For patients who are unable to assign a number to their fatigue, using the words "none, mild, moderate, and severe" is recommended [52].

As baseline CRF severity levels have been shown to be predictive of severity levels over time in patients undergoing treatment [53], it is important to assess and document these levels before patients begin treatment and to repeat and compare these screening assessments periodically over time during treatment [7]. Because CRF can persist for months, even years following

treatment cessation, repeated assessments post-treatment are recommended [52, 54]. These assessments can be supplemented by having patients' complete daily diaries prior to their next clinical visit [7]. Previous report showed moderate associations in assessing CRF using patient-reported outcomes and functional performance status, offering unique information that can improve the assessment of CRF [55].

## Focused Workup

The focused workup helps health-care providers develop a differential diagnosis for CRF that can be used to inform treatment decisions. A focused workup is recommended for patients who are experiencing moderate to severe levels of CRF (4–10 on the 0–10 NRS). This recommendation was supported by a previous study which confirmed that patients with less severe CRF had significantly better total quality of life (QoL) and QoL domains scores than those with more severe CRF, using the clinically-relevant four-level criteria of categorizing CRF severity [56]

Important components of the focused workup include a detailed symptom history, an assessment of the patient's current disease status including the type and length of cancer treatment planned as well as its potential to cause CRF, and whether CRF is due to disease recurrence or progression [7]. A review of systems should also be included.

Guidelines vary slightly in terms of their recommended approaches for the focused workup, but the intention is to identify contributors to fatigue, such as other symptoms, which could potentially be managed more effectively. For example, it is important to distinguish CRF from other diagnoses such as depression [57] as the treatments may vary. It is also essential to assess the presence of common contributing and treatable factors of CRF [52, 58]. These factors include anemia, comorbidities and medication side effects, activity levels and deconditioning, emotional distress (depression and/or anxiety), nutrition, pain, and sleep disturbance [7, 52]. To improve assessment of symptoms related to cancer and cancer treatment, such as CRF especially during follow-up visits, a previous report showed moderate agreements in the US National Cancer Institute's Common Terminology Criteria for Adverse Events and PRO ratings, supporting the idea that PROs assessing symptoms can be integrated with the clinician reporting of adverse events [59]. In pediatric oncology, the Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric short form was highly correlated with the legacy fatigue measures used in this clinical population, such as the Fatigue Scale–Child and the Fatigue Scale–Adolescent when used during chemotherapy [60]. In addition, a recent review found that patients with cancer find electronic symptom reporting easy to use and can improve communication with their providers [61], offering new options to improve the assessment of symptoms associated with cancer and cancer therapy.

## Barriers to Assessment

Despite the prevalence of CRF and the availability of guidelines, assessment is still not routinely performed in many institutions and oncology practice settings [18, 58, 62]. Numerous patient-, provider-, and system-related barriers hinder the translation of these guidelines into practice settings [18, 62]. In one study, the most frequent patient-related barrier was the patient's belief that the physician would ask about CRF if it were important, followed by the patient's desire to play the "good patient role" and not bring the subject up for discussion unless the physician did. Provider- and systems-related barriers included the lack of documentation in the medical record for guideline adherence and lack of supportive care referrals [7]. When the intervention phase of this study was implemented, which included educational materials and teaching sessions for both patients and their providers [18], many of the patient-related barriers including the severity of CRF decreased over time compared to the usual care (control) group [18]. This suggests that many of the patient-related barriers to the

assessment and management of CRF including its severity can be reduced by patient and provider education.

## Management of CRF

The management of CRF is complex. There is a growing body of literature in this area, but the results are far from conclusive. In a recent meta-analysis of fatigue interventions, the authors noted that their work was the first to compare pharmaceutical, psychological, and exercise treatments for CRF [63]. In this section, we begin with an outline of general treatment principles. Next we discuss studies that explored the co-management of CRF and other symptoms that commonly occur with it. Last, we discuss the importance of building strong educational programs for providers, patients, and families.

## General Treatment Principles

Treatment must always be tailored to the patient [52], taking into account the patient's disease and treatment status, preferences, and goals of treatment [7]. Treatment planning is based on a differential diagnosis and so will vary depending on the most likely underlying cause of CRF and whether referrals to other health-care providers or supportive care disciplines are needed [52]. Treatment should be first directed at treatable factors associated with CRF [7]. It should be noted, however, that by the time patients realize that fatigue has become unusual for them, CRF most likely is multicausal and will probably require a treatment plan with multiple components [7]. If no treatable causes are identified or the patient continues to have moderate to severe fatigue despite treatment, additional workup and treatment planning must occur [52]. Each of these common contributing factors is discussed in more depth in the following sections [7].

Despite the fact that comorbidities are identified as one of the common contributing and treatable factors to CRF [52], studies of links between specific types of comorbidities and their medications and CRF are limited [7]. A few research teams are beginning to report consistent and significant findings about links between specific comorbidities such as arthritis [64], as well as the number of comorbidities and increased CRF severity [65]. The CRF guidelines recommend that each comorbidity be reviewed to determine whether any changes in the management of the comorbidity or its medications need to be made in the context of the patient's CRF [52]. Referral to an internist or specialist and/or consultation with a clinical pharmacist may be helpful [7], and patients should be advised if there are possible links between the management of their comorbidities and CRF.

### Co-management of CRF and Other Symptoms

Fatigue, like most symptoms, seldom occurs on its own. In this section we discuss a number of symptoms that frequently occur with CRF. At the end of this section, we discuss the concept of symptom clusters and some of the challenges associated with identifying and studying them.

### Reduced Activity, Deconditioning, and Muscle Weakness

Cancer patients often report decreased activity patterns and reductions in physical performance. As a consequence, deconditioning and reports of muscle weakness are common. Deconditioning is identified as one of the common contributing and treatable contributors to CRF [52]. It is therefore important that activity levels are assessed at baseline when patients are first diagnosed and before treatment begins [7]. Thereafter, they need to be periodically reassessed over time to identify changes in exercise or activity patterns and to identify if there is any evidence that deconditioning is developing due to their malignancy, CRF, other comorbidities, treatments, or other symptoms such as pain [7].

Patients need to be educated about the high risk for developing deconditioning, the multiple causes of deconditioning that can occur, and how it can lead to a downward spiral of secondary fatigue as a consequence. Based on the strength of the evidence for exercise, patients need to be edu-

cated about the need to engage in moderate levels of physical activity during and following treatment [52]. This is critically important as one of the more persistent patient-related barriers is the belief that one should rest more when fatigued and that exercise would increase rather than decrease CRF [7, 18]. Being diagnosed with cancer constitutes a "teachable" moment [66]. Patients need to be educated not only about the barriers to exercise (patient-, provider-, and systems-related) [7] but also about the other benefits of exercise that include the prevention of disease recurrence; the prevention and treatment of comorbidities such as diabetes, hypertension, and obesity; and the positive effects on sleep disturbance, depression, and cognition [52]. For patients not currently exercising, progression needs to occur slowly over time as they are taught how to monitor their own progress along with being closely monitored by trained professionals [7].

Providers may be hesitant to prescribe an exercise program for cancer patients without having cancer-specific, evidence-based guidelines specific to follow [7]. Fewer than 20% of medical oncologists recommend exercise to their patients [66, 67]. Providers may be unaware of just how powerful their recommendations for exercise prescriptions can be [7]. Maintaining or enhancing activity and exercise patterns in cancer patients has the highest level of evidence associated with decreasing CRF [52]. In a recent systematic and meta-analytic review of 57 nonpharmacologic randomized clinical trials (RCTs) [15] of exercise (physical activity, walking, yoga) and psychosocial interventions (counseling, stress management, and coping strategies), both interventions were equally and moderately effective in reducing CRF [7]. This review suggested that multimodal therapy that combines these two types of interventions into an integrative intervention trial could potentially be more likely to reduce CRF and improve vigor and vitality [15]. While more study is needed in this area, walking and multimodal exercise programs appear to have the greatest potential for reducing CRF and enhancing vigor and vitality [15]. Complementary or alternative therapies to aerobic exercise, such as Tai Chi and yoga, have shown great promise in reducing CRF [68, 69]. A recent review concluded that exercise and psychological interventions are significantly better in reducing CRF during and after cancer treatment than the available pharmaceutical options [63]. Based on these findings, it seems reasonable to encourage all patients to engage in a moderate level of physical activity during and following treatment cessation [15, 52]. For patients who are severely deconditioned, who are not currently exercising, or who have comorbidities (i.e., arthritis, COPD), recent surgery, or functional or anatomical issues, referral to health-care providers or exercise specialists such as physical therapy, physical medicine, or rehabilitation should be considered [52]. There is some evidence that exercise may be beneficial in maintaining activity patterns and reducing or at least stabilizing CRF in patients with advanced disease at end of life as well [52]. Caution is needed in tailoring an exercise prescription in patients who have bone metastases, fever or infection, anemia, thrombocytopenia, neutropenia, or immunosuppression [52]. In addition, prescribing healthy eating guidelines in combination with resistance training and aerobic exercise has been shown to improve CRF [70].

### Lack of Energy

Cancer patients frequently report a lack of energy. The connection between lack of energy and muscle deconditioning is not entirely clear. For the purposes of this chapter, we have considered lack of energy separately. The most commonly used intervention for lack of energy is energy conservation [71] and distraction techniques such as games, music, reading, and socializing [52]. Energy conservation techniques use a common sense approach to help patients prioritize and pace activities and to delegate less essential activities [52, 71]. Daily or weekly diaries can inform the patient about peak energy periods allowing them to plan their activities accordingly [52]. Energy conservation and exercise needed to be planned together to ensure that the benefits of both can be realized.

### Pain

Pain is one of the common contributing and treatable contributors to CRF [52, 72]. Pain commonly co-occurs with CRF but may be more

common in certain subgroups of patients [7]. For example, one study in 841 patients age ≥ 65 years, diagnosed with breast, colon, lung, or prostate cancers, found that women (versus men), patients with late-stage cancer (versus early stage), patients with lung cancer (versus other solid tumors), and those with three or more comorbidities were more likely to experience pain and fatigue concurrently [14]. In another study, when the control or usual care (Phase 1: $N = 83$) and intervention groups (Phase 2: $N = 104$) were combined for analysis ($N = 187$), 10.7% ($N = 20$) had pain only; 56.2% ($N = 105$) had fatigue only; and 33.2% ($N = 62$) had both symptoms [18]. Of importance, the higher the baseline pain intensity, the higher it was 3 months later ($\beta = 0.268$, $p = 0.012$). Again, this finding emphasizes the importance of assessing symptoms like pain at baseline before treatment is started and perhaps intervening earlier to prevent or lessen this symptom's intensity over time [7]. More study is needed to determine actual prevalence rates and risk factors for pain and CRF co-occurring and how treatment of one symptom or combining therapy to treat both affects this symptom cluster. See the symptom cluster discussion that follows this section [7]. For pain assessment and management, refer to the NCCN pain guidelines [73].

In addition to education about pain, its causes, treatments, associated side effects, and their management, patients need to be taught that pain is a common contributing and treatable factor for CRF [52]. They also need to be taught about barriers to effective pain assessment and management [7]. In a recent review of pain studies, patient education improved knowledge and attitudes about pain and reduced average and worst pain intensity scores [74]. Similarly, in another study, patients in the education intervention group demonstrated significantly more improvements in pain knowledge scores and fewer patient-related barriers at 1 and 3 months after the intervention compared to the control group (Phase 1) [18]. This suggests that these changes were sustained over time. Two persistent areas of lack of knowledge in the intervention group, however, were the belief that cancer pain can only be treated with medication and that pain medication can be stopped abruptly (i.e., instead of being titrated downward over time) if no longer needed [7]. For guidance on how to treat pain, please refer to the NCCN pain guidelines [73].

## Anemia

Decreased hematocrit [75] and hemoglobin levels are associated with CRF [75]. In one study, the degree of anemia (mild, moderate, severe) predicted fatigue severity ($p < 0.001$) [76]. The NCCN CRF guidelines [52] identify anemia as one of CRF's common contributing and treatable factors. In many instances, however, anemia may be only a partial contributing factor to CRF, as the level of fatigue in cancer patients without anemia is greater than that reported by the general population at large [7, 76]. Since CRF and anemia can both be multifactorial, the NCCN guidelines for cancer- and chemotherapy-related anemia [77] recommend assessing both subjective and objective symptoms associated with each, to better identify the underlying causes and to tailor treatment accordingly [77].

Patients need to be educated about the relationship between CRF and anemia [7]. They need to receive information about the possible underlying causes of anemia and how treatment may vary depending on a number of factors, including the underlying cause of their anemia, the indications and rationale for the various types of anemia treatments including iron supplements, and their risks, benefits, and associated side effects [7, 52, 77]. Correction of anemia within the context of CRF will depend upon whether the anemia is cancer-related (nontreatment-related), treatment-related due to the myelosuppressive effects of CT, or due to other causes [77]. Anemia treatment will also depend on the goals of CT treatment (curative versus noncurative), how rapidly the anemia must be corrected, and the presence of comorbidities [7].

## Emotional Distress

The NCCN distress guidelines [78] use the term "distress" in their definition because it is believed to be less stigmatizing than other terms that can be used to describe psychosocial problems like anxiety and depression [7]. In cancer patients, prevalence rates for depression range between 25% and

33% [52], and anxiety can occur at all times and in all cancer patients [7]. Emotional distress (i.e., anxiety and depression) is one of the common contributing factors of CRF [52]. While CRF and depression are common concurrent symptoms in cancer patients [52], one study in RT patients concluded that CRF and depression were independent conditions with different patterns over time [79].

The distress guidelines recommend asking cancer patients about their distress in the past week, including today, on a 0–10 numerical rating scale, with scores of 4 or more indicating clinically significant distress [78] requiring further follow-up. In addition, distress assessment typically includes a review of common problems that cancer patients sometimes experience, such as family, emotional, spiritual/religious, physical (symptoms), or memory/concentration concerns. This screening assessment should be completed prior to treatment and then be repeated periodically during and following treatment [7]. Patients should be taught that CRF may be related to emotional distress and that emotional distress is one of the common contributing and treatable contributors to CRF. Patients should also be counseled about stress management techniques and methods and resources that may help not only reduce anxiety and depression and but also CRF associated with emotional distress [7].

Several nonpharmacologic, randomized clinical trials using psychosocial interventions, such as participation in support groups, individual counseling sessions, and cognitive–behavioral training (identification and correction of inaccurate thoughts associated with depressed feelings using relaxation and enhancing problem-solving skills, stress management training, using a comprehensive coping strategy, and a tailored behavioral intervention), have consistently shown that not only can emotional distress be reduced but also CRF can be reduced when associated with depression or anxiety [15, 52, 78]. Interdisciplinary approaches that include nursing, social services, psychology, and chaplaincy/pastoral services often are indicated and can be very beneficial [7]. A variety of pharmacologic interventions to treat emotional distress exist including anxiolytics and antidepressants [7]. In one antidepressant study, depression was decreased, but the treatment had no effect on CRF [80]. For further information, please refer to the NCCN distress guidelines [52], the NCI's PDQ websites for anxiety [81] and depression [82], and the review by Breitbart and Alici [83].

### Cognitive Impairment

Another problem that some cancer patients experience particularly when undergoing treatment is cognitive impairment [84]. Signs and symptoms include forgetfulness, lack of mental clarity, and impaired concentration [7]. While relationships between CRF and cognitive impairment have not been well studied, attentional fatigue, the decreased capacity to concentrate or to direct attention, is considered one aspect of sensory CRF [52]. Use of attention-restoring interventions in women with breast cancer has positively affected concentration, problem-solving, and the ability to direct attention on neurocognitive tests [52]. Bird watching and sitting in a park are examples of attention-restoring activities in natural environments [85].

### Sleep–Wake Disturbances

Sleep–wake disturbance is a general term used to describe perceived or actual alterations in nighttime sleep with concomitant daytime impairment [86]. This term is used when a specific diagnosis of a sleep disorder has not been made [87]. While a variety of sleep disturbances can occur in healthy adults and adults with cancer, insomnia is the most common disorder that occurs in cancer patients [88]. Common descriptors of insomnia include problems in falling asleep, staying asleep, early-morning awakenings, an inability to fall back to sleep, and sleep described as being nonrestorative, nonrefreshing, and with some form of daytime impairment [86].

Insomnia is a serious issue in cancer patients as it is associated with other symptoms such as CRF and pain during and following treatment. In one study, the co-occurrence of the symptom cluster of pain, fatigue, and insomnia in elderly cancer patients was associated with an increased risk of death during the first year following cancer diagnosis [89]. While most studies have assessed the

relationship between CRF and sleep disturbances in women with breast cancer receiving CT, correlations also are reported in patients undergoing RT and surgery and in patients with other malignancies. Reviews of some of these studies are available [7, 90]. Approximately 30–75% of cancer patients have sleep disturbances. As a consequence, sleep disturbances are identified as one of the common, contributing, and treatable factors of CRF [52]. Treating sleep disturbances with cognitive–behavioral strategies is thought to reduce the incidence and prevalence of CRF [5, 90, 91]. Patients need to be asked at diagnosis and periodically over time whether they are experiencing any sleep disturbances [86].

Patients need education about how common sleep disturbances are in cancer patients and that sleep disturbances are one of the common contributing and treatable factors of CRF [52]. Patients need to be taught to report disturbances to their providers and how to use some of the more common cognitive and behavioral therapies (CBT) available to treat insomnia. These include stimulus control, such as going to bed when sleepy; sleep restriction, such as limiting the total time in bed [92]; relaxation training, including complementary therapies; and sleep hygiene methods, such as avoiding caffeine after noontime [52]. Patients also need to be taught about other interventions that can enhance sleep patterns such as exercise, sleep medications, controlling other symptoms such as pain, and using complementary therapies to enhance relaxation before bedtime [52].

Nonpharmacological therapies to manage sleep disturbances include CBTs, complementary therapies, and exercise, as mentioned above. There is some evidence that these same therapies may also improve CRF [52, 93], but more study is needed. There also are a wide variety of pharmacologic options available, including the sedatives–hypnotics, but there is little evidence of their use in cancer patients or how they may affect CRF [86]. These medications are not without their own side effects, and concerns have been raised about drug-to-drug interactions when taken with tamoxifen or selective serotonin reuptake inhibitors [52, 86, 88]. For further information about these sleep-enhancing medications, please see the National Cancer Institute's PDQ website on sleep disorders [94]. Consultation and referral to a sleep specialist may be indicated in some patients [7].

When indicated in medically induced fatigue such as opioid-induced sedation for pain and when treating depression or cognitive impairment, psychostimulants can be considered [83]. The NCCN CRF guidelines state that pharmacological interventions for CRF remain investigational, but there is more evidence for methylphenidate [95] than modafinil at present. These agents need to be used cautiously, and optimal dosing and schedules have not been established [52].

### Nutrition-Related Problems

In cancer patients, nutritional problems are common [7, 52, 96, 97]. It is estimated that 20–80% of cancer patients develop malnutrition during the course of their illness [98]. While nutritional problems are one of the common contributing and treatable factors of CRF [52], their relationships to CRF have not received much study [7]. There are only two studies in cancer patients that examined these relationships, and both found no relationship between nutritional status and CRF [99, 100].

Nutritional assessment within the context of CRF includes determining the presence of any unintentional weight gain or loss and the extent to which the patient is experiencing nutritional problems such as fluid and electrolyte disturbances [52]. The degree to which CRF may be limiting the patient's ability to shop and prepare food needs to be assessed [7]. Frequently, patients alter their dietary patterns when they receive a cancer diagnosis, disease recurrence, or during survivorship following treatment cessation [66]. They may take numerous over-the-counter supplements, vitamins, and other herbal remedies that may affect not only their nutritional status and treatments but also CRF. The relationship between CRF and these over-the-counter supplements, vitamins, and other herbal remedies has not received much study.

All cancer patients need to be taught that nutritional problems are common in cancer and its treatments, and while not well studied, nutri-

tional problems are one of the common contributable and treatable factors associated with CRF. Because of the lack of studies investigating the relationships among nutritional status, nutritional problems, and CRF, counseling patients about general nutritional guidelines such as eating a balanced diet low in fat and high in vegetables and fruits as appropriate to their condition and goals of their treatment seems a reasonable approach to include [5, 66, 101, 102]. When indicated by the patient's condition and goals of treatment, both pharmacologic and nonpharmacologic therapies may be considered to improve nutritional status [7] including referring the patient for a nutritional consultation [52].

### Symptom Clusters

The co-occurrence of fatigue with other symptoms contributes to the challenges associated with its management. Researchers have reported the co-occurrence of CRF and pain, depression (i.e., emotional distress) [72], and insomnia [8, 103–105]. Some authors have proposed that these symptom clusters may share a common underlying pathway or mechanism [75, 106–108]. Thus, the treatment of one or more of these symptoms might beneficially affect the other symptoms [108] including CRF [52]. There is also some evidence, however, that the relationships among symptoms may change over time [109–111], which further complicates the management of groups of symptoms. A recent review showed a central role of immune and inflammatory pathways in the clustering of symptoms in cancer survivors [112].

The cumulative burden of symptoms is thought to exacerbate CRF [113]. In one study on pain and fatigue, more patients experienced CRF alone (≥4 on a 0–10 NRS), followed by pain and fatigue (≥4) co-occurring together, followed by pain alone (≥4) [7, 18]. Another study investigated women, newly diagnosed with stage I–III breast cancer receiving at least four cycles of adjuvant or neoadjuvant anthracycline-based CT who had a symptom cluster that included sleep disturbance, fatigue, and depression [114]. Prior to treatment, these women were subdivided into three groups based on the number of symptoms scores above the cut scores for standard fatigue, sleep, and depression scales. The authors found that 19.7% had no symptoms, 56.6% had 1–2 symptoms, and 23.7% had 3 symptoms [114]. Prior to treatment, 66% of the women reported poor sleep, 63% reported fatigue, and 25% reported depressive symptoms, and the severity scores of the symptoms were significantly correlated with one another. All participants reported increased severity in all three symptoms during treatment, compared to baseline. Women who had reported three symptoms at baseline continued to report higher levels of symptoms than those who reported 1–2 symptoms or no symptoms [7, 114]. Research on symptom clusters is extremely scant and scientists are just beginning to understand on how to investigate symptom clusters [115].

## Education for Providers, Patients, and Families

Despite the increased emphasis on fatigue in the last 10 years and the growing number of clinical practice guidelines, the systematic use of these guidelines in clinical practice has been limited. At one national meeting held in the USA, approximately 50% of health-care providers (mostly nurses) were only somewhat familiar with the NCCN CRF guidelines, and 41% were not at all familiar with them [116]. In another survey conducted by the NCCN nationally of more than 1000 oncology clinicians, roughly one third were not aware of the CRF guidelines, and 34% of oncology specialist physicians ($N$ = 293/863) were unaware of the guidelines, compared to 17% of advanced practitioners and nurses ($N$ = 27/157) [117]. These findings indicate that health-care providers might benefit from more information about the existence of CRF evidence-based guidelines and assistance in how to translate and implement them in their practice settings.

Patients and family members need to receive education about CRF before they even start treatment to better prepare them for how to manage it, should they experience it. The patient version of the Physician Data Query on fatigue contains rel-

evant information on the causes and treatment of CRF [118]. There are now several studies that have evaluated nurse-led educational programs focused on CRF during treatment [18, 119–125]. All but one [123] demonstrated decreased fatigue in the experimental groups receiving the educational intervention; the small sample size in this study may have affected its conflicting results. In two of these studies [18, 71, 124], the intervention effect on fatigue was maintained during the follow-up period [126]. Each of these studies used short educational interventions, consisting of three to four individual patient sessions lasting 10–60 min [126], and, to a large extent, the same elements, such as information about CRF, self-care or coping skills, and activity management, such as learning how to balance activities and rest [126]. Patients should be encouraged to discuss CRF with their health-care provider, even if the provider does not do so on their own [7].

## Summary and Future Directions

Cancer-related fatigue (CRF) is a complex, multicausal, and multidimensional symptom [58]. Both the intensity of CRF and its impact need to be assessed and measured in practice and research settings. Different phenotypes or manifestations of CRF may exist and may vary by stage of disease and treatment trajectory (i.e., active treatment, survivorship [off treatment without evidence of disease], and palliative end-of-life care) [21]. Hence, researchers should include homogeneous samples whenever possible and biomarkers that will help to identify underlying mechanisms. It is also important to remember that the words patients use to describe CRF may vary by language and culture [127] and that the words energy, vigor, and vitality are not interchangeable with the terms tiredness, fatigue, and exhaustion [15]. When patients report tiredness that is different from the tiredness they usually experience, it warrants careful screening and assessment to identify the best management strategies. More study is needed using sophisticated statistical procedures to longitudinally follow other symptoms that cluster with CRF at baseline so that any changes in these relationships can be monitored and used to plan treatments. More research is warranted to determine how to best translate and implement clinical practice guidelines so their impact can be evaluated [62].

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# Sleep and Cancer

4

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Sleep disturbances are reported in up to 60% of patients with cancers of many types and stages [1–4]. Impaired sleep has an array of detrimental effects on the health of individuals with cancer and their family caregivers [5–7], with significant societal costs [8]. Cancer-related sleep disturbances can also affect health-related quality of life by way of persistent fatigue [9–11] and altered mood [12, 13]. Chronic sleep loss may lead to poor adherence to cancer treatments [14] and higher morbidity and mortality [15]. Sleep disturbances can range from perceived or actual alterations in usual sleep patterns to diagnosed sleep disorders meeting precise diagnostic criteria [16, 17]. New onset or worsening of sleep disturbances are common and disabling problems for those with cancer before treatment, during treatments such as chemotherapy and radiation therapy, and after completion of treatments [4, 18, 19]. Cancer pathology, treatments, and symptoms such as pain and hot flashes, disruption of daily activity and circadian rhythms, and unhealthy sleep habits contribute to acute and chronic sleep disturbances [19–21]. In this chapter, we describe the prevalence of common sleep problems in adults with cancer and define key terms. This chapter also provides information about biological and behavioral conceptual models of sleep and guidelines for the assessment and management of sleep disturbances. Emphasis is given to the latest non-pharmacological evidence-based treatments. We discuss the importance of provider awareness of sleep problems and patient education. Finally, we identify barriers to behavioral change and strategies to assist the cancer patient and family to self-manage sleep problems.

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## Introduction and Significance

The psychological impact of cancer, time-consuming treatments, and range of distressing symptoms are known to disrupt sleep patterns and sleep quality in cancer patients and posttreatment survivors. Yet, the true prevalence of sleep disturbance in cancer populations is not well established, in part because of the underreporting of sleep problems by patients and providers. Also, most studies of sleep in adults with cancer use cross-sectional designs, convenience sampling, and a variety of definitions and measures. Despite



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these methodological issues, evidence suggests approximately 30–60% of adults with cancer experience insomnia or other sleep disorders at some time during diagnosis, treatment, and long after primary treatment has ended [21, 22]. To put these rates into context, sleep disturbance affects 10–15% of the general public, and only 6–13% experience "insomnia syndrome" characterized as persistent insomnia at least 3 nights per week [23–25]. Advances in treatment and improved survival rates have resulted in greater numbers of cancer survivors [26] who require ongoing treatment of late and long-term effects of cancer. Sleep disturbance is a recurrent long-term effect of cancer. It is one of the top concerns of cancer survivors with significant effects on quality of life and functioning [10, 27, 28].

Across the cancer trajectory, consequences of poor sleep include lower quality of life [9, 19] and physical and cognitive function [29]. Several studies have reported links between sleep disturbances and other symptoms, including mood disturbances [12, 13], pain [30], hot flashes [31, 32], and persistent cancer-related fatigue [9–11]. These associations may be bidirectional. For example, cancer-related pain may cause a delay in falling asleep, frequent awakenings, and poor sleep quality [10, 33, 34]. In turn, a poor night's sleep can lead to increased pain intensity and decreased ability to control pain the next day. Other studies have reported that impaired sleep can result in diminished immune responses [35, 36], increased risk of infection [37], and poor adherence to cancer treatments [14].

Despite its frequency and negative impact, sleep disturbances remain underreported, underdiagnosed, and inadequately treated [38]. Some cancer survivors and healthcare providers may believe that sleep disturbances are normal and a temporary response to cancer and its treatment. Other cancer-related symptoms and concerns about survival appear to take priority over sleep assessment and management [38]. Although reported to be one of the most bothersome issues to patients with cancer, disturbed sleep often is not one of the symptoms and treatment side effects discussed with healthcare providers [39]. Even in palliative care settings where symptom management is a primary objective, evidence suggests few patients report sleep problems to healthcare providers [40]. Yet, frequent use of hypnotics has been documented in large samples of cancer patients [41], suggesting the actual extent of sleep problems is underappreciated. Even when patients in ambulatory oncology clinics do report sleep problems, clinicians may prescribe effective pharmacological and non-pharmacological treatments only half the time [38].

## Definitions

Sleep is an active, biobehavioral process defined as a state of temporary perceptual disengagement from and unresponsiveness to the environment [42]. The function of sleep is to conserve energy, maintain homeostasis and immune functioning, and restore physiological processes that degrade during wakefulness [43]. Thus, sleep disturbances compromise the restorative functions of sleep. Because sleep disturbances take many forms, definitions and terms for sleep disturbances often are used inconsistently. The terms sleep disorders, sleep disturbances (also referred to as sleep-wake disturbances), and insomnia are often used interchangeably. Yet, there are essential distinctions among these terms.

*Sleep disorders* comprise the nearly 100 diagnostic entities identified by criteria in the International Classification of Sleep Disorders, 3rd edition (ICSD-3) [16], and the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [17]. The most common sleep disorders in primary care and oncology populations include chronic insomnia, sleep-disordered breathing (e.g., obstructive sleep apnea), movement disorders (e.g., restless legs syndrome), and circadian rhythm disorders [44].

*Sleep disturbances* are the perceived or actual alterations in nighttime sleep (quantity and quality), with subsequent daytime impairment, in the absence of a diagnostic label [45]. Sleep disturbances occur at any time during the cancer trajectory and present with various features. Oncology literature focuses primarily on sleep

disturbance in terms of the usual symptoms of insomnia such as difficulty falling asleep (sleep initiation), staying asleep (sleep maintenance), and not feeling restored or refreshed on awakening.

*Insomnia* is defined by the ICSD-3 [16] as the persistent difficulty with sleep initiation, maintenance, duration, or quality accompanied by some form of daytime impairment, which occurs despite adequate opportunity for sleep. Additional terms for subcategories of insomnia by duration and severity are used frequently in oncology and sleep publications. For example, *chronic insomnia disorder* is the presence of insomnia for at least 3 months, as described in the ICSD-3 [16]. *Insomnia syndrome* was created to differentiate between mild insomnia symptoms and more severe clinical insomnia by applying established insomnia algorithms to a large population-based sample [46]. Insomnia syndrome refers to the subjective complaint of sleep difficulties, a sleep-onset latency >30 min, ≥3 nights per week, duration of ≥1 month, associated with impaired daytime functioning or marked distress, or the use of hypnotic medication for at least three nights per week [46]. *Hypersomnia*, a common cancer-related disorder, refers to a group of sleep disorders in which the main complaint is daytime sleepiness that is not caused by disturbed nocturnal sleep or misaligned circadian rhythms [16].

To more effectively assess and diagnose sleep problems such as insomnia, basic sleep parameter terminology was developed [47]. The following sleep parameter terms are used in both research and clinical settings. Sleep latency (SL) refers to the number of minutes it takes to fall asleep after turning out the lights and intending to sleep. Total sleep time (TST) is the number of minutes of actual sleep during a usual sleep period. Sleep efficiency (SE) is the ratio of time in bed to actual sleep time, expressed as a percentage. Wakefulness after sleep onset (WASO) is the number of minutes awake during the main sleep period. Good sleepers are characterized as having SL < 30 min, SE of >85%, nocturnal awakenings totaling <30 min of WASO [47], and TST of at least 7 h [48].

## Underlying Mechanisms

The causes and risk factors for cancer-related sleep disturbances are extensive and may be superimposed on precancer sleep issues [49]. Tumor pathology, advanced stage of cancer, treatments, medications, environmental factors, psychosocial disturbances, and other comorbid medical conditions increase the risk of sleep disturbances. These risk factors have been categorized as predisposing, precipitating, and perpetuating factors [17, 50–52] as described in Spielman's "3 P" model of insomnia [53]. This model illustrates three categories of biological and behavioral factors underlying sleep disturbance [53]. *Predisposing factors* are enduring psychological or biological traits that increase the likelihood of developing sleep problems during the cancer experience. Predisposing factors include advanced age, female gender, anxiety-prone personality, family or personal history of insomnia and/or psychiatric disorder, and genetic factors [2].

*Precipitating factors* are life events and medical, psychological, and environmental factors that trigger insomnia. Examples in people living with cancer include cancer treatments and side effects that disrupt circadian rhythms, hospitalization, and emotional distress [54]. Side effects such as respiratory conditions, gastrointestinal complications (e.g., diarrhea, nausea), and genitourinary problems (e.g., incontinence, retention) can negatively impact sleep [55]. Estrogen deficiency induced by chemotherapy and hormone therapy can trigger or exacerbate nighttime menopausal symptoms [56]. Cancer-related pain may delay sleep onset or cause frequent awakenings and poor sleep quality [10, 33, 34]. Hospitalization or changes in cancer patients' usual sleeping environment may precipitate sleep disturbances. Family problems and financial and occupational stressors may emerge as additional precipitating factors [34].

*Perpetuating factors* are maladaptive behaviors and beliefs used to cope with sleep difficulties [53]. Behaviors that perpetuate sleep disturbances include extending time in bed, frequent and long naps, irregular sleep schedule, and

physical inactivity [55]. Beliefs such as fear of sleeplessness and excessive worries about daytime consequences of poor sleep may delay sleep onset and cause frequent, prolonged awakenings.

Another relevant model is the two-process model of sleep-wake regulation that posits that the sleep-wake cycle is regulated by two biological mechanisms: circadian rhythm and sleep-wake homeostasis [57]. An internal circadian clock in the hypothalamus regulates the timing of sleep and alertness levels. Sleep-wake homeostasis involves the accumulation of sleep-inducing substances in the brain, which generates the homeostatic sleep drive. Internal and external circadian factors (e.g., light exposure) interact with homeostatic components to regulate the nearly 24-h sleep-wake rhythm [57]. Healthy rhythms occur when there is synchrony of timing between the circadian and homeostatic processes. Cancer and its treatment interfere with both processes through changes in usual sleep behaviors, environment changes, and altered hypothalamic-pituitary-adrenal axis regulation [50].

## Assessment

### Screening Guidelines

There is expert consensus advocating, at minimum, a brief and focused screening and assessment for sleep disturbances in cancer patients and survivors [58–61]. With growing evidence from high-quality studies, leading organizations such as the National Comprehensive Cancer Network (NCCN) [58] and the Oncology Nursing Society (ONS) [59] have developed guidelines for screening, assessment, and/or interventions for cancer-related sleep disturbances in adult cancer populations. Similarly, an interdisciplinary expert panel from Canada developed the Pan-Canadian practice guideline for the prevention, screening, assessment, and treatment of sleep disturbances in adults with cancer based on available evidence [60]. The first step in these guidelines is an initial screening by healthcare providers using standardized tools or a few brief questions, at regular intervals and when there is a change in clinical status or treatment. The NCCN Guidelines include the following screening questions: (1) Are you having problems falling asleep or staying asleep? (2) Are you experiencing excessive sleepiness? (3) Have you been told that you snore frequently or stop breathing during sleep [58]? If the screening is positive, the next step is additional assessment of the nature of the sleep disturbance, contributing factors, and daytime consequences.

## Assessment

A health history, including sleep disorders and medical, surgical, and psychiatric conditions, provides key information about factors that may be associated with impaired sleep [58]. Common side effects of cancer or its treatment that can precipitate insomnia, such as altered mood, pain, or fatigue, also should be assessed [62]. Self-report questionnaires provide essential patient perspectives. For example, brief tools with established validity in cancer populations [63] such as the Insomnia Severity Index (ISI) [64] evaluate insomnia. The Epworth Sleepiness Scale (ESS) [65] evaluates excessive daytime sleepiness, a symptom of obstructive sleep apnea (OSA) and other sleep disorders. Sleep diaries are often used to identify circadian rhythm disorders and contributing factors in insomnia development [66]. The Pittsburgh Sleep Quality Index (PSQI) [67] is a well-established but lengthy measure of sleep characteristics and history in the past month. The scope of sleep assessments may vary according to the setting, health status, and developmental stage of the patients with cancer. Minimally, sleep-related questions could be incorporated into the health history and review of medication.

### Focused Workup

For patients experiencing moderate to severe levels of sleep disturbance, further assessment of the underlying causes is indicated. Physical exams provide needed data about cancer-related or medical factors contributing to sleep problems

such as anatomical alterations. The NCCN Survivorship Guidelines include recommendations for assessment and management of sleep disorders [58]. Recommendations for a focused workup include a more in-depth general medical, sleep, and cancer history and medication review. A thorough physical examination may uncover potential sleep disorders. Referrals for specialized sleep assessment such as polysomnography and actigraphy may be indicated when specific sleep disorders are suspected. Early identification of sleep disorders such as OSA or restless legs syndrome (RLS; also referred to as Willis-Ekbom disease) allows for timely referral to a sleep specialist for diagnostic studies and treatment as indicated [58].

### Barriers

Despite the prevalence of cancer-related sleep disorders and the availability of guidelines, assessment is not routinely performed in many institutions and oncology practice settings [68]. Numerous patient-, provider-, and system-related barriers hinder the translation of these guidelines into practice settings [68]. There are comparable barriers to the implementation of evidence-based fatigue guidelines [69]. These challenges include patient's attitudes and beliefs, clinician's lack of knowledge and ability to provide relatively complex interventions, and the lack of access to reimbursement and resources (e.g., sleep experts for referrals) on a systems level [69].

## Non-pharmacologic and Pharmacological Treatments

This section focuses on treatments to prevent and manage sleep disturbances in patients with cancer. The selected treatments reflect the strongest evidence-based interventions for patients who screened positive for sleep disturbances (see the section "Screening Guidelines") but have not been diagnosed or treated for insomnia by a clinician. These patients also were screened and tested negative for the other most common sleep disorders [OSA, movement disorders (e.g., RLS), and circadian rhythm disorders].

First, all cancer patients and survivors need to receive education on how to prevent sleep disturbances, especially during stressful periods. The importance of both the quality and quantity of sleep needs to be emphasized. Patients need to be taught how to recognize sleep problems and when to discuss sleep issues with clinicians. The NCI supports a Physician Data Query (PDQ®) website that summarizes general information about sleep disorders for patients. This website provides up-to-date information about its causes, assessment, and treatment. However, the NCI PDQ website does not provide formal guidelines for making decisions about healthcare [70]. A preventive-supportive education intervention for all patients with cancer is also available for use [60].

Management of sleep disturbances varies based on several factors. A good place to start is to examine the patient's severity score on the Insomnia Severity Index [63]. Current functional status also needs to be assessed before selecting a treatment. A combined approach is needed that targets any contributing factor (hot flashes, pain, nocturia) and the altered beliefs that may be maintaining maladaptive sleep behaviors [60]. All patients need to engage in developing an individualized plan based on the severity of sleep disturbances, functional status, accompanying symptoms, altered beliefs, and treatment acceptability [47].

### Non-pharmacologic Treatments

Over the last 15 years, growing evidence suggests that patients with cancer who experience sleep disturbances can benefit from treatments that were originally developed and tested in patients without cancer who had chronic insomnia [71, 72]. Table 4.1 provides key information about components of non-pharmacologic interventions. The evidence is reviewed annually by ONS putting evidence into practice (PEP) program. After detailed review and analyses of published studies, the ONS-PEP team rates interventions in one of several categories: (1)

**Table 4.1** Non-pharmacologic interventions for sleep disturbances in cancer patients [47, 74, 75]

| | |
|---|---|
| 1.0 | **Cognitive behavioral interventions/approach** |
| 1.1 | *Deliver **cognitive therapy** to alter dysfunctional beliefs* about sleep |
| 1.2 | Determine altered dysfunctional beliefs and attitudes about sleep |
| 1.3 | Help patients develop realistic sleep expectations |
| 2.0 | Instruct patients in the following ***stimulus control techniques*** |
| 2.1 | Go to bed only when sleepy and at about the same time each night |
| 2.2 | Get out of bed and go to another room whenever unable to fall asleep within 20–30 min, return to bed only when sleepy again; repeat as often as needed throughout the night |
| 2.3 | Use the bedroom for sleep and sex only |
| 3.0 | Instruct patients in the following ***sleep restriction techniques*** |
| 3.1 | Maintain a regular bedtime and rising time each day |
| 3.2 | Avoid daytime napping; if needed, limit to 1 h or less early to midday; avoid unnecessary time in bed during the day |
| 4.0 | Instruct patients in the following ***relaxation techniques*** |
| 4.1 | Use a relaxation technique within 2 h before going to bed |
| 4.2 | Schedule a "clear your head time" 90 min before going to bed |
| 5.0 | Instruct patients in the following ***sleep hygiene techniques*** |
| 5.1 | Avoid caffeine, nicotine, and other stimulants after noon; finish dinner 3 h before bedtime; do not go to bed hungry |
| 5.2 | Create a bedtime routine. Keep the bedroom dark, cool, and quiet; avoid pets in bedroom |
| 5.3 | Do not watch television or use computers or tablets in the bedroom |
| 5.4 | Replace mattress every 10–12 years, pillows more frequently; use light sleepwear and covers |
| 5.5 | Ensure at least 20 min of daily exposure to bright, natural light soon after awakening |
| 6.0 | **Exercise** |
| 6.1 | Rule out bone metastasis or exercise contraindications |
| 6.2 | Have patient complete moderate exercise (e.g., brisk walking 30 min four to five times per week) at least 3 h before bedtime |
| 6.3 | Encourage patients to perform strength and resistance training |
| 7.0 | **Complementary therapies** |
| 7.1 | Encourage patients to decrease stress by selecting a relaxation technique that suit him/her |
| 7.2 | Encourage patients to decrease stress by focusing on and isolating various muscle groups while moving progressively up and down the body |
| 7.3 | Encourage focused breathing, with all attention centered on the sensations of breathing, including the rhythm and rise and fall of the chest |
| 8.0 | **Education** |
| 8.1 | Provide patients with information regarding specifics of treatment and expected side effects, including sleep disturbances |
| 8.2 | Provide anticipatory education to patients about healthy sleep techniques |
| 8.3 | Repeat this information throughout the treatment |
| 8.4 | Ensure that the patient's sleep expectations are realistic |

recommended for practice, (2) likely to be effective, (3) effectiveness not established, (4) benefits balanced with harms, (5) not beneficial, and (6) expert opinion [59]. The NCCN Survivorship Guidelines section on sleep disorders also contains valuable information and is updated annually. All recommendations by NCCN are category 2A unless otherwise specified; they are based on lower-level evidence and there is uniform consensus that the intervention is appropriate [73].

## Cognitive Behavioral Therapy-Insomnia (CBTI)

CBTI is the only intervention *Recommended for Practice* by ONS-PEP. CBTI is a type of psychotherapy that assists patients in making changes in thoughts and behaviors. The goal of this treatment is to explore and understand a person's thoughts and beliefs related to sleep and to select new, healthier approaches to thinking, coping, and sleep behaviors [47, 74, 75]. There are a

variety of strategies, with the highest evidence for chronic insomnia being the components of CBTI, sleep restriction, stimulus control, and relaxation [76]. Another strategy, known as sleep hygiene, is essential in preventing insomnia and has been shown to work in association with the others, but does not have evidence to be an effective, independent strategy. These strategies are designed to reduce the hyperarousal response and the perpetuating factors described in the section "Underlying Mechanisms." Despite the high level of evidence for CBTI's effect, a limitation is that the majority of studies have been conducted in women with breast cancer and evidence of effect in other cancer diagnoses is needed. Studies can be viewed by clicking on CBTI on the ONS website. Another limitation is that the majority of the trials' inclusion criteria in cancer patients did not require a cutoff score to indicate the presence of moderate to severe insomnia. Cognitive behavioral therapy is a recommended treatment for insomnia disorder in patients with cancer. CBTI may be particularly helpful in patients with irregular sleep patterns and a history of poor sleep habits. CBTI is ready for dissemination in oncology clinical practice.

## Mindfulness-Based Stress Reduction (MBSR)

The ONS-PEP category labeled *Likely to be Effective* currently includes two treatments: mindfulness-based stress reduction (MBSR) and exercise [59]. The NCCN Guidelines do not include either of these interventions [73]. Similar to CBTI, the majority of evidence for MBSR in cancer has come from patients with early-stage breast cancer. MBSR is a program that helps a person learn to calm his/her mind and body to help cope with illness, pain, and stress. The goal of MBSR is to deal with experiences through awareness of feelings, thoughts, and body sensations in the present moment using techniques such as body scan and exercises for yoga and meditation [77]. Results of several large, randomized controlled trials led ONS-PEP reviewers to conclude that MBSR is effective in improving sleep disturbances in patients with cancer [59]. However, programs have been inconsistent, conducted using a variety of components, both in a clinic and at home, and in different doses. This intervention may be particularly helpful in patients with anxiety. More evidence from large, rigorously designed studies with patients with different types and stages of cancer are needed.

## Exercise

Exercise is defined by ONS-PEP as a physical activity that involves bodily movement performed to improve or preserve physical fitness that includes one or more of the following components: cardiorespiratory endurance (aerobic fitness), muscular strength, muscular endurance, flexibility, and body composition [59]. A variety of physical activities are included, with all of them characterized by frequency, intensity, time, and type (FITT) [78]. Exercise has been shown to improve sleep in patients both during and following cancer treatments [79] including recent positive benefits in patients with lung cancer [80] . Guidelines for cancer patients with normal functional status are similar to healthy populations; the exercise prescription is for 30 min/day 5 days a week, for a total of 150 min/week [81]. Exercise/physical activity interventions of moderate intensity have been effective in producing short-term behavior changes in physical activity, with highly structured interventions resulting in larger behavior change effects overall [82]. When a patient's health status is lower than normal, the FITT schedule can be modified by an exercise trainer for cancer patients in order to maintain current function and prevent further decrease in strength and health status. Aerobic exercise also has been reported to maintain and/or improve mental and emotional health in stressful times. Exercise also may assist in strengthening 24-h circadian activity rhythms, a factor associated with longer survival in patients with advanced cancer [83].

The ONS-PEP category of *Effectiveness Not Established* includes several additional behavioral interventions. Although some positive

results have been reported, these interventions need further testing in rigorously designed research studies and should not be given higher priority when discussing interventions with patients. The point to emphasize is that clinicians should only recommend strategies that have been given the "green light" for practice, as displayed at the ONS-PEP website [59] and the NCCN website [73].

### Pharmacological Treatments/ Interventions

Pharmacological treatments are rated by ONS-PEP as "Benefits Balanced with Harms" [59]. NCCN includes a pharmacologic treatment intervention, if safe, for difficulty falling asleep and difficulty maintaining sleep. NCCN provides a detailed table of principles for choosing a FDA-approved hypnotic [73]. Prescription and over-the-counter agents may be beneficial as short-term strategies and are suggested to accompany the behavioral strategies listed in Table 4.1 that take more time to show benefits. There have not been any studies specifically exploring the benefits versus harms of hypnotic agents in patients with cancer.

When patients with cancer approach a clinician requesting sleep medications, providers need to explain the potential risks to patients. The decision to use pharmacological agents needs to be made carefully by the clinician, patient, and caregiver in full awareness of potential side effects. Drug-drug interactions need to be considered but most interactions with chemotherapy agents are not known. Concerns have been raised about potential interactions between tamoxifen and certain antidepressants [44]. Safety issues also need to be considered and include potential for tolerance, dependence, and withdrawal.

The preferred classification of prescription drugs that may be used short-term for patients with sleep disturbances is benzodiazepine hypnotics, benzodiazepine-receptor agonists [61]. Daytime effects of hypnotics and sedatives include a "hangover" effect upon awakening and during the morning, resulting in effects on memory and performance, leading to reduced, rather than improved, daytime functioning. These effects are less likely with agents with a short half-life. This effect also may occur when over-the-counter sleep aids are used that contain antihistamines in addition to acetaminophen. Sleep experts recommend starting medications at a low dose, monitoring closely for side effects, and tapering slowly to prevent withdrawal symptoms [84]. Patients should be encouraged to discuss the use of any herbal sleep aids with their healthcare provider. Herbal agents are strongly discouraged during chemotherapy as there have been no studies that examined drug-drug interactions. Clinicians are advised to carefully weigh the benefits versus the harmful effects of medications for sleep disturbances and to use an individualized approach [59].

## Implications for Management of Sleep-Wake Disturbances

### Patient and Family Self-Management

The success of any behavioral program relies upon one's ability to adapt and stick with a new behavior. It is reasonable to say that behavior change has become integral to the future of population health and, certainly, to preventive medicine. The problem is that behavior change has been relatively elusive to most of us. It seems intuitive, but it is not. It is difficult. It is transient. It is often emotional. The good news is that the field of psychology has studied behavior change for many decades, and there are some useful insights from practice and research on how to support behavior change. These techniques work when applied to sleep behaviors; for a review, see [75]. Perhaps the first thing to realize is that there will always be barriers to change. Barriers should not be ignored. Trying to eliminate them, however, can be a daunting task, as new barriers to change will arise once old ones are eliminated. We all know some patients who manage change despite barriers, while others are unable to maintain changes if barriers are not removed. Knowing this, we can focus on the broad aspects of

behavior change that exist regardless of the specific behavior(s) being targeted. The literature is filled with models that support behavior change; we present some of the most relevant components of change here, referencing models where appropriate.

## Provider Awareness

One thing to consider regarding behavior change is to support the autonomy of the patient in making a change. Motivational interviewing is a strong proponent of supporting the patient's autonomy to change [85]. Clinicians often see it as their role to create desired change(s) in our patients, but forcing change rarely works. Clinicians need to see their role as facilitators of change and encourage family members to see themselves in a similar role. By pushing for change, we sometimes create a dynamic where the patient plays devil's advocate against change. It is better instead to gauge the patient's desire to change and use her/his own internal motivation to create lasting change.

One technique used in motivational interviewing to accomplish this is scaling. One example of scaling would be to ask the patient, "On a scale of 1–10, how motivated are you to (create the specific change requested)?" The follow-up questions are critical. The first follow-up question pulls for the barriers to change. The question is, "Why is your rating not higher?" The patient's answers should be acknowledged with empathy and an understanding that barriers exist to change and will need to be managed. The next question is even more useful. You ask, "Why is your rating not lower?" The answer to this question reflects that person's own motivations to change, in her/his own words. We often assume that a person's motivation for change is similar to our motivations for them, when, in fact, it may be different. When possible, reflect back their statements using their own words, to increase the personal aspect of the facilitators to change. These facilitators provide a useful mechanism to enhance change when the patient is struggling through the process of change.

Confidence, or self-efficacy [86], is perhaps the greatest predictor of success in behavior change. Self-efficacy refers to one's confidence that she/he can stick with change when it is difficult. Building confidence, then, is one of the greatest challenges around change. Confidence can be built in a number of ways. Proper goal setting can make targets very reachable, resulting in quick successes toward change and, therefore, building confidence. For example, achieving 10,000 steps per day can be a very reasonable goal for someone who is already achieving 8500 steps, but it may decrease motivation if it is set as a goal for someone who is achieving only 4000 steps. Reached goals can then result in setting a new, slightly higher, goal allowing clinicians to shape patients toward a long-term target. There is evidence that having both long-term and short-term goals is beneficial in helping to create lasting change [87].

Social support is another significant enabler in creating change [88]. Social support can take numerous forms, but it should be encouraged in family members and friends, broadly. It is best if the patient tells her/his social network what type of support helps her/him best. This provides the social network some guidelines under which to operate. The proper social support can go a long way. This has been demonstrated among specific cancer populations in notable ways. One thing to remember, however, is that social support can lead to poor behaviors as well, especially where sleep is concerned. If one or more people in the group express the feeling that more rest is what is needed when sleep is disturbed, it can lead to more people exhibiting maladaptive sleep behaviors. Therefore, the proper information should be provided to the group, and the role of the network should be to support efforts toward productive sleep behaviors. Proper sleep behaviors are not always intuitive to patients or their social networks.

Our job is to educate to a receptive patient, provide emotional support, and set the stage for effective change. The change must come, however, from the patient herself/himself and from the network upon which they receive most of their support. We can facilitate that by adhering

to some of the fundamental aspects of behavior change outlined above. We rarely have to teach cancer patients that sleep is necessary, but we do need to educate that "trying" to sleep too much or "resting" too much can lead to more maladaptive sleep behaviors. Sleep should be scheduled and valued, but so should the other behaviors highlighted in the intervention section, such as stress management and exercise.

## Summary and Future Directions

This chapter emphasizes the significance of the problem of sleep disturbances in those with cancer. We stressed the critical need to improve screening and further assessment using valid and reliable measurements/tools both during cancer treatment and in survivorship. Insomnia is the most prevalent sleep disorder in patients with cancer, but OSA, movement disorders, and circadian rhythm disorders need to be ruled out before initiating interventions for insomnia. Three types of non-pharmacologic interventions that have had their effectiveness established were presented (CBTI, MBSR, and exercise/physical activity) and are ready for dissemination and adoption in clinical settings. Clinicians need to routinely assess and treat other symptoms that cluster with sleep disturbances such as pain, anxiety, and nausea. Pharmacologic agents are recommended for short-term use only, and patients need to be made aware of both the potential benefits and risks before recommending any remedies for sleep. The role of the healthcare team is to increase the patient's awareness and education about sleep, and resources for patients and professionals were shared. Advice was provided on how clinicians can assist patients and their families/support network in making the behavior changes to improve management of sleep disturbances. Strategies to enhance behaviors to promote sleep include educating about behaviors for healthy sleep, identifying and decreasing barriers, motivational interviewing to promote autonomy to change, building confidence/self-efficacy for maintaining changes, and using positive social support to maintain adaptive sleep behaviors.

Future directions include dissemination and adoption of strategies to manage sleep disturbances in patients with cancer in community settings. The current situation is minimal awareness and assessment of sleep disturbances in oncology patients and settings. Resources for cancer patients experiencing sleep disturbances are inadequate to meet the needs. We need to develop resources that can be accessed by vulnerable populations such as older adults and those living in rural and medically underserved areas. Self-management strategies need to be accessible via technology and will become more prevalent and offer individualization.

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# Palliative Care: End-of-Life Symptoms

5

Gregory B. Crawford, Katherine A. Hauser, and Wendy I. Jansen

## Introduction

The World Health Organization defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [1]. The word "palliative" is derived from the Latin word pallium, which means, "a cloak" [2]. One important facet of palliative care is the relief of symptoms, that is, the covering or cloaking of symptoms. Caring for people at the end of their life is another important aspect of palliative care. However, there are international variations in language. In the United Kingdom and Australia, hospice generally refers to a philosophy of care but also relates to inpatient care, whereas in the USA hospice care is generally community-based [3]. Even the meaning of "end of life" should be clarified. In the United Kingdom, "approaching the end of life" is when they are likely to die within the next 12 months. This includes those patients whose death is expected within hours or days; those who have advanced, progressive incurable conditions; those with general frailty and coexisting conditions that mean they are expected to die within 12 months; those at risk of dying from a sudden acute crisis of an existing condition; and those with life-threatening acute conditions caused by "sudden catastrophic events" [4]. In the USA "end of life" tends to be related to the hospice admission criteria of 6 months or less of life expectancy [3, 5] and in Australia is commonly used to refer to the last few days of life when a person is irreversibly dying [6]. We will discuss the care of people in the last days to weeks of life.

The care of people approaching the end of their life is best provided by a multidisciplinary team [7]. This will of course depend on local resources and the patient's needs. Caring for people with non-curative cancers is likely to be part of the work of medical and nursing staff in almost all areas of healthcare. There will be times to seek

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specialist palliative care medical and nursing assistance or advice, but there is an imperative that generalists, including general practitioners or family physicians and oncologists, can provide a palliative approach to care when this is appropriate.

## Ceasing Active Therapies

For cancer patients and their treating physicians, one particularly challenging issue is if or when disease-modifying therapies should be ceased. To accurately prognosticate for an individual person, and assess the likely risk/benefit ratio of a therapy, and thus advise about further disease-modifying options is a complex task. Decision-making should ideally be shared between the doctor and the patient and family, where culturally appropriate. Evidence about benefits and potential burdens of new targeted therapies for individuals with advanced disease may be limited or relatively unknown. Goals of therapy and likely future outcomes are generally discussed at the onset of treatment, but nonetheless when therapeutic options are diminishing and the disease is progressing, many people may not have "heard" or retained understanding about these issues. Discussions should generally involve patient and family and may occur over several consultations, and it is clearly best if a consensus can be reached. There are likely to be specific societal, cultural, and religious norms that should be understood or asked of patients and their families, to inform with whom these discussions might occur and when. To have an open discussion about ceasing active therapies may not be easy and can take considerable time. However, this approach is likely to provide patients and their families with the opportunity to understand and plan for the approaching end of their life, rather than following a pathway of chemotherapy until death inevitably intervenes. It is useful to frame such decisions in terms of "no longer prescribing chemotherapy" rather than ceasing treatment, with the associated implication of "giving up," a sense of abandonment and of ceasing to care.

## Specialist Palliative Care

Involvement of specialist palliative care and taking a palliative approach to care should be encouraged early, not merely at the end of active disease-modifying therapies. There is evidence that early involvement of palliative care may even have a survival benefit [8]. Specialist palliative care services can provide an important coordinating service when contemplating cessation of chemotherapy. Disease progression is frequently associated with increasing symptoms and deteriorating physical function. Palliative care services provide comprehensive symptom assessment and management, equipment, and direct nursing care ideally in the home if preferred, but also in a hospice or palliative care unit, an acute hospital, or a residential care facility. Discussions about options or choices and the patient and family's preferences about where death might occur may also be very useful, despite possibly being difficult to raise.

## Prognostication

Patients do expect their doctors to initiate conversations about end of life, and these conversations can reduce the use of intensive medical treatment at the end of life [9]. An important part of decision-making is the discussion about likely prognosis and how their disease might unfold. This information may affect decisions about treatment, and may change personal choices and priorities.

If possible it is best to avoid these discussions when the patient is acutely ill or distressed. What the clinician is being asked to perform is the use of population-based statistics to give a likely framework of the future for an individual patient and/or their family. A useful start is the "surprise question," i.e., "Would I be surprised if this patient were to die in the next 6 to 12 months?" [10]. Another instrument is the Supportive and Palliative Care Indicators Tool [11]. This uses general indicators of deteriorating health (e.g., recent unplanned hospital admissions, dependence on others for care) and indicators of other illnesses or comorbidities including cancer, dementia, and

kidney disease and is designed to assist in recognizing key points in the clinical trajectory.

In advanced cancer, performance status has prognostic significance [12]. The rate of change in performance is generally correlated with increasing burden of disease and increasing constitutional symptoms, e.g., anorexia, cachexia, and fatigue. Scores of the Australia-modified Karnofsky Performance Scale (AKPS) [13] of less than 40 (out of 100) or an Eastern Cooperative Oncology Group (ECOG) performance status score of 3 (out of 4) correlates to a median survival of around 3 months for patients with advanced cancer.

Most patients and their families want specific and honest information about their prognosis. This should be delivered with compassion, to help them make decisions and plan for whatever time that might remain. If a person does not wish to discuss prognostic information, this should of course be respected, but it may be useful to discuss how the discussion may be helpful for planning and decision-making. There may be cultural or religious reasons why some people and families may prefer not to discuss prognostic information at all, or may want a specific family member rather than the individual to receive such information.

When discussing prognosis, it is best to explore why the question is being asked, consider who is asking, check what information they have been given previously, and then provide information about prognosis sensitively in terms of "days," "weeks," or "months" that might be reasonably expected. The uncertainty of the prediction and the potential for unforeseeable events such as thromboembolism and infection should generally also be mentioned. When assessing limited prognosis, it is wise to review patient and family needs and care, e.g., undertake a medication review, discuss goals of care, and consider whether referral to specialist palliative care or other community supports might provide benefit.

It is also important to identify the onset of the terminal phase. The diagnosis of impending death is not always easy but is important to ensure appropriate care is provided. Common signs and symptoms include very poor performance status, i.e., usually bedbound, reduced conscious state, difficulty swallowing, reduced urine output, changes in respiratory pattern, and signs of peripheral shutdown with mottled skin and cold extremities.

## Symptom Control

Symptom control is a significant part of the healthcare interventions provided by a palliative care team. Physical symptoms are generally well recognized and have a considerable prevalence (e.g., lack of energy (73.4%), pain (63.1%), nausea (44.7%), lack of appetite (44.5%), constipation (33.6%), cough (29.4%), and shortness of breath (22.9%)) [14]. Psychological symptoms are much more challenging to elicit, and more controversy exists about what is normal and what might require intervention. Symptoms such as anxiety and depression may not be as easily acknowledged, diagnosed, or treated by patients, carers, or healthcare providers [15–20].

## Ethical Decision-Making

The ethical principles of autonomy, beneficence, non-maleficence, and justice are useful to guide decisions at the end of life. When ethical dilemmas arise there may not be one correct answer. Despite a patient's needs and desires being central to good healthcare, there are limits to individual autonomy. Healthcare providers need to offer choice when there is truly a choice. There are times when patient and family preference may not be possible, because of disease, limitations to therapeutic options, the terminal nature of the condition, and limited resources of public systems and of families.

The central practice of palliative care is a patient-centered approach to care, attention to symptom control, and open communication about what choices there are for the patient as they approach the end of their life. And although the WHO defines the unit of care as being "patient and family," the patient's right to autonomy and confidentiality remains.

There is real potential for misunderstanding and conflict when negotiating options for care. Decisions may be clinically quite complex and there may be limited evidence to support clini-

cians. The principle of autonomy supports patients making their own individual choice. In a clinical situation this means respecting an individual's decision to accept or reject investigations and therapies that might provide some benefit. Further difficulties can arise because of concerns about patient capacity or competence and then who might legitimately be charged with making any decisions about care. Many jurisdictions will have legislation to support care and substitute decision-making at the end of life. Common sense should guide discussions in areas where there is less clarity. Clear and honest communication is likely to minimize misunderstandings.

### Rationalizing Medications and Interventions and Deprescribing

Best palliative care practice is neither to hasten or postpone death; however as a patient's condition deteriorates, the likely benefits and burden or harm of treatments are likely to change. To raise the possibility of ceasing medications that have been taken for many years, with the expectation of prolonging well-being or avoiding future medical complications, can be emotionally confronting. Medications that are unlikely to provide benefit may include lipid-lowering medicines. Equally even anticoagulants for cardiac or thromboembolic events may present potentially greater risk if continued, rather than ceased. The relative risk may be greater with continuing, e.g., a patient who is anticoagulated but is experiencing frequent falls. There is a small but growing body of literature to assist with this decision-making [21, 22]. Defibrillator deactivation should be considered in patients who have one implanted [23].

## Symptom Management

### General Principles

For any new or progressive symptoms near the end of life, it is important to consider whether potentially reversible causes are contributing and whether treatment aimed at reversal is appropriate, considering the patient's prognosis, their goals, and the location of care and burden and side effects of treatment. Many symptoms occurring at the end of life may respond at least in part to non-pharmacological management. Due to an impaired ability to swallow safely and reduced consciousness, non-oral routes for medications are likely to be required. Many end-of-life care medications can be given subcutaneously (SC), sublingually (SL), or per rectum (PR), if intravenous (IV) access is not available or inappropriate, e.g., in the home setting [24, 25]. Continuous subcutaneous infusions (CSCI) or SC syringe drivers may contain a combination of medications aimed at multiple symptoms.

Anticipatory prescribing allows common symptoms to be managed more easily if or when they develop and crises potentially averted, regardless of whether the site of care is hospital, residential aged care facility, or in the home. A basic kit of four medications (an opioid, benzodiazepine, antipsychotic, and anticholinergic) can be provided for home use or prescribed in hospital to manage most common symptom issues in the terminal phase [25–27]. Medications used to manage the terminal phase vary according to local availability, and regional guidelines should be consulted [27–31]. Regular review and titration of doses is required to ensure symptoms are adequately managed. For persistent symptoms both a continuous background and as needed (PRN or breakthrough) doses will usually be required. The routine use of end-of-life care pathways has not been demonstrated to improve the quality of care of dying patients [32].

Education and support of family members regarding what to expect and basic symptom management is necessary both at home and in the hospital or hospice. Family caregivers will often be required to give medications in the home and may be anxious about the potential of these medications to cause harm or to hasten death.

### Pain

Assessment of pain requires a thorough clinical history and examination followed by correlation of symptoms with known sites of disease and

judicious use of investigations. Validated pain rating scales (e.g., a numerical rating scale, visual analogue scale, or faces pain scale) should be used [33]. In the terminal phase, assessment may need to rely on nonverbal indicators, e.g., frown, grimace, muscle tension, restlessness, guarding, or withdrawal when being touched or moved. Validated scales are available for cognitively impaired people, e.g., the Abbey Pain Scale [34]. Delirium, anxiety, and psychosocial and existential distress may contribute to a lower pain threshold and complicate pain assessment [33]. New or increasing pain may be due to progressive disease, new bone lesions or complications, general aches and pains from bedrest, skin pressure, urinary retention, constipation, and mouth ulcers. Attention to good nursing care, to relief of pressure areas with appropriate mattresses or other pressure-relieving devices, and to bladder and bowel function are all important to minimize pain.

Many people with cancer will have had pain prior to entering the terminal phase and thus have an established analgesic regimen, usually based on a long-acting opioid, either oral or topical patch. Oral pain medications may need to be converted to parenteral (either IV or SC) when patients are no longer able to swallow. This is generally done using opioid equivalency charts [28, 35, 36]. Fentanyl patches can remain in situ at the end of life, and additional opioid needs can be managed as for other patients [37]. Most will need additional as required (breakthrough) analgesia. Initially breakthrough doses are typically 5–15% of the background dose and are then titrated to effect [38]. For those who are opioid-naïve, initially small frequent doses of an appropriate opioid should be prescribed and available "as required" and titrated to effect. Once the 24 h effective dose is established, a continuous infusion can be commenced either SC or IV [28]. Breakthrough doses may still be required and the infusion is then titrated based on use. Proportionate opioid titration does not shorten life even in the final days to weeks [39].

Signs of opioid toxicity may include myoclonus, delirium, hyperalgesia, and allodynia. Options for management include dose reduction or switching of the opioid [40]. If this is not appropriate, e.g., very short prognosis, toxicity can be managed with benzodiazepines for myoclonus or antipsychotics for delirium. There is no consistent evidence that routine use of parenteral fluids alters symptoms at the end of life, including opioid toxicity [41, 42]. Constipation should be anticipated and a prophylactic aperient prescribed if the patient can swallow [43]. In the last days of life, constipation may not be a symptomatic issue. Rectal suppositories may be used if there are signs of discomfort [44].

Renal impairment can impair the clearance of active metabolites of morphine, hydromorphone, and oxycodone which may contribute to toxicity [45]. Fentanyl, buprenorphine, and methadone have no active metabolites and thus may be better initial opioids for patients with renal failure [43, 45]. Metabolites may also accumulate with impaired renal function occurring as part of the dying process. Hepatic impairment prolongs the half-life of many opiates (morphine, hydromorphone, oxycodone, methadone) and thus may also contribute to accumulation. Cautious dose titration and consideration of increased dosing intervals is recommended [46, 47]. Fentanyl may be a safer opioid in hepatic failure [46]. Patients already on an opioid who develop liver failure should be observed for signs of toxicity.

Adjuvant analgesics prescribed for neuropathic pain (e.g., anticonvulsants, antidepressants) are generally continued while patients can swallow. Anticonvulsant doses may need to be adjusted if the patient has renal impairment. Non-oral adjuvants include nonsteroidal anti-inflammatory drugs (ketorolac IV, diclofenac PR, paracetamol IV or suppository) and dexamethasone (SC or IV), used commonly for pain from bone lesions, tumor compression of nerves or other structures, bowel obstruction, or headache from intracranial pressure [48–50]. Topical analgesia, e.g., lidocaine, may be useful for painful wounds. Short-course radiotherapy may provide effective analgesia for painful bone and other tumors in appropriate patients [40].

## Gastrointestinal Symptoms: Nausea and Vomiting, Constipation, Nutrition, and Hydration

Nausea and vomiting are frequent in cancer patients and often multifactorial [51]. These symptoms can be less severe in the last days of life due to reduced oral intake [52]. Nausea and vomiting may be prominent where there is a bowel obstruction, peritoneal disease, large hepatomegaly, or severe constipation. Hypercalcemia may contribute to both nausea and constipation. Constipation is very common due to bedrest, medications, particularly opioids, and low fluid intake. Non-pharmacological management of nausea and vomiting includes taking only sips of fluid or ice chips. A nasogastric tube may be required if there is a bowel obstruction and vomiting is not responding to pharmacological measures.

Management of nausea and vomiting also includes management of constipation. This may be administered via the rectum if aperients are unable to be swallowed. First-line antiemetics are usually metoclopramide or haloperidol, both of which may be given SC [27, 28]. Ondansetron is used less often as it is constipating; however it is available in wafer form making administration relatively simple.

### Hydration and Nutrition

Declining appetite and alertness and poor swallowing cause a natural reduction in fluid and food intake at the end of life. Dry mouth is a common symptom and is generally managed with meticulous mouth care and saliva substitutes. Small amounts of fluid and food should be offered when patients are alert and wish to eat and drink. Artificial hydration does not improve symptoms of dehydration at the end of life and is not associated with a survival benefit [41]. Anecdotally, artificial hydration has the potential to worsen fluid overload, ascites, pulmonary edema, and respiratory secretions although evidence is lacking [42]. Decisions around artificial hydration and nutrition frequently cause family distress, with concerns that the patient is dying of dehydration or starvation. Patients are often less concerned due to lack of appetite and reduced awareness. Pros and cons of artificial hydration should be considered and discussed with the patient and family and if desired a time limited trial of hydration commenced with negotiated outcome measures. Up to 1 L of normal saline can be delivered subcutaneously over 24 h in the absence of IV access.

Artificial nutrition is not recommended for cancer patients in the last days to weeks of life. Both enteral and parenteral nutrition are associated with numerous complications and unlikely to alter prognosis in advanced cancer at the end of life [42].

## Dyspnea

Dyspnea is a subjective sensation of difficulty breathing. In the last days of life, patients may not be able to communicate this sensation. Tachypnea and increased work of breathing in a nonverbal or confused patient may indicate respiratory distress, but do not always correlate with subjective symptoms [53]. Dyspnea can cause anxiety which in turn worsens the sensation of breathlessness. Potentially reversible factors include bronchospasm, pleural or pericardial effusion, pulmonary edema, anemia, infection, and pulmonary embolism. Treatment options should be based on consideration of goals of care and prognosis. Therapeutic drainage of effusions may provide symptomatic relief but can be burdensome for a dying patient.

Non-pharmacological measures to relieve dyspnea include adopting a seated position, a fan blowing toward the face, opening doors and windows, reassurance, and controlled breathing [54, 55]. Oxygen is only of symptomatic benefit if there is hypoxia [56]. Opioids are the first-line palliative pharmacological management of refractory dyspnea [57]. If already on an opioid for pain, the dose can be increased by 25–50% [28, 31] and the patient and carer encouraged to use breakthrough opioid medication for dyspnea or pain. If the patient is opioid-naïve, the same or

slightly lower doses as for pain are usually prescribed [58]. Benzodiazepines are often used for anxiety secondary to dyspnea. Clinical trials of benzodiazepines for dyspnea have in general been negative; however midazolam has been demonstrated to relieve dyspnea in the last week of life in cancer [59, 60]. Bronchodilators, diuretics, and corticosteroids are generally continued if they are providing therapeutic benefit. Steroids may be useful if there is airway compression or lymphangitic carcinomatosis [61]. Anticholinergics are considered if excessive secretions are contributing to breathlessness. A small study of cancer patients with dyspnea refractory to opioids has demonstrated symptom benefit from both high flow oxygen and BiPAP [53]. Patients who were enrolled had poor performance status but greater than 1-week life expectancy, so this may not be applicable to the terminal phase. If dyspnea is severe and persists despite appropriate doses of opioid and benzodiazepine, palliative sedation may be considered [62].

Airway obstruction can present as acute severe distress. If it is not possible to relieve the obstruction by corticosteroids or interventional procedures or radiotherapy (if appropriate), sedation may be required to achieve comfort.

## Delirium

Delirium is common at the end of life [63]. It presents as fluctuating consciousness, attention, and cognition, often accompanied by perceptual abnormalities including hallucinations and agitation. Delirium may be hyperactive or hypoactive, which is more often underdiagnosed [63]. Screening for delirium is recommended, and brief simple tools can be utilized, e.g., I believe these need capitals as they are the names of specific instruments i.e., the Confusion Assessment Method and the Nursing Delirium Screening Scale but this may be your style [64]. Environmental and general care measures are advocated routinely to prevent delirium in the elderly hospitalized population [63].

Potentially reversible factors should be sought and treated where appropriate [65]. These include infection, e.g., urinary or respiratory tract infection, hypercalcemia, drug toxicity (opioids, steroids, anticholinergics, anticonvulsants), dehydration, and nicotine, drug, or alcohol withdrawal. Delirium may be aggravated by urinary retention, constipation, or undertreated pain. Irreversible factors may include progressive disease, central nervous system involvement by cancer, organ failure, and metabolic abnormalities. Routine parenteral administration of fluids in the terminal phase has not been demonstrated to prevent delirium [42].

Non-pharmacological management includes calm reassurance, reducing excessive stimulation, providing vision and hearing aids if indicated, clear environmental cues for day and night, and family education and support. Despite lack of supporting evidence, the standard first-line pharmacological management has been either typical (e.g., haloperidol) or atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine) [65]. Haloperidol is the commonest first-line medication and can be given orally or SC. Olanzapine is available in a wafer which may make administration easier. A recent randomized controlled trial in palliative care inpatients with mild to moderate delirium and an expected prognosis of greater than 7 days found increased agitation and shortened survival in those prescribed regular antipsychotic medications [66]. This has led to particular caution in prescribing psychoactive medications in this population. However, there is evidence that delirium is distressing for patients and families and unmet symptom distress should be proactively addressed with non-pharmacological interventions including family education and support [67]. Antipsychotics are probably best reserved for those with severe agitation despite these measures.

Vigilance is required to detect extrapyramidal side effects in those prescribed antipsychotics, e.g., akathisia which may manifest as worsening agitation. Caution should be exercised in patients with a diagnosis of Parkinson's disease as typical antipsychotics may worsen movement disorders. Older highly sedating antipsychotics (e.g., chlorpromazine, levomepromazine) may be considered if agitation is refractory and distressing in patients with a short prognosis [68].

Benzodiazepines are generally used as rescue medications and have a specific role in management of alcohol withdrawal. Short-acting benzodiazepines may be preferable, e.g., midazolam (SC) and lorazepam (oral, SL), to avoid daytime drowsiness and sleep-wake reversal. Nicotine replacement should be considered in cigarette smokers.

## Respiratory Secretions

Retained respiratory secretions are common in the last days of life [69, 70]. Impaired swallow and cough mechanisms and reduced consciousness are likely mechanisms. Audible secretions cause rattling breathing ("death rattle") which is often very distressing for the family. Patients are often unconscious at this stage and are thought to be spared the distress of this symptom [69]. The onset of audible secretions usually implies a prognosis of less than 48 h [70].

Secretions may be difficult to eliminate once established. Non-pharmacological management consists of placing the patient in a semi-prone or head-up position, meticulous mouth care, cautious suction if secretions are in the mouth, and cessation of parenteral hydration if being administered [71]. The mainstay of pharmacological management is anticholinergic medication, despite limited evidence of effectiveness [72, 73]. Those that do not cross the blood-brain barrier (hyoscine butylbromide, glycopyrrolate) are used preferentially due to the theoretical lowered risk of precipitating delirium [62]. There is no evidence of differences in efficacy between the available medications [74, 75].

## Other Symptoms

### Hemorrhage

Bleeding issues are not uncommon in advanced cancer. However, catastrophic hemorrhage is a rare but very distressing event [44]. Patients predisposed to bleeding include those with head and neck cancer, bone marrow failure, liver failure, and tumors close to major arteries or those eroding hollow organs or the airway. Cessation of anticoagulants and appropriate correction of coagulopathies (e.g., vitamin K replacement, platelet transfusion) may be considered if clinically appropriate. Malignant wounds may bleed and are frequently managed with topical application of hemostatic dressings or agents such as epinephrine or thromboplastin [76]. Antifibrinolytic medications (e.g., tranexamic acid and aminocaproic acid) may be used for patients with thrombocytopenia, altered coagulation, or a bleeding tumor, commonly gastrointestinal or gynecological cancers [76]. Prescribing must also balance the risk of clotting with any potential benefits. Antifibrinolytic medications should be used cautiously in hematuria, due to the risk of clot retention [77]. Local radiotherapy may also have a hemostatic effect for tumors or malignant wounds. Interventional techniques such as endoscopic injection or arterial embolization may also be considered.

Management of catastrophic hemorrhage includes calm reassurance of the patient and family, application of local pressure, suction, and dark towels to conceal and absorb blood. Pharmacological management includes immediate sedation with high-dose benzodiazepine and/or opioids given intravenously or intramuscularly (not SC due to impaired peripheral circulation) [78].

### Seizures

Seizures are a common complication in the last days to weeks of life for patients with brain tumors [79]. Seizure frequency is lower in those with metastatic rather than primary tumors [79, 80]. Other causes of seizures include leptomeningeal carcinomatosis, metabolic abnormalities, organ failure, medications (i.e., may lower seizure threshold), drug interactions, and drug withdrawal. Many patients with a primary or secondary brain tumor are taking antiepileptic drugs at the end of life [81]. If merely prescribed prophylactically at the time of surgery (i.e., no history of seizure), these may be discontinued relatively safely [82].

When there is a history of seizures, the risk of recurrent seizure activity needs to be considered when a patient is no longer able to swallow oral medication. Often antiepileptic medications are replaced by non-oral medications. If IV access is available, phenytoin, levetiracetam, or sodium valproate may be used. For acute treatment of seizures, benzodiazepines are the recommended first-line medication. Midazolam may be administered SC, intranasally, or IV and diazepam or lorazepam IV or rectally [83]. For seizure prevention in the absence of IV access, a continuous infusion of midazolam SC or clonazepam once or twice daily SC can be prescribed [84]. For refractory seizures phenobarbital may be used IV, SC, or IM [83].

## Psychosocial Care

Emotional distress is common and important to recognize at the end of life. The source of distress may be multifactorial: anticipatory grief, fear of dying, spiritual distress, poorly managed symptoms or fear of worsening symptoms, loss of independence and continence, sense of being a burden on caregivers, concern about family and loved ones, family conflict, or unfinished business which may be psychosocial, financial, or legal. It is important to consider that poorly controlled physical symptoms (e.g., pain, dyspnea, delirium) and some medications (e.g., corticosteroids, bronchodilators) may contribute to symptoms of psychological distress. Supportive therapies, including spiritual support, should be offered, but participation may be limited due to impaired cognition and fatigue. There is evidence that interventions that concentrate on meaning, hope, and stress reduction are effective [85]. Support for completing unfinished business should be provided where possible.

Depression may be difficult to diagnose at the end of life as many symptoms of depression overlap with those of normal dying (e.g., loss of appetite, poor sleep, loss of energy, poor concentration) [86]. Grief and other forms of emotional distress may complicate evaluation. Symptoms of pervasive hopelessness, loss of interest and pleasure, guilt, and suicidal ideation may suggest a diagnosis of depression [87]. A single question "Are you depressed" is a useful screening tool [88]. Collateral history from family members may assist in diagnosis. Management of depression should use a combined approach. Supportive psychotherapeutic interventions may be beneficial unless precluded by lack of energy or cognitive deficits [89]. Most antidepressants take several weeks to provide a therapeutic benefit [90]. Prescribing will be influenced by the patient's anticipated prognosis [91]. Sedating antidepressants, e.g., mirtazapine and trazodone, may help insomnia and improve appetite [89]. For patients established on antidepressants, these are generally continued until they are unable to be swallowed. Psychostimulants may have some symptomatic benefit for depressed mood, fatigue, and poor concentration [86].

Anxiety is common, either as a preexisting condition or a new symptom, and can in turn exacerbate other symptoms. This may be managed with psychological techniques, e.g., controlled breathing, visualization, distraction, and hypnosis. Benzodiazepines are frequently prescribed at the end of life, either PRN or regularly for anxiety. These may be given sublingually, rectally, or subcutaneously when they cannot be swallowed. Serotonergic antidepressants may be indicated for the treatment of anxiety for those with a longer prognosis (i.e., weeks) [92].

It is important to acknowledge, respect, and support spiritual and cultural beliefs and rituals around dying [93]. Spirituality may contribute to a person's beliefs about their illness and its treatment, their sense of meaning, and belief in an afterlife [94]. Cultural beliefs may impact on the role of family in information-sharing and decision-making, as well as preferences for end-of-life care [95, 96]. Clinicians have an important role in eliciting the impact of spiritual and cultural beliefs on patient care [94, 95].

Family support is important. Family meetings have a role for providing information and support to caregivers, managing family discord, navigating substitute decision-making, and planning future goals and location of care. Ideally these should be formalized multidisciplinary meetings

following a recommended agenda or framework [97, 98]. Usually the patient will participate unless they have impaired decision-making capacity, choose not to, or are unable to contribute due to the severity of their illness [99]. Caregivers may need support with issues such as caregiving burden, psychological distress, grief, and practical, financial, and legal matters.

## Requests for Hastened Death

Requests for hastened death may be a sign of existential or global distress, uncontrolled symptoms, depression or hopelessness, or a sense of being a burden. These requests may fluctuate over time [100].

Clinician's responses should focus on exploring underlying reasons for the request and a supportive response to these concerns [101]. A request for hastened death may represent a need to exercise control over the circumstances of dying [100]. In jurisdictions where physician-assisted dying is legal, it is an uncommon cause of cancer death, and many who request assisted dying do not eventually use this method [100, 102].

## Palliative Sedation

Palliative sedation is deep continuous sedation prescribed for patients with very short life expectancy with refractory symptom distress when all other symptom control measures have been exhausted or considered inappropriate. A palliative care consultation should be considered to ensure symptoms are indeed refractory to therapy and for advice on prescription and monitoring of sedation [103].

## Caring at Home

For most people with an ultimately terminal cancer, the vast majority of time is spent at home. Some people may have a clear choice about where they wish to be as death approaches [104]. A decision to die at home generally needs to be an active one, with support from family and friends, family doctor, and community nursing teams as a minimum. Some people will want and be able to engage in such discussion, and others will not. Many aspire to a home death, but death at home is not necessarily the best death [105, 106].

Managing the care of someone at home has specific challenges that are different from inpatient care or clinic management. Clinicians will still need to assess patient needs, and access to supports will vary between countries and within regions. As disease progresses, most people will experience some decline in physical function. There is generally a need for simple equipment such as a commode chair, a walking frame, and possibly something to raise the toilet seat. Hand rails may improve mobility and safety as well. Mattress protectors and measures to increase comfort and even a hospital-type bed may be available and desired. Many would prefer to remain in their own bed, but sometimes a compromise between personal choice and ease of nursing care may require negotiation. It is important to know how to access any publicly funded equipment sources as well as how to hire or purchase other aids that may be of assistance. For some people and their families, the best choice may be anticipating death in a residential aged care facility or nursing home, acute hospital, or a purpose-built palliative care/hospice facility. Symptom issues, carer fatigue or carer illness, or a change of mind may result in a changed site of care and ultimately site of death [107, 108]. Systems should be responsive to ensure that such changes in location of care are as seamless as possible.

To manage at home, most people will require the support of a personal carer or family member. As the disease progresses and function deteriorates, this need may become almost constant supervision. Between jurisdictions there will be varying access to nursing care in the home and other respite options. Nevertheless, a significant burden of personal care will generally fall to family caregivers.

Research has identified that access to assessment and support from healthcare professionals

is vital [109]. Many carers are fearful about deterioration and knowing whether an intervention is required or not [110]. They report a lack of skills to assess and manage symptoms. Concern about medication management is frequent [111]. Other family members may add to the burden, perhaps inadvertently, and carers may find that they have little or no time to perform other tasks for themselves. There is a significant risk to the health of a person who is caring [112]. Both they and the patient are likely to need significant psychological support as well as physical support.

As death approaches and patients are increasingly frail, particular attention will need to be paid to skin care. Simple measures such as clean, taut sheets and measures to minimize moisture or soiling from urinary or fecal incontinence are important. Mattress underlays and incontinence pads and other devices assist. Attention to mouth hygiene, clean teeth, and hydration of lips and tongue is important. Infections such as candida and herpes can reduce quality of life significantly. There are various proprietary preparations to moderate many of these symptoms.

In summary, it is important to ensure that every person who is approaching the end of their lives from cancer is provided with a patient-centered focus to care and has responsive assessment of their needs and there is attention to physical, emotional, psychological, and spiritual aspects of care using therapeutic communication skills and a collaborative approach by a clinical team.

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# 6 Supportive Care in Elderly Cancer Patients

Matti Aapro

## Introduction

It is widely accepted that after the age of 70, comorbidities become more frequent and organ function decreases. Supportive care in the elderly patient is based on the same principles as for younger patients, but elderly patients are at an increased risk of toxicity from any drug due to age-related decrease in organ function, the use of polypharmacy with increased risk of drug–drug interactions, and comorbidity. The comprehensive geriatric assessment is a multidisciplinary evaluation of the older patient encompassing a number of essential clinical domains, which provides an important method to evaluate a patient who is to undergo a major medical procedure. The specificities of depression in elderly cancer patients remain a largely unexplored field of research. Not all tools for the assessment of pain are equally reliable in the elderly. Analgesics should be used with care in the elderly who are more susceptible to drug side effects. Guidelines on the use of granulocyte colony-stimulating factors recognize older individuals above the age of 65 as a group at high risk. Malnutrition is observed frequently and leads to low albumin levels, a determinant of toxicity for drug therapy. Compliance needs to be carefully evaluated, particularly in patients with high risk of noncompliance such as elderly with dementia and impaired vision. Osteopenia and osteoporosis are frequent in the elderly, both in females and males. Besides exercise and use of calcium and vitamin D, bisphosphonates or denosumab is recommended for some patients.

There is not one precise definition of the age of "geriatric" patients, although it is widely accepted that after the age of 70, comorbidities become more frequent and organ function decreases. Thus, this is the age limit that is suggested to be used in future studies [1].

While cancer and cancer treatment are one of the prime causes of disability in older individuals, not only of mortality, the adverse outcomes of inadequate dosing and of lack of supportive care in both curative and palliative treatments have been demonstrated in a number of treatment settings [2]. The challenges of aging, comorbidities, and polypharmacy require special considerations for supportive care in the elderly, as outlined in this chapter.

## Evaluation of the Elderly Patient

The comprehensive geriatric assessment (CGA) developed by geriatricians is a multidisciplinary evaluation of the older patient encompassing a number of essential clinical domains (Table 6.1) [3], which is superior to simple assessments like

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**Table 6.1** Comprehensive geriatric assessment

| Domain | Instrument to assess |
|---|---|
| Dependency | Activities of daily living (ADL) |
| Dependency | Instrumental activities of daily living (IADL) |
| Depression | Geriatric depression scale (GDS) |
| Cognition | Mini-mental state examination (MMSE) |
| Comorbidity | Charlson comorbidity index (CCI) |
| | Cumulative illness rating scale-geriatric (CIRS-G) |
| Nutrition | Mini nutritional assessment (MNA) and body mass index |
| Polypharmacy | |
| Geriatric syndromes | |
| Mobility/falls | Timed Up and Go test/Tinetti test |

*Source*: modified from Extermann [3]

performance status (PS) [4]. It can reliably identify patients with a short life expectancy, and it allows for the correction of one or many clinically relevant issues, thus forming an essential basis for adequate support of many elderly patients who will undergo cancer therapy (Table 6.1).

However, as the CGA is a complex tool that is not reliably predictive of cancer treatment toxicity, ongoing studies are trying to define a screening tool and improve on its predictive value for the use of cytotoxic therapy in daily practice. It should nevertheless be emphasized that this tool, along with other evaluations, provides an important method to follow a patient who is to undergo a major surgical procedure [5]. Poor health in relation to disability assessed using the instrumental activities of daily living (IADL), fatigue, and PS is associated with a 50% increase in the relative risk of postoperative complications. Multivariate analyses have identified moderate/severe fatigue, a dependent IADL, and an abnormal PS as the most important independent predictors of postsurgical complications. Disabilities assessed by the activities of daily living (ADL), IADL, and PS are associated with extended hospital stays.

## Depression and the Elderly Cancer Patient

Depressive disorders are frequent in cancer patients and in elderly people, but the specificities of depression in elderly cancer patients remain a largely unexplored field of research [6]. Depression, in the elderly as well as the younger cancer patients, is at risk of being underrecognized and untreated. As recently reviewed, in clinical practice, the assessment and treatment of depressive symptoms in elderly cancer patients are largely based on data obtained from the general medical population [7]. However, in spite of the paucity of randomized placebo-controlled trials, there is evidence that depressive disorders in cancer patients can be successfully treated with antidepressants when such drugs are needed [8]. Elderly cancer patients differ from younger ones in their tolerance to some of the side effects of antidepressant agents that need to be introduced with caution. Obviously, data on some potentially important drug interactions, like that of some selective serotonin-reuptake inhibitors and tamoxifen, need to be taken into account [9].

## Pain Control in the Elderly

The elderly population will often suffer from noncancer-related pain due to comorbid conditions such as arthritis or osteoporotic fractures. This makes the evaluation of pain even more complex in the elderly than in younger patients. Not all tools for the assessment of pain are equally reliable in the elderly, and it is suggested that numerical rating scales, pictorial pain scales, and verbal descriptor scales are more reliable than visual analog scales [10]. Analgesics, as described in this book (Chap. 2), should be used with care in the elderly as the elderly are generally more susceptible to changes in doses and to drug side effects and they receive many drugs that may affect the metabolism of some pain-relieving agents. However, this should not deter the use of analgesics, in particular opioids, in the treatment of elderly patients who suffer from cancer-related pain [11]. Particular attention should be paid to the use of nonsteroidal anti-inflammatory drugs that often decrease the renal function. Another issue is that somnolence, dizziness, cognitive function, and gait impairment are often seen in the elderly who started on analgesics, and this can lead to falls and fractures.

## Neutropenia

Guidelines on the use of white blood cell growth factors (Chap. 22) recognize older individuals above the age of 65 as a group at high risk [12], confirming a previous position paper of the European Organization for Research and Treatment of Cancer (EORTC) in which we concluded that increasing age is not, in itself, a contraindication to cancer chemotherapy [13]. However, the risk of the development of febrile neutropenia may contribute to a reluctance to administer chemotherapy in the elderly patient population. Sufficient evidence allows us to affirm that prophylactic granulocyte colony-stimulating factor (G-CSF) reduces the incidence of chemotherapy-induced neutropenia, febrile neutropenia, and infections in elderly patients receiving myelotoxic chemotherapy for several tumor types. An agent of interest for the elderly population is pegfilgrastim, which is administered in a single injection, instead of repeated administrations like filgrastim or lenograstim. Accumulating data from "real-world" clinical practice settings indicate that patients often receive abbreviated courses of daily G-CSF and consequently obtain a reduced level of febrile neutropenia protection. Prospective studies are, however, needed to validate the importance of delivering the full dose intensity of standard chemotherapy regimens, with G-CSF support where appropriate, across a range of settings. These studies should also incorporate the prospective evaluation of risk stratification for neutropenia and its complications, including patient's age [14].

## Undernutrition: A Cause of Unexpected Toxicities

The clinical and biological factors of the elderly cancer patients that can lead to decreased treatment tolerance and increased need of support include nutritional aspects. Tumoral cachexia (molecular and physiological) and undernutrition are detailed elsewhere in this volume (Chap. 23). Malnutrition is observed in a third to two thirds of hospitalized or institutionalized elderly persons. A comprehensive screening tool for assessment of nutritional status is needed, but guidelines for the elderly are basically nonexistent [15]. If malnutrition is suggested by screening tests like the one included in the CGA, conventional nutritional assessment as per ESPEN guidelines is recommended before treatment is planned [16]. The most important factor related to undernutrition is the albumin level of the patient, which is a determinant of toxicity for chemotherapy as well as for targeted agents, as volume of distribution of many drugs is highly dependent on its level [17].

## Immunotherapy

Immune checkpoint inhibitors play an increasing role in the management of various malignancies. In general, these agents seem to be better tolerated in most patients and less toxic compared to conventional chemotherapy, and this is also true for the older patients that were fit enough to be included in the studies. However, immune-related adverse events (irAEs) are unique and different from commonly observed chemotherapy-related side effects. There is no prospective data on these toxicities specifically in the elderly, and guidelines or recommendations are currently based on symptomatic management from the ongoing clinical trials. Although most irAEs are low grade and manageable, they have the potential to be life-threatening and extremely severe if not promptly treated, and a prime example is diarrhea [18].

## Nausea and Vomiting

Elderly patients are somewhat less prone to nausea and vomiting related to cancer therapy, but guidelines do not indicate that they can or should be treated preventatively in a different manner from younger patients as documented in this book (Chap. 26). Some specific problems related to these patients are an increased risk of toxicity from antiemetics due to an age-related decrease in organ function, the use of polypharmacy with increased risk of drug–drug interactions, and comorbidity (hypertension, cardiac issues

(including the QTc interval on the electrocardiogram, a cause of concern for registration authorities), diabetes (which can be decompensated by corticosteroids given as antiemetics). Elderly patients have a higher risk of constipation and electrolyte disturbances than younger patients. Compliance needs to be carefully evaluated, particularly in patients with a high risk of noncompliance, such as the elderly with dementia and impaired vision [19].

## Osteopenia and Osteoporosis and Bone Metastases

Osteopenia and osteoporosis are frequent in the elderly, both in females and males. By definition, osteoporosis is associated with an increased incidence of fractures, but osteopenic patients being the majority, the majority of fractures actually occur in such patients. Age-related osteoporotic fractures result not only in an increase in morbidity for elderly patients but also in a decreased survival and an increase in the consumption of scarce health resources. In addition to the prevalent osteoporotic status, bone metastases cause considerable morbidity, particularly in the elderly population, including pain, impaired mobility, hypercalcemia, pathologic fractures, spinal cord or nerve root compression, and bone marrow infiltration. Besides exercise and use of calcium and vitamin D, bisphosphonates or denosumab is recommended for these patients, with or without osteoporosis. Several guidelines have been put forward [20, 21], and some address specifically the elderly cancer patient [22]. Besides their effect on delaying skeletal-related events in the setting of metastatic disease to the bones, bone-modifying agents can effectively contribute to relieving metastatic bone pain. Bisphosphonates have also been discussed as agents which might have an anticancer effect of their own, which would make them even more indicated for the elderly [21, 23]. Creatinine clearance should be monitored in every patient receiving these agents. The assessment and optimization of hydration status are recommended especially in elderly patients who are often dehydrated. Due to the risk from osteonecrosis of the jaw, routine oral examination and treatment of dental problems by a dental team are recommended before the use of bisphosphonates or denosumab.

### Conclusion

Supportive care in the elderly patient is based on the same principles as for younger patients. As older patients can have serious problems related to side effects that are considered of minor or modest importance in younger patients (like diarrhea or drowsiness), the use of any drug needs special precaution. A major topic of supportive care in the elderly, social support has not been addressed as it depends too much on specificities of the various health-care systems.

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# Supportive Care in Paediatric Oncology

7

M. D. van de Wetering and W. J. E. Tissing

## Introduction Epidemiology and Incidence of Childhood Cancer

Although childhood cancer represents about 1% of all cancer cases, it comprises worldwide around 250,000 children yearly. Globally this gives an age-standardised incidence rate of 140 per million per year [1].

Of these 250,000 children, 50,000 are diagnosed in the developed countries and 200,000 in middle- or low-income countries. Of the 50,000 children in the developed countries, around 85% survive. Of the 200,000 in middle- and low-income countries. only 25% survive. International collaboration is necessary to create possibilities to improve the care and cure of the paediatric cancer patients worldwide. The UICC (Union for International Cancer Control) initiated a world cancer campaign in 2005 to increase awareness, improve care and coordinate training of professionals (www.uicc.org) [2].

The types of childhood cancer (0–18 years) vary greatly from those seen in adults. The most common childhood cancers are leukaemia (30%, mainly acute lymphoblastic leukaemias) and brain tumours (mainly gliomas and medulloblastomas, 25%) (Fig. 7.1). Together they account for more than half of all new childhood cancer patients. The mixed group of solid tumours (45%) are tumours that mainly occur in children and sometimes in young adults and are related to the growth and development of the organs. Children can tolerate far more intense therapy than adults, and over the years, with combination of chemotherapy, surgery and/or radiotherapy, survival rates have improved (Fig. 7.2). Children in the high-income countries are mostly registered in trials, and (international) collaborations within these trials have led to the success of reaching around 85% survival in these children. Important trial and registration groups are the COG (Children's Oncology Group) and the SIOP (International Society for Paediatric Oncology) [3].

Supportive care of the paediatric cancer patient has played an increasingly important role in the management of these patients. As intensity of primary treatment has escalated, so have the side-effects such as myelosuppression and infection [4]. Children who receive aggressive chemotherapy such as the induction phase of leukaemia or lymphoma treatment or patients with any stem cell transplant have a chance of around 40% of getting a febrile episode during neutropenia; this is one episode per 30 days at risk. Around 10–15% of patients will have a proven bacteraemia. Only 2%

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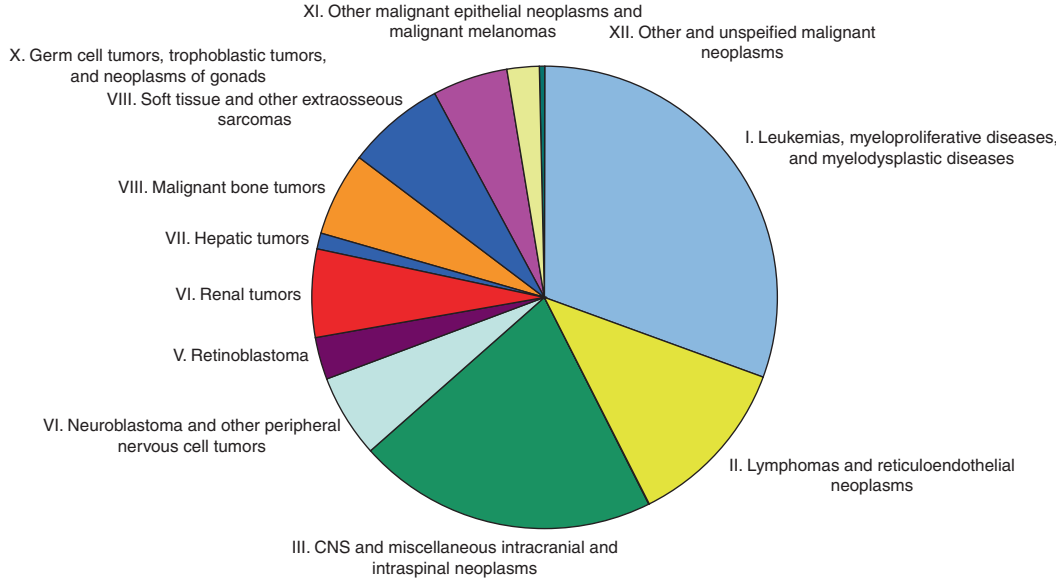


**Fig. 7.1** Childhood malignancies (Dutch registry DCOG)

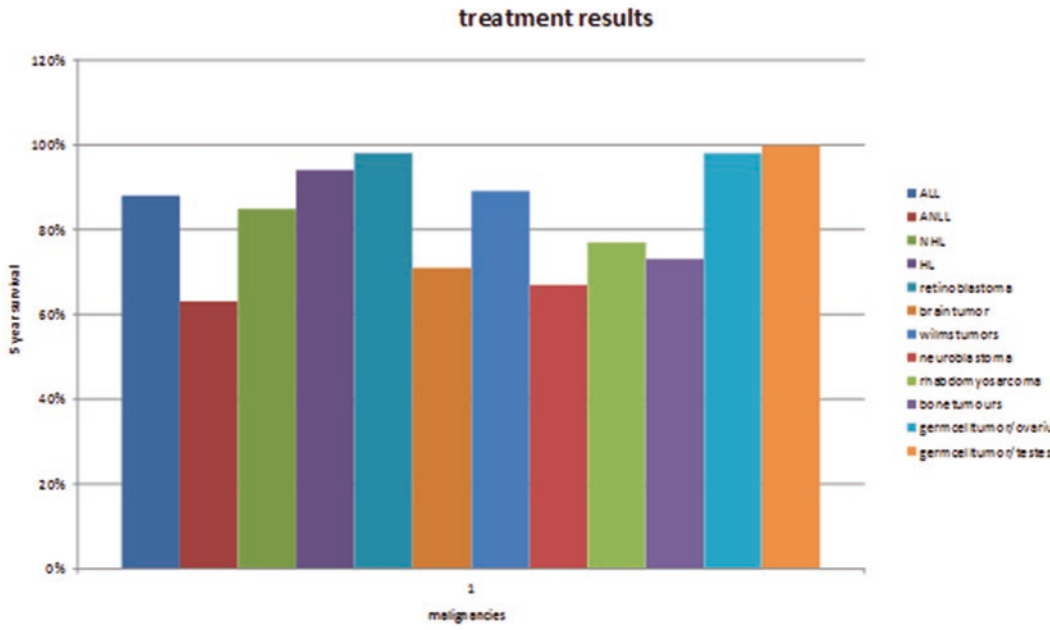


**Fig. 7.2** Treatment results 5-year survival (Dutch registry DCOG)

will present with invasive mycoses. Children with neutropenic fever more often present with fever of unknown origin (FUO) than adults. Therefore guidelines from adults cannot easily be translated to guidelines for paediatric oncology patients [5]. The more intensive treatment schedules also come with more nausea and vomiting, making adequate antiemetic treatment even more necessary.

Thus, optimal evidence-based supportive care is necessary to be able to prescribe the heavy

treatment protocols from these days [6]. The improvement that has come with modern treatment protocols consisting of surgery, radiotherapy and chemotherapy could not have happened without adequate supportive care. Internationally a collaboration has been started in 2014 developing and endorsing clinical practice guidelines for supportive care of children with cancer (www.sickkids.ca/research/ipog).

In this chapter, several aspects of supportive care in children with cancer will be highlighted concentrating on:

1. Infection prevention and management
2. The role of central venous catheters in children with cancer
3. Vaccinations during and after treatment
4. Emergency situations in paediatric oncology (tumour lysis syndrome)
5. Pain management
6. Antiemetic management

Unfortunately, improved prognosis of the children with cancer has also led to increased long-term adverse effects. The severity of these late effects is dependent on the type of cancer treated, the age of the child at time of treatment, type of treatment and agents used. These effects include second neoplasms, organ dysfunction, endocrine and metabolic problems, orthopaedic problems and psychosocial and cognitive problems [7]. Because of the importance of being aware of long-term adverse effects and the absolute need for a long-term follow-up clinic, the chapter will end with an overview of the most important long-term adverse effects that can be expected after treatment for childhood cancer.

## Infection Prevention and Management

### Prevention of Infection

The use of chemotherapy in childhood cancer can have a devastating effect on the immune system, reducing defences against infections, especially bacterial infections.

Patients and parents need to be instructed on how to avoid these infections. Of absolute importance is good hand hygiene and careful management of what the child eats and drinks, and advice needs to be given on how to manage the environment of the child. Most important is to create a balance between avoiding infection and allowing the child to lead a normal social life, including attending school.

Concerning the environment of the child during neutropenia (ANC < 500 cells/mm$^3$), one tries to encourage a normal lifestyle where children continue their school life and hobbies. Teachers should be informed about the situation and asked to inform the parents when contact with viral infections such as varicella or measles has taken place.

Concerning nutrition/diet, there is no proof of the usefulness of special measures concerning food products during neutropenia (ANC < 500 cells/mm$^3$), but it is recommended to avoid raw food, soft cheeses and "snack foods". A comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukaemia was done, and no difference in the two groups was found in severity of infection, time to major infection or mortality due to infection [8]. A Cochrane review was performed (with an update in 2016) summarising the evidence concerning this topic; as the evidence is very poor no definite recommendation could be given for clinical practice [9]. The parents should be aware that in case of any signs of infection during neutropenia, their physician should be notified, and this type of care should be available 24 h per day [10].

Other ways to possibly prevent infection include the use of (selective) gut decontamination: oral non-absorbable and absorbable antibiotics are used to preserve beneficial anaerobic organisms while preventing colonisation of the gut by pathogenic aerobic organisms.

Antibiotics are given orally before and during neutropenia. Systematic reviews have been published confirming that antibiotic prophylaxis significantly decreased the risk for death from infection when compared with placebo or no intervention (RR, 0.66 [95% CI 0.54–0.81])

[11–14]. The most significant reduction in mortality was observed in trials assessing prophylaxis with quinolones. The benefit demonstrated in these reviews outweighs harm, such as adverse effects, and development of resistance, since all-cause mortality is reduced. In patients with an estimated risk of infection exceeding 10%, such as patients with haematological cancer, bone marrow transplant patients and relapse patients, prophylaxis, preferably with a quinolone, should be considered. Because very few paediatric trials have been performed, it was not possible in these reviews to separately analyse the paediatric oncology population. Newer studies combining quinolones or TMP/SMX with erythromycin or roxithromycin to decrease Gram-positive bacteraemia have not been shown to give a significant reduction. Based on this systematic review and two other published systematic reviews, it is recommended that prophylactic antibiotics should be started before the expected neutropenia and continued until the neutrophil count is >500/mm$^3$.

The need for fungal prophylaxis is not as clearly stated as for bacterial prophylaxis, but with the increasing intensity of chemotherapy, antifungal prophylaxis is recommended as standard of care in high-risk patients (i.e., bone marrow transplant patients, haematological patients and relapse patients). This recommendation is stated by the IDSA (Infectious Diseases Society of America) guidelines, the CDC (Centers for Disease Control and Prevention) and the ASBMT (American Society for Blood and Marrow Transplantation). Early diagnosis is expected to improve results of treatment, but prevention of invasive fungal infection remains the ultimate goal [15].

Two meta-analyses performed by Bow et al. [10] and Glasmacher et al. [11] concluded that itraconazole prophylaxis is effective in reducing invasive aspergillus mortality (OR 0.58). However, if subgroup analyses were performed for paediatric studies, this advantage could not be verified. This might be caused by not giving adequate dosages of itraconazole [12, 16].

Newer studies in adults with posaconazole seem promising [13], and paediatric trials have been performed, but results are still awaiting. Although good RCTs are lacking, the current recommendation for prophylaxis in high-risk patients is itraconazole oral solution (5 mg/kg/day 1–2× daily max 400 mg) or posaconazole (600 mg/day in three divided doses but not approved in EU yet in patients <18 years) or fluconazole (6–12 mg/kg/day once daily max 400 mg but active only against yeasts). An important consideration is that children display differences in the disposition and clearance of antifungal compounds. Therefore, the optimal balance between efficacy and toxicity is not well understood. We do know that itraconazole capsules are not advised because of large inter- and intra-individual differences in bioavailability [17]. One must be cautious in children receiving vincristine as inhibition of cytochrome 450 and blocking of the p glycoprotein pump interferes with vincristine metabolism, causing severe toxicity in these children [18, 19]. In those children, one can either choose to monitor carefully for invasive aspergillus signs and not give prophylaxis or only give fluconazole prophylaxis to prevent yeast infections. Newer agents are not worldwide available as yet, and paediatric data are scarce, but one should be aware of trying to prevent invasive fungal infections in the high-risk child with cancer [16].

Another very important infection to prevent in immunocompromised patients is PCP (*Pneumocystis carinii* pneumonia) or *Pneumocystis jiroveci* infection. Over two thirds of children have antibodies by the age of 4, but this infection can have serious implications for the immunocompromised paediatric oncology population. Because of the widespread use of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis, morbidity and mortality have decreased [20]. TMP inhibits dihydrofolate reductase, and SMZ inhibits dihydropteroate synthase, and by inhibiting both steps in the folic acid synthesis pathway, the combination stops thymidine synthesis and ultimately DNA replication [21]. All patients with leukaemia, lymphoma and BMT (allogeneic or autologous) receive prophylaxis. Children with solid tumours who are expected to have prolonged episodes of neutropenia are also advised to use TMP/SMZ as

prophylaxis. The CDC advice is 150 mg/m$^2$/day TMP dose on three consecutive days or 3 mg/kg TMP, 15 mg/kg SMZ 2× daily all days of the week. An alternative to this prophylaxis is aerosolised pentamidine (300 mg/m$^2$ every 4 weeks). A disadvantage of this approach is the need for specialised equipment and personnel [22]. Another alternative is intravenous pentamidine 4 mg/kg diluted with dextrose 5% and given over 2 h [22]. In smaller studies, the breakthrough rate was 1.3% so i.v. pentamidine is considered a good alternative.

Other possible ways to decrease duration and severity of infections is with the use of granulocyte colony-stimulating factor (GCSF). This can be administered as a daily subcutaneous injection at a dose of 5 μg/kg/day or in pegylated form at 100 μg/kg/ only once administered. Concerning the pegylated form, trials have been performed in the transplant setting on mobilisation of stem cells in children, but not many trials have been done in children receiving chemotherapy and neutropenia in need of GCSF [23, 24]. The pegylated form has not been registered for use in children, the dose that is known is from small trials only. Guidelines of the American Society of Clinical Oncology suggest that CSFs be used as primary prophylaxis (before the onset of neutropenia) when the expected incidence of febrile neutropenia is 40% or more [25]. Since these guidelines are not that clear in children, a meta-analysis was performed by Sung et al. [26] in which 16 studies were included. They concluded that prophylactic CSFs (5 μg/kg/day sc) reduced the rate of febrile neutropenia by 20% and decreased duration of hospitalisation by 2 days. It also reduced the documented infection rate by 22% and amphotericin B use by 50%. But GCSFs did not reduce the infection-related mortality rate. Subanalysis in children with haematological malignancies showed the same results. GCSF should be administered to children as standard treatment only if the tumour treatment protocol requires it. Otherwise the use of GCSF should be advocated only if it improves the quality of life of the child. Therefore, future studies on the use of prophylactic GCSF also in the pegylated form and QOL measurements should be performed.

## Treatment of Infection in Children with Cancer

The frequency and severity of infections that occur in cancer patients depend on a complex interaction of a number of factors of which granulocytopenia is the most important. Granulocytopenia (or neutropenia) is defined as an absolute neutrophil count of less than 500 cells/mm$^3$. The frequency and severity of infections increase even more as the neutrophil count drops below 100 cells/mm$^3$. The duration of neutropenia influences the outcome of the infectious episode. Patients with neutropenia shorter than 7 days had a 95% response rate to initial antibiotic therapy compared to a 35% response rate in patients with neutropenia duration of more than 15 days [5]. Incidence of infections in neutropenic patients is around 10–15%, with children aged 10–19 at higher risk than children 1–9 years old. Poor outcome has been reported in between 7% and 10% of patients [27]. Thus, patients presenting with febrile neutropenia need specific attention. Children more often present with febrile neutropenia without an apparent site of infection than adults, making this an even more important issue in children than in adults [28].

Guidelines for the management of fever in neutropenic adult cancer patients include broad-spectrum antibiotic therapy at the onset of fever as outlined by the Infectious Diseases Society of America [29]. These guidelines describe both the evaluation of the patient as well as the empirical treatment. For children, such guidelines have been done and are presented on the IPOG website (www.sickkids.ca/research/ipog). They guide us through the specific groups on what to do in an evidence-based way [30]. These guidelines also identify research gaps; therefore there is room for improvement [31].

Fever is defined as a single temperature >38.5 °C or a temperature of >38 °C for more than 1 h. In the management, the clinician is directed to carefully and repeatedly evaluate for specific signs and symptoms of a focus or type of infection. Lack of neutrophils leads to minimal signs of inflammation at the site of infection. In children on presentation, a thorough

physical examination is needed, including emphasis on the mucosal membranes, the lungs, soft tissues (e.g. perianal inspection) and the central venous catheter.

Laboratory evaluation should include a complete blood count, liver enzymes, renal function and blood cultures (if a central venous catheter is present, a culture should be taken from this orifice). Blood cultures from both the ventral venous catheter and the peripheral line (when both are present) should only be advocated if the department of microbiology can perform semi-quantitative cultures. In that case, it can help to distinguish between a central venous line infection and a bacteraemia. Urine culture, stool culture and testing for Clostridium toxin should only be done if indicated. Routine culture of the cerebrospinal fluid is not recommended unless signs or symptoms of meningitis are present. Chest X-ray should only be done when signs are present suggesting a pulmonary infection [5].

The management of febrile, neutropenic children with cancer differs due to institutional variations in the spectrum of infections, antimicrobial susceptibility patterns of pathogenic microorganisms and the underlying aetiology of the neutropenia.

The pattern of infective pathogens has changed significantly over time. Whereas in the 1960s and the 1970s, Gram-negative bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the most frequent bacteria isolated in patients with febrile neutropenia, more recently Gram-positive bacteria are the predominant species, accounting for 70% of proven bacteraemia [5]. Of the Gram-positive organisms, the *coagulase-negative staphylococci* are the most common, but enterococcal and viridans group streptococcal species are becoming increasingly problematic, because of increasing antibiotic resistance [27]. Of the Gram-negative organisms, the most frequently observed pathogens are *Escherichia coli*, *Klebsiella* species, *Serratia* species, *Proteus* species and *Pseudomonas aeruginosa*. The organisms of significance include multidrug-resistant *Acinetobacter baumannii*, ESBL-producing *Enterobacter* spp. and carbapenem-resistant *Enterobacter* spp. With more intensive chemotherapeutic protocols and bone marrow transplantation, other serious infections emerge because of the prolonged severe neutropenia. Infections with fungal organisms such as *Candida* species, *Aspergillus* species or other opportunistic fungi occur (now 2% of all bloodstream infections, with high mortality).

## Empirical Therapy for Children Presenting with Febrile Neutropenia

### Initial Antibiotic Therapy

Because the progression of infection in neutropenic patients can be rapid, and because such patients with early bacterial infections cannot be reliably distinguished from noninfected patients at presentation, empirical antibiotic therapy should be started promptly. The initial goal is to provide broad-spectrum antimicrobial cover, for both Gram-negative and Gram-positive organisms, including pseudomonas species (therefore a contraindication for third-generation cephalosporins for Gram-negative coverage). In their clinical practice guideline, Lehrnbecher et al. recommend the use of an antipseudomonal beta-lactam or a carbapenem as empiric therapy in paediatric high-risk febrile neutropenia, FN (1A; strong recommendation, high-quality evidence). Reserve addition of a second Gram-negative agent or glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centres with a high rate of resistant pathogens (1B; strong recommendation, moderate-quality evidence) [30].

### Modification of Treatment

The therapeutic plan should be reassessed after 3–5 days. If the patient becomes afebrile within 3–5 days and has a positive blood culture, one should provide optimal cover for that specific organism, although broad-spectrum antibiotic cover should be maintained to prevent breakthrough bacteraemia. Antibiotic treatment in case of a positive blood culture should be continued for a minimum of 7 days or until the organism is eradicated. It is not necessary to continue until the neutrophils recover. If the patient has persistent fever after 3–5 days of treatment, reassess

the patient carefully, and add diagnostic tests such as an abdominal ultrasound and chest X-ray looking for a focus. If neutrophils are recovering and the child is not septic, the same antibiotics can be continued despite the continuing fever. The second option is adding antibiotics with better Gram-positive coverage (e.g. coagulase-negative streptococci are not covered by ceftazidime) in case monotherapy is started initially. The third option is to change antibiotics to target anaerobes. The fourth option is to add antifungal agents especially if one expects neutropenia to be prolonged (patients at higher risk of developing fungal infections; patients with acute lymphoblastic leukaemia (ALL), AML, stage III and IV non-Hodgkin's lymphoma and aplastic anaemia). In these patients, galactomannan values should be determined, and a high-resolution CT scan of the chest should be performed (even in patients with normal chest X-rays). In case of abnormal signs on the chest CT scan, a bronchoalveolar lavage should be done, or in cases of high suspicion, a biopsy should be taken, if possible. Awaiting the results of these evaluations, antifungal drugs should be started [32]. The fifth option of stopping all antibiotics on the grounds that fever may be due to the medication as such is not recommended by the CDC guidelines.

In adults, several risk stratifications have been validated, for example, to start with oral antibiotics at presentation with febrile neutropenia, instead of intravenous antibiotics [33, 34]. In paediatric oncology patients presenting with febrile neutropenia, much research has been done to determine a subgroup patients in whom no antibiotics or antibiotics for a shorter duration of time can be considered. To date, several risk assessment models have been developed, although none have found broad clinical implementation. In the guideline by Lerhnbecher et al., it is recommended to stop antibiotics in low-risk patients after 72 h, if blood culture is negative, and the patient is afebrile for at least 25 h, irrespective of marrow recovery [30].

### Treatment of Fever Without Neutropenia

Good evaluation and physical examination is an absolute necessity. Laboratory evaluation will include a blood count, C-reactive protein (CRP) and blood cultures from the central venous catheter (CVC). If there is no CVC, one can wait for the blood culture result before starting antibiotics. If there is a CVC present, antibiotics can be given orally, for instance, Amoxicillin, or Augmentin, until the blood culture result is known.

### Antiviral Drugs

Because of the increased use of high-dose chemotherapy, cellular immunity can also be depressed, and therefore the chance of acquiring viral infections is increased, especially in bone marrow transplant patients. However, the real incidence of viral infections in children with febrile neutropenia remains unknown, especially since viruses are not always studied. Hakim et al. described the aetiology, clinical course and outcome of fever and neutropenia in children with cancer in the United States and showed that viral pathogens were identified in 34% of episodes of febrile neutropenia in paediatric cancer patients [35]. Like other children, the viruses that were found were respiratory tract viruses like respiratory syncytial virus (RSV), parainfluenza virus, influenza and rhinovirus or viruses in the gastrointestinal tract like adenovirus and rhinovirus. These viruses are usually not related to severe illness in the neutropenic child but in rare cases can cause serious morbidity. Treatment is largely supportive; in case of severe RSV infection, ribavirin may offer therapeutic benefit. In patients after stem cell transplant, these viruses can cause serious infections.

The viruses causing most problems in the immunocompromised children are the herpes viruses including herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV). These viruses can cause infections as a primary infection which usually occurs during childhood or by reactivation of viral replication during the immunocompromised stage. Herpesviruses can result in mucosal lesions, skin lesions and neurologic symptoms. Systemic treatment with acyclovir is needed at a dose of 750 mg/m$^2$/day, divided in three doses intravenously for at

least 5 days. Primary infection with VZV results in chickenpox. In the immunocompromised, severe complications may be seen leading to a fulminant illness with visceral dissemination of the virus. Untreated VZV pneumonitis can be fatal in up to 7% of affected children. Treatment should be systemic with acyclovir or the newer oral drugs such as Famciclovir® or Valaciclovir® which show a better oral absorption than acyclovir. Cytomegalovirus (CMV) can result in fever, rash, hepatosplenomegaly, pneumonia, neurologic symptoms and retinitis. Treatment is with ganciclovir 10 mg/kg/day in two divided doses intravenously or foscarnet 90 mg/kg every 12 h. Prolonged courses of therapy are necessary to eradicate the infection.

## The Role of Central Venous Catheters in Children with Cancer

In high-income countries, most children receiving chemotherapeutic treatment will have a central venous catheter inserted (>80–90%), in contrast to adults. The catheters that are inserted are internal long-term catheters called port-a-caths or external long-term catheters such as the Broviac or Hickman catheter. These catheters have many advantages to administer chemotherapy, blood products and fluids. Complications related to the long-term use of central venous catheters are minimised by recommended protocols for catheter placement, dressing, care, administration of solutions and monitoring [36]. The two most important complications in central venous catheters are infections and thrombosis. Infections in central venous catheters in children with cancer occur in about 30% of patients and vary according to the CVC inserted where internal catheters (pac 0.1–0.5 per 1000 catheter days) have a lower infection rate than external CVCs (Hickman/Broviac 1.7–2.3 per 1000 catheter days) [37].

Infectious complications are those that result in infection of the bloodstream and/or device, the subcutaneous pocket, the tunnel or exit site. Treatment of the infected catheter can be successful in more than 80% of documented catheter-related infections. Usually these infections are caused by Gram-positive organisms (mainly *coagulase-negative staphylococci*). However, cover for Gram-negative organisms is necessary until an organism is identified. Treatment failures result from infections with multiple organisms, fungi, *Pseudomonas aeruginosa*, resistant Gram-negative organisms and tunnel infections. Thus, in cases of persistent fever despite adequate antibiotics, removal of the catheter should be considered.

In case of a *Staph. aureus* infection, the treatment should be administered for at least 2–3 weeks if the catheter is left in place, as *Staph. aureus* is associated with a late complication rate of 6.1%. If the catheter is left in place, the systemic antibiotics should be administered through the catheter. Cycling antibiotics through each lumen or placing concentrated antibiotics within the locked catheter hub (antibiotic-lock technique) is not widely validated yet for children so it cannot be recommended [36, 38].

Thrombosis is far less well documented, but it is thought that at least 50% of the children experience an episode of occlusion during the duration of the catheter for which intervention is needed. If the catheter is occluded, mechanical obstruction has to be ruled out. If this is not the case, causes could be the precipitation of drugs, the use of parenteral nutrition or the formation of a thrombus. In children, not many studies have been performed to establish the optimal management of thrombosis in central venous catheters. If the catheter is not needed anymore, then remove; otherwise treat with low molecular weight heparin for at least 3 months, and measure anti-Xa concentration until it is in an adequate range (0.6–1.0 U/mL) [39–41].

**Table 7.1** Vaccination recommendations during and after chemotherapy treatment

| Time related to chemotherapy | Vaccination | Recommendation |
|---|---|---|
| During chemotherapy | MMR[a] | Low herd immunity then single Ag—measles vaccine |
| | OPV[b] | Not allowed. If needed then eIPV[c] |
| | DTP[d] | Prefer to wait after stop chemo<br>If needed DtaP[e] |
| | Hepatitis B | High-risk area's Recombivax HB |
| Special vaccinations | Influenzae vaccine | Not contraindicated during chemo<br>Degree of protection low<br>No evidence based recommendation |
| | Varicella zoster | Degree of protection uncertain |
| | Pneumococcal vaccine | Splenic dysfunction, Hodgkin, post-radiotherapy (radiation spleen) |
| After chemotherapy | DTP/MMR/HiB[f]/ pneumococcal<br>HPV (age related)[g] | Restart schedule 6 months after stop chemotherapy |

[a]Measles-mumps-rubella vaccine
[b]Oral polio vaccine
[c]Enhanced inactivated polio vaccine
[d]Diphtheria-tetanus-pertussis vaccine
[e]Diphtheria-tetanus-acellular-pertussis vaccine
[f]Haemophilus influenzae b conjugate vaccine
[g]Human papilloma virus

## Vaccinations

Children with cancer who receive high-dose chemotherapy (autologous or allogeneic bone marrow transplant) or patients with haematological malignancies (leukaemia and lymphoma) will not only become granulocytopenic but will also have low lymphocytes and therefore most likely lose their antibody response to their vaccinations which were administered pre-chemotherapy. Thus, these children need attention concerning the vaccinations needed during chemotherapy, and reimmunisation schedules need to be given after chemotherapy (see also Table 7.1) [42]. Children on standard chemotherapy with an increased chance of lymphocyte dysfunction are reimmunised no sooner than 6 months after stopping chemotherapy. Allogeneic transplant children are revaccinated 12–18 months after BMT (according to the guidelines of the country they live in).

### Immunisation During Chemotherapy

Even if small children diagnosed with cancer have not completed their immunisation schedule, it should be clear that these children are NOT allowed live vaccines such as measles-mumps-rubella (MMR), oral polio (OPV), oral typhoid and yellow fever vaccine. In countries where tuberculosis is prevalent, the BCG vaccination is not allowed to be administered. Killed or inactivated vaccines do not represent a danger to the immunocompromised host, although it is well known that the immunogenic response to vaccinations is decreased during chemotherapy. However, this immunogenic response is not zero, which makes it possible to vaccinate with certain vaccines, especially in areas where herd immunity is low. Certain conditions should be met which include an adequate number of lymphocytes (>1000 × $10^9$/L), an adequate number of granulocytes (>1000 × $10^9$/L) and no use of dexamethasone 14 days before the vaccine and 1 week

after the vaccine. If herd immunity for measles is low, single antigen measles vaccine should be given before starting chemotherapy with the understanding that this should be repeated after stopping chemotherapy. If herd immunity for polio is low, eIPV (enhanced inactivated polio vaccine) is recommended in the household contacts and for the immunocompromised patient. It is safe and can confer some degree of protection. DTP (diphtheria-tetanus-pertussis) can be administered to the immunocompromised patient, including the use of acellular pertussis containing vaccines (DtaP). Haemophilus influenzae b conjugate vaccine (Hib) should be administered in those situations where the risk of haemophilus influenzae type b is high, in persons with anatomical or functional asplenia or additional sickle cell anaemia. Hepatitis B vaccination should ideally be given after stopping chemotherapy, but in high-risk groups or areas, it can be given to the immunocompromised with a lesser immunogenic response. The vaccine advised then is Recombivax HB 40 μg/mL. Periodic booster doses are usually necessary following successful immunisation, with the timing determined by serologic testing at 12-month intervals.

## Special Vaccinations During Chemotherapy

### Influenza Vaccination

A Cochrane systematic review was published emphasising the paucity of data on this vaccine [43]. Serological responses are generally lower than expected in healthy controls, and antibody levels considered protective in healthy individuals may not prevent clinical infection in those with malignant disease. There are no data on whether vaccination of paediatric cancer patients protects for clinical infection. The vaccine is well tolerated; therefore it is not contraindicated. Most countries recommend yearly vaccination and to vaccinate household contacts, but to date there is no evidence that this will decrease complications due to influenza.

### Varicella Zoster Vaccination

Although this is a live vaccine, it has been proven to be possible to administer safely during chemotherapy and raise an adequate immune response. As more complications of varicella zoster infection are seen in immunocompromised patients, it would be of great benefit if oncological patients with no detectable antibodies to VZV could receive the vaccine and seroconvert. It is however not yet routinely recommended. If considered appropriate to give the VZV vaccine, then chemotherapy should be suspended for 1 week before and 1 week [44, 45] after vaccination, and the patient should not be receiving steroids. Two doses are required. Cases of vaccine-associated varicella have been reported, and oral or intravenous acyclovir, as appropriate, should be used if the child develops a skin rash consistent with varicella. Seroconversion to VZV occurred in 82% of vaccines after one dose and in 95% after two doses. In addition, the incidence of clinical reactivation in vaccinated children is lower than in unvaccinated leukaemic children. Therefore, varicella vaccine administered under these conditions might be beneficial to the leukaemic patient [44]. However larger trials are necessary to confirm this.

### Pneumococcal Vaccine

This is recommended for use in persons >2 years of age with increased risk of pneumococcal disease, such as patients with splenic dysfunction or anatomical asplenia and Hodgkin's disease with involvement of the spleen or after radiotherapy, to the spleen.

## Immunisation Post-chemotherapy

Patients with haematological malignancies (leukaemia, lymphoma) after standard chemotherapy are recommended in most countries to be revaccinated 6 months post-chemotherapy. Most programmes recommend a booster dose for the routine childhood vaccines (Hib conjugate, diphtheria/tetanus/acellular pertussis (DtaP), MMR, inactivated poliovirus (IPV) and meningococcal C conjugate), and in some countries, the pneumo-

coccus conjugate vaccine (PCV7) is included, although no studies have been done on the response to PCV7 after chemotherapy [42]. Those patients who have undergone an allogeneic bone marrow transplant or autologous BMT need to be revaccinated a year to 18 months after transplant, and the immunogenic response should be measured.

## Tumour Lysis Syndrome (TLS)

TLS is a set of complications that can arise from treatment of rapidly proliferating and drug-sensitive neoplasms. In children, it mostly occurs in Burkitt's lymphoma, lymphoblastic lymphoma, acute lymphocytic leukaemia (ALL) with hyperleukocytosis and T-cell ALL. The chance of developing a TLS in above-mentioned cancers in childhood is around 2–4%. In acute myeloid leukaemia, the chance of TLS is much less. In very rare cases, TLS has been reported in solid tumours such as neuroblastoma, medulloblastoma and germ cell tumours [46]. The metabolic disturbances include hyperuricaemia, hyperphosphatemia, hypocalcaemia and hyperkalaemia.

Low-risk patients should be treated with allopurinol (100–200 mg/m$^2$ 2× dd) combined with hyperhydration (2–3 L/m$^2$ per 24 h). Urine output is extremely important and should be measured at 3 mL/kg/h. If not adequate, loop diuretics are administered, furosemide at 1 mg/kg/iv. High-risk patients (such as Burkitt's lymphoma and ALL with hyperleukocytosis) should receive urate-oxidase Uricozyme$^R$ or the recombinant form rasburicase (Europe Fasturtec$^R$ and in the United States Elitek$^R$) at the dose of 0.20 mg/kg/day, infused over 30 min, administering the first dose at least 4 h before the start of tumour-specific therapy and continuing for at least 3–5 days. In these patients, concomitant use of allopurinol is not allowed [46]. In a randomised prospective multicentre trial, it was shown that the risk of developing renal complications requiring dialysis in patients treated on rasburicase was 0.4%. Therefore in the high-risk groups, this is the drug of choice [47]. Note, if rasburicase is used, blood samples for uric acid measurement should be taken on ice, to prevent false low values. Depending on the risk of severe tumour lysis syndrome, once or twice daily blood should be drawn for levels of potassium, phosphate, calcium, uric acid, creatinine, etc. [48].

## Pain Management

Pain in children with cancer is mainly therapy or procedure related. This is in contrast to adult patients where pain is mainly tumour related. Fortunately children have a much better survival rate than the adult patients, and only 15% of patients have pain related to the tumour, either in the initial stage or in their palliative phase [49]. The first step in managing pain is to accurately assess the presence of pain. In children less than 4 years old, the assessment relies on behavioural pain scales, where crying, posture and facial expression are tools used to assess pain. Over 4 years of age, different validated scales are used, for instance, the FACES Pain Rating Scale (see Fig. 7.3) [50] or the word-graphic rating scale. It is extremely important that the pain is assessed at regular intervals over the day by parents or nursing staff and the score found is acted on.


**Fig. 7.3** FACES pain rating scale. From Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr Nurs*. 1988;14(1):9–17, with permission of Elsevier

### Therapy-Related Pain or Tumour-Related Pain

Since the initial WHO guidance, there have been significant changes in the understanding of pain, and it is recognised that there are different types of pain (nociceptive, neuropathic, etc.) and that pain is multimodal; therefore it is less effective to treat pain according to the level of pain but to treat it according to the analgesic's mechanism of action with the underlying physiology of the pain [51].

For children, the WHO 2012 guidelines guide the way in optimising pain control. It is recommended to use a two-step strategy according to the child's level of pain severity. The first step is mild pain mostly paracetamol, and in some cases ibuprofen can be used as well. The second step is moderate to severe pain for which a strong opioid is necessary [52]. If the patient does not achieve adequate pain control on the above stepwise approach, or if based on the physiology of the pain the above stepwise approach is not appropriate, then adjuvant therapy should be considered (see Table 7.2). Children need pain control most often for less than 1 week, much shorter than the adult patient. This applies mainly to the therapy-related pain, which is given in an in-patient setting.

### Special Pain Syndromes

Vincristine-induced neuropathy is a special pain syndrome. Symptoms vary from a feeling of paraesthesia underneath the feet to severe pain in the extremities. Regular opiates usually do not relieve it optimally. Antiepileptic drugs like gabapentin can be used, tricyclic antidepressants such as amitriptyline can be of support as can selective serotonin reuptake inhibitors such as Fluoxetine and sometimes a combination with other drugs is necessary. Trials however are needed to test the optimal treatment for neuropathic pain.

Methotrexate and other chemotherapeutic drugs can induce oral mucositis. When the patient needs pain medication, the pain is usually of such a magnitude that strong opioids are needed usually i.v. morphine, when possible using PCA (patient-controlled analgesia). Other ways of decreasing the intensity of oral mucositis might be offering low laser therapy local to the painful area in the mouth. This is currently (2017) being investigated in children.

Beyond the use of pharmacologic and medical care, one needs to consider nonpharmacologic adjunctive therapy. Although much less evidence is available, it is well known that hypnosis, fantasy, art therapy, etc. can help relieve anxiety and

**Table 7.2** Adjuvant pharmacological therapy

| Group of drugs | Example | Dose | Indication |
|---|---|---|---|
| Anxiolytics | Diazepam | 0.1–0.2 mg/kg/dose tid | Muscle relaxant |
| | Oxazepam | <6 years 2.5–10 mg/dose tid<br>>6 years 2.5–15 mg/dose tid | |
| Sedatives | Nitrazepam | 1–6 years 2.5–5 mg/dose opd<br>>6 years 5 mg/dose opd | |
| | Temazepam | 10–20 mg opd | |
| Antidepressants | Amitriptyline | Start dose 0.2–0.5 mg/kg bid. Dose can be increased to 3 mg/kg/day | Neuropathic pain |
| Antiepileptics | Carbamazepine<br>Gabapentin<br>Rivotril | 1.5–3 mg/kg/dose increase to 2.5–5 mg/kg/dose tid<br>5 mg/kg opd, 10 mg/kg tid<br>0.05–0.1 mg/kg/dose apply mucosal | Neuropathic pain and phantom pain |
| Steroids | Prednisone<br>Dexamethasone | 1 mg/kg/day oral<br>10 mg/m$^2$/day oral | Intracranial raised pressure brain tumours<br>And severe end stage tumours |

stress, and therefore the experience of pain will hopefully be less severe [53].

### Treatment of Pain Associated with Diagnostic Procedures

The main goal during paediatric procedures is to make the child comfortable so that the child and parents will not dread the subsequent procedures. Since paediatric oncology patients frequently need invasive, painful procedures, it is of utmost importance that the child gets optimal pain management during the first of a series of procedures. Both pain and anxiety have to be managed to achieve adequate control. In general, one must achieve a situation in the treatment room where adequate staff will create a calm environment where the procedure can be performed rapidly and efficiently.

Sedation is performed in many different ways. The *American Academy of Pediatrics* [54] and The *American Society of Anesthesiologists* [55] have set up guidelines, but these have to be individualised to the particular situation for that specific child.

1. For minor procedures such as venipunctures or access to subcutaneous reservoirs, topical anaesthetic cream can be used 1 h before the procedure (EMLA$^{R}$ or Rapydan$^{R}$).
2. For procedures such as bone marrow puncture, conscious sedation can be given. Usually this will consist of midazolam (Versed$^{R}$) 0.15–0.03 mg/kg rectally 15 min before the procedure or 0.05 mg/kg/i.v. slowly, but if the i.v. route is followed, trained anaesthetic personnel should be available as midazolam can give respiratory depression. In countries where anaesthetics can be given, it is preferred to do bone marrow aspirations and lumbar punctures under general anaesthetic (propofol).
3. Procedures such as bone marrow trephine are always performed under general anaesthetic where airway patency, breathing and circulation can be assured.

In all above steps, it is also important to help the child with nonpharmacologic methods in reducing stress and anxiety. Although the evidence available is poor, it is important to find a way to minimise stress and anxiety [53].

## Antiemetics

Nausea and vomiting (N+V) remain an important concern in cancer treatment. The American Society of Clinical Oncology has updated the guidelines in 2011 and added an update of a recommendation in 2016 [56, 57], and MASCC/ESMO performed the latest update in 2016 [58, 59]. In this latest update, a paediatric panel performed a guideline for only paediatric data. First it is important to assess with a validated nausea and vomiting tool how severe the score is for nausea and vomiting (N+V). This scale was developed and is called the PENAT score [60] and is comparable with the FACES pain rating scale for assessment of pain. It is extremely important that the N+V is assessed at regular intervals over the day by parents or nursing staff and that the score found is acted on, only then will it be possible to optimally manage N+V in the child with cancer.

Chemotherapeutic agents are grouped in four classes: minimal emetogenic (<10% of patients experience nausea and vomiting), low risk (10–<30%), moderate emetogenic (30–<90%) and high emetogenic (90% and greater). Medication is adjusted to the degree of emetogenicity. In low emetogenic chemotherapy, no antiemetic therapy is needed. Occasionally agents such as metoclopramide, domperidone or promethazine can be used. In moderately emetogenic chemotherapy, a serotonin receptor antagonist should be used, usually Ondansetron$^{R}$. If this is not effective alone, corticosteroids should be added. Both drugs will work synergistically. In high emetogenic chemotherapy, the combination of a serotonin

receptor antagonist plus aprepitant plus steroids (in adjusted dose) should be used. In this group, it is recommended to continue one of the antiemetics till 72 h after stopping the chemotherapy (to prevent delayed emesis). Beware that aprepitant is a moderate inhibitor of CYP3A4 and a weak inhibitor of CYP1A2, 2C8, 2C9 and 2E1. By definition, a moderate inhibitor increases the area under the concentration vs. time curve (AUC) of a sensitive substrate by two- to less than fivefold, whereas a weak inhibitor increases the AUC of a sensitive substrate by 1.25- to less than twofold. Aprepitant consequently may decrease the clearance of many chemotherapy agents commonly used in paediatric oncology. Thus, potentially increased cumulative chemotherapy exposure may pose concerns regarding a heightened risk of late effects in children. In every individual child, calculate on the type of chemotherapy given the level of emetogenicity what is best for this child now.

It is very important to attempt an aggressive plan at the start of therapy to avoid or minimise the initial experience of nausea, since there is a greater chance of preventing the development of anticipatory nausea and vomiting. If anticipatory vomiting does occur, benzodiazepines are usually effective (summary see Table 7.3).

Radiotherapy can also lead to nausea and vomiting. Therefore, it is recommended that a serotonin receptor antagonist is given about 30 min before the start of radiotherapy. Obviously the above-mentioned guidelines are recommended based on the best available evidence. However, discomfort associated with nausea and vomiting is a very subjective experience; therefore treatment should be individualised allowing the patient's and parent's opinions to influence antiemetic regimens with subsequent courses [61].

## Late Adverse Effects

The prognosis of childhood cancer has improved dramatically; unfortunately this has come with a rising incidence of treatment-related (long-term) complications. Adverse effects that occur one or more years later are called long-term adverse effects and are caused by all the treatments given, surgery, chemotherapy and radiotherapy. Because of the potential long-term effects, follow-up care is extremely important. In many countries, this has been realised already, which gives a much better insight into all the late effects that occur. At 5-year follow-up, nearly 75% of childhood cancer survivors had at least one adverse event, and 40% had at least one severe or life-threatening disabling adverse event. Radiotherapy is the most important cause for adverse events in follow-up, leading to cardiovascular, endocrine, neurological, second malignancies and psychosocial and cognitive adverse events. Some chemotherapeutic agents can have severe long-term sequelae. Risk of cardiovascular adverse events is increased following anthracycline-containing chemotherapy. Alkylating agents can give an increased risk of renal adverse events and of infertility. This is also the case after platinum-containing chemotherapy. One of the adverse effects with major impact on the quality of life is the development of a second malignancy. This chance is increased if compared to the general population but will depend on the chemotherapy or radiotherapy given (Table 7.4). Radiotherapy was the strongest risk factor for new primary malignancies, and this excess risk remains even after 25 years of follow-up. All these long-term effects stress the need for long-term follow-up, to monitor these children into adulthood and evaluate possible subclinical events and possibly treat these adverse events in an early stage (for instance, hypertension or cardiac failure) and try to improve the quality of life after childhood cancer [7, 62, 63].

**Table 7.3** Antiemetic agents (see also Ref. [59])

| Emetogenic potential | Drug | Antiemetic therapy | Delayed emesis |
|---|---|---|---|
| Minimal emetogenic (<10% emesis) | Asparaginase<br>Bevacizumab<br>Bleomycin<br>Busulfan oral<br>Steroids<br>Fludarabine<br>Hydroxyurea<br>Interferon<br>Melphalan oral<br>Mercaptopurine<br>Methotrexate < 50 mg/m$^2$<br>Rituximab<br>Sorafenib<br>Thalidomide<br>Thioguanine<br>Vinblastine<br>Vincristine<br>Vinorelbine | None | None |
| Low emetogenic (10–30% emesis) | Busulfan<br>Capecitabine<br>Docetaxel<br>Doxorubicine (liposomal)<br>Etoposide<br>5-Fluorouracil<br>Gemcitabine<br>Methotrexate −1 g/m$^2$<br>Thiotepa<br>Topotecan | 5 HT3 antagonist (e.g. ondansetron/ granisetron) | |
| Moderate emetogenic (30–90%) | Busulfan<br>Carmustine < 250 mg/m$^2$<br>Clofarabine<br>Daunorubicin<br>Doxorubicin<br>Epirubicin<br>Etoposide<br>Idarubicin<br>Ifosfamide<br>Imatinib<br>Intrathecal therapy<br>Irinotecan<br>Lomustine<br>Melphalan > 50 mg/m$^2$<br>Methotrexate > 1 g < 12 g/m$^2$<br>Oxaliplatin<br>Temozolomide | 5 HT3 antagonist (e.g. ondansetron/ granisetron) and dexamethasone | None |
| High (>90% emesis) | Carboplatin<br>Carmustine<br>Cisplatin<br>Cyclophosphamide > 1 g/m$^2$<br>Cytarabine > 3 g/m$^2$<br>Actinomycin<br>Doxorubicin > 60 mg/m$^2$<br>Melphalan (iv)<br>Methotrexate > 12 g/m$^2$<br>Mitoxantrone > 15 mg/m$^2$<br>Procarbazine<br>Thiotepa > 300 mg/m$^2$ | 5 HT3 antagonist (e.g. ondansetron/ granisetron) + dexamethasone (adjusted dose) + NK1 antagonist (aprepitant)<br>If an NK1 antagonist is not used usual dose of dexamethasone | Continue Ondansetron × 72 h |

**Table 7.4** Risk of second malignancies in long-term survivors of childhood cancer

| | | Observed cases[a] | Expected cases | SIR[b] | 95% CI[c] | Absolute excess risk[d] |
|---|---|---|---|---|---|---|
| Second malignancy | All second malignancies (incl. benign meningiomas)[e] | 60 | 5.37 | 11.2 | 8.53–14.4 | 3.20 |
| | All second malignancies (excl. benign meningiomas) | 48 | 5.08 | 9.45 | 6.97–12.5 | 2.51 |
| | Solid tumours[f] | 51 | 4.20 | 12.1 | 9.05–16.0 | 2.74 |
| | Solid tumours including third primary tumours[g] | 56 | 4.20 | 13.3 | 10.1–17.3 | 3.03 |
| | Bone | 5 | 0.18 | 28.1 | 9.14–65.7 | 0.28 |
| | Connective tissue | 10 | 0.21 | 48.6 | 23.3–89.4 | 0.57 |
| | Breast | 3 | 0.50 | 5.98 | 1.23–17.5 | 0.15 |
| | Ovary | 2 | 0.12 | 16.1 | 1.95–58.2 | 0.11 |
| | Brain | 4 | 0.37 | 10.8 | 2.93–27.6 | 0.21 |
| | CNS[h] | 13 | 0.32 | 40.1 | 21.4–68.6 | 0.74 |
| | Meningioma | 12 | 0.29 | 41.2 | 21.3–71.9 | 0.69 |
| | Thyroid[i] | 6 | 0.16 | 38.7 | 14.2–84.2 | 0.34 |
| | Basal cell carcinoma[j] | 18 | 2.01 | 8.95 | 5.30–14.1 | 0.94 |
| | Leukaemia and lymphoma[k] | 9 | 1.16 | 7.76 | 3.55–14.7 | 0.46 |
| | Leukaemia | 4 | 0.36 | 11.1 | 3.02–28.3 | 0.21 |
| | Leukaemia and MDS[l] | 7 | 0.36 | 19.4 | 7.79–39.9 | 0.39 |
| | Non-Hodgkin's lymphoma | 4 | 0.32 | 12.7 | 3.45–32.4 | 0.22 |
| | Lymphoma | 9 | 1.15 | 7.82 | 3.58–14.9 | 2.40 |

*Source*: Reprinted with permission from Ref. [62]

[a]At least two observed cases per category are represented in table

[b]Standardised incidence ratio

[c]Confidence interval

[d]Per 1000 person-years

[e]12 benign meningioma cases are included in the analysis; expected rate is based on the incidence of benign CNS tumours. 3 MDS cases and 16 basal cell carcinoma cases are excluded, since incidence rates in population are not available

[f]Includes, other than the specific sites denoted below, 12 benign meningiomas, and 2 malignant orbital tumours, 2 melanomas, 1 abdominal adenosarcoma, 1 cervical carcinoma, 1 carcinoma sinus maxillaris, 1 carcinoma colon and 1 carcinoma of tongue

[g]Includes also 5 third primary cancers (2 lung carcinomas, 1 meningioma, 1 thyroid carcinoma and 1 rectal carcinoma)

[h]Includes 12 second benign meningiomas

[i]Including one third malignant thyroid carcinoma

[j]Expected rate of basal cell carcinoma was calculated using the incidence rates of the Eindhoven Cancer Registries; observed number includes two third primary basal cell carcinomas

[k]2 ALL, 1 AML, 1 CML, 4 non-Hodgkin's lymphomas, 1 Hodgkin's lymphoma

[l]Includes three second myelodysplastic syndromes; MDS only included in this subgroup

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# Health-Related Quality of Life in Cancer

8

Claudia Rutherford, Rebecca Mercieca-Bebber, and Madeleine King

## Introduction

### Terminology and Definitions: HRQOL and PROs

*Quality of life* is a complex concept, meaning different things to different people, taking different forms depending on the specific circumstances and purpose of its application. It therefore does not have a universal definition or a standard for its measurement [1]. While it is often used as an ill-defined umbrella term, it must be defined clearly in order to be clinically useful.

In its broadest sense, *quality of life* covers aspects of life that are beyond the scope of healthcare, such as living standards, housing, education, employment and the environment. It has been used in this sense in the context of economics and welfare since 1920. Since the 1970s, QOL has been used increasingly in the context of health, where its meaning is restricted to aspects that relate to health and healthcare [2]. This health focus is made explicit in the term *health-related quality of life* (HRQOL), and we recommend use of this term, noting that when the term *quality of life* is used in the health context, HRQOL is implied.

While there are many approaches to defining HRQOL, from different perspectives and for different applications, a widely accepted definition that is useful for clinical trials and health services research is:

> Health-related quality of life (HRQOL) is a multidimensional construct encompassing perceptions of both positive and negative aspects of dimensions, such as physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment [3].

Integral to the HRQOL definition is that it is *multidimensional*, including core domains plus symptoms that will differ across diseases and treatments. It is a *subjective* phenomenon, so the patient's assessment is preferred to that of a proxy such as a relative or attending nurse or doctor [3, 4].

As well as functioning and symptoms, there are many other important aspects of a person's experience of disease and treatment that may have a direct impact on HRQOL, such as satisfaction with care, unmet needs for information or support services and psychological adjustment to illness. Often the term HRQOL is used when any *patient-reported outcome* is measured. The difficulty of finding a universal definition and standard

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measurement approach for HRQOL and related concepts led to a new term:

> A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [5].

The term PRO does not tell us what is being measured, only that the patient is providing the data. PROs can be symptoms (e.g. pain, anxiety, nausea, fatigue), aspects of functioning (e.g. role, physical, emotional, social) and multidimensional constructs (e.g. HRQOL). For the purpose of this chapter, the PRO of interest is HRQOL.

## The Rise of HRQOL Research in Cancer

The oncology field has led advancements in HRQOL assessment and research. One of the first reports of the quality of survival was in 1966, from a clinical trial of radical mastectomy or limited surgery in which breast cancer patients self-reported lymphedema and activity status [6]. In 1969, Feinstein et al. [7] called for better methods to measure the quality of survival, proposing the need for assessment of a patient's pain, distress or suffering, after observing that cancer patients were often distressed by the adverse (but unmeasured) symptomatic effects of radiotherapy and chemotherapy. The 1980s saw exponential growth of methods to measure HRQOL and inclusion of HRQOL as an endpoint in cancer clinical trials. In 1985, the US Food and Drug Administration required HRQOL data as one of the "key efficacy parameters" in clinical trials for new anticancer therapies [8]. Shortly after, in 1986, HRQOL was used as the primary outcome in a randomised trial published in the *New England Journal of Medicine* [9]. In 1996, the American Society of Clinical Oncology (ASCO) treatment guidelines reinforced that HRQOL was one of three key endpoints for cancer clinical trials in addition to response and survival [10]. The need to consider patient experiences during treatment and beyond contributed to the growing awareness that HRQOL outcomes are crucial to patients and complement survival and treatment toxicity outcomes. More recently, the European Society for Medical Oncology (ESMO) and ASCO proposed standardised measures of the magnitude of clinical benefit [11] and the net health benefit [12] in clinical trials that incorporate effects on survival time, toxicity and HRQOL to determine whether patients are living better and/or longer as a result of their anticancer treatment.

## How Cancer Affects HRQOL

### Proximal Versus Distal Effects on HRQOL

Figure 8.1 illustrates how cancer and its treatments may affect a person's HRQOL. Proximal effects occur directly as a consequence of the cancer and/or treatment for the disease, such as symptoms of the cancer itself (e.g. pain, fatigue) and side-effects and toxicities from treatment (e.g. nausea, vomiting) [13]. These may consequently affect a person's ability to function and their overall sense of well-being, i.e. cause distal effects. Cancer diagnosis, recurrence and treatment can directly (i.e. proximal) impact psychological well-being, or indirectly, via experience of symptoms, side-effects and loss of functional ability.

The proximal/distal distinction is important when choosing a PRO instrument because it leads us to expect that distal outcomes will be influenced by factors external to healthcare, such that the effects of treatment will be increasingly smaller the more distal the measure becomes [13]. Therefore, a proximal outcome is more likely to be more sensitive to treatment effects than a distal measure and therefore appropriate as the sole or key PRO.

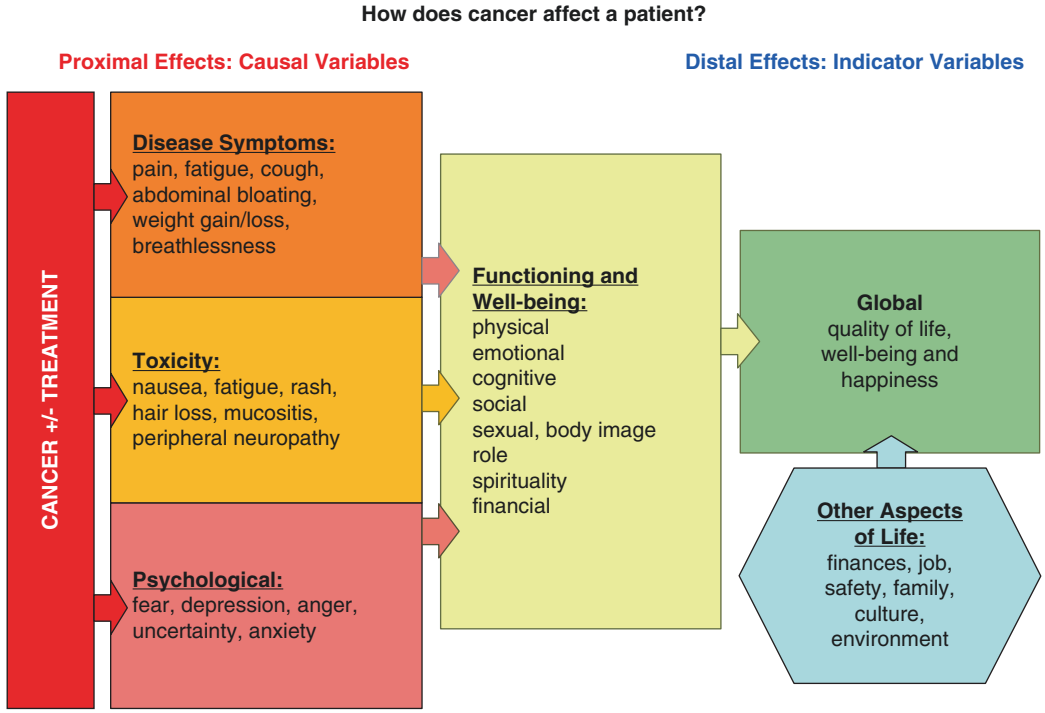


**Fig. 8.1** How cancer affects HRQOL: proximal versus distal effects

## Impacts on HRQOL Across the Care Continuum

Cancer and its treatments can affect HRQOL in many ways, from diagnosis through curative, adjuvant, palliative and end-of-life care. During these various phases, treatments may be preventative, curative or palliative. There will be differences in symptoms and side-effects [14] and differences during the acute treatment and survivorship phases. Patients will also differ in which HRQOL outcomes they are willing to trade off for specific treatment benefits (symptom palliation or increased chances of survival). Patients value benefits and harms of treatment differently and vary in how much risk, loss, regret or challenge to their personal life they prefer.

Some patients may experience signs and symptoms of the cancer even before diagnosis, such as pain, fatigue, skin changes, fever and unexplained weight loss. Signs and symptoms will depend on where the cancer is, how big it is, and how much it affects the organs or tissues. Not all people are symptomatic at diagnosis; e.g. ductal carcinoma in situ of the breast may be found upon mammographic screening in asymptomatic patients. A diagnosis of cancer will often have a major impact on a person's feelings, causing fear, anxiety and depression, and recurrence of cancer can have similar effects.

Treatments vary in type and intent according to the site, stage and biology of the cancer. All common treatments affect HRQOL in one way or another. Solid tumours are often first subject to surgery, which may cause the patient pain, mutilation and loss of normal function. Radiotherapy and chemotherapy kill normal cells as well as cancer cells and may disrupt the function of the bone marrow, lymphatic system and kidney, and adversely affect other organs. Subsequent side-effects may include nausea, vomiting, diarrhoea,

loss of appetite (anorexia) and hair (alopecia) and susceptibility to infection. Immunotherapies may cause rash, fatigue, nausea and other side-effects, while hormone therapies can cause osteoporosis, anaemia, muscle wasting, decline in cognitive function, depression, increase in body fat and metabolic changes. During treatment, patients may experience side-effects that can hinder HRQOL and make it difficult for some patients to complete treatment. Patient reports of treatment toxicity may be a useful adjunct to clinician ratings of adverse event criteria and may be more reliable [15].

Depending on the type of cancer, disease progression may be associated with pain, fatigue, nausea and vomiting, anorexia, constipation, depression and problems with breathing (dyspnoea) and sleeping (insomnia). These physical and psychological disturbances may adversely affect a patient's ability to perform usual roles and activities. Some patients may also experience positive outcomes, such as a return to previous levels of functioning as a result of treatment [16].

Some side-effects, such as neurotoxicity caused by chemotherapy, bowel problems caused by pelvic radiotherapy, scarring and body image issues in patients who have had surgery, and psychological distress may persist long after treatment completion. For example, about 30% of cancer patients suffer from clinically significant psychological distress [17], and up to 97% of cancer survivors report some degree of fear of cancer recurrence [18].

Surgery to excise the cancer may be followed by adjuvant therapy to decrease the chance of the cancer returning or spreading. This proves curative for some patients and prolongs survival for others. If the disease spreads to other tissues (metastases), palliative therapy is intended to reduce disease activity and symptoms, and may also prolong survival, but may also cause toxicity, so this is a context where PROs and HRQOL are particularly important and may even be included as primary endpoints in clinical trials [19].

Despite life-preserving benefits, treatments for cancer are not without cost. Acute, chronic and delayed treatment toxicity and other side-effects have been associated with many anticancer treatments, and these side-effects can be more than just minor inconveniences. Patients may experience considerable dysfunction due to their treatment, with adverse effects to their HRQOL, during the course and after completion of treatment. Some effects may persist into the long term, while others will return to pre-disease and pretreatment levels. Both the number and severity of symptoms contribute to overall symptom burden. As one might expect, greater symptom burden tends to be associated with a greater reduction in HRQOL [14].

## Surgery

Surgery is often the primary treatment for many cancers, especially when the cancer is localised (i.e. not spread), for example, in localised thyroid cancer [20]. Surgery in the form of biopsy may take place at the diagnostic stage to determine the stage and size of the tumour; as first-line treatment, to remove as much of the tumour as possible; as part of an adjuvant treatment schedule to remove the bulk of the tumour, without causing harm to other organs, prior to or following other therapies; or as a palliative measure to relieve pain or reduce obstruction to other organs.

Potential side-effects and the functional impact of surgery will depend on the type, site and extent of surgery. For example, prostate cancer patients may be offered a radical prostatectomy, which involves removal of the entire prostate gland and some surrounding tissue and seminal vesicles. Common side-effects may include urinary incontinence, erectile dysfunction and even impotence. These issues understandably can have an impact on a man's social activities, sexual functioning, emotional functioning, sexuality and HRQOL [21].

Women with breast cancer will typically receive diagnostic surgery and possibly more extensive surgery to remove the tumorous lump (lumpectomy) or even the whole breast (mastectomy).

The type of surgery will depend on the preferences of the patient and the risks and benefits of the surgery in controlling the cancer. Women who have a lumpectomy will experience pain and possibly impaired arm and shoulder function in the short term and scarring. Some women who have more extensive surgery, including removal of lymph nodes, may experience lymphedema, swelling, restricted arm and shoulder movement and recurring infections [22]. Women who receive a mastectomy may also choose to have a breast reconstruction, possibly using tissue from their own body. This surgery may be associated with pain and swelling of the breast and donor tissue site, functional difficulties with the shoulder girdle and abdomen, scarring and loss of sensation and psychosocial morbidity, contributing to problems with body image, sexuality, physical functioning and HRQOL [23].

Surgery for gastrointestinal cancer may lead to temporary or permanent functional problems with the bowel. These patients may be fitted with an ostomy appliance, which allows intestinal waste to pass through the abdomen into a stoma bag. Patients who have an ostomy appliance may experience distress, skin irritation, anxiety (particularly about odour and leakage), depression, reduced physical functioning, trouble eating and problems with sexual function [24].

The likely negative impacts of surgery on HRQOL must be considered by patients and clinicians during treatment decision-making. Because the impact and outcomes of surgery are specific to the cancer site and type of surgery, there are no generic surgical HRQOL instruments. However many surgical issues are addressed in cancer-specific HRQOL instruments (see the section "Types of HRQOL Instruments" in this chapter).

## Chemotherapy

Chemotherapy can affect the HRQOL of patients both positively, through alleviating symptoms and slowing, halting or reversing deteriorations in functioning, and negatively, through toxic side-effects. Due to its systemic nature, chemotherapy tends to present with similar side-effects regardless of cancer type; where side-effects vary, this tends to be a function of the drug regimens recommended in treating each cancer type [25]. The acute toxic effects of chemotherapy are a particular concern in cancer care. Since they last only a few days, there is a small window of opportunity for assessing them [26].

Chemotherapy commonly causes nausea, vomiting, fatigue, pain, hair loss, constipation, depression, anxiety and dread of treatment, difficulty sleeping, loss of appetite and weight changes [27, 28]. Nausea and vomiting continue to be problematic for some patients despite the progress made in treatment with antiemetics [29]. Nausea and vomiting are associated with loss of physical, cognitive and social functioning, global HRQOL, fatigue, anorexia, insomnia and dyspnea [30]. Patients with uncontrolled symptoms are more likely to suffer from depression and fatigue [30]. Fatigue is often associated with pain, sleep problems and depression, and correlates with reduced HRQOL, particularly physical and emotional functioning and daily living [31]. While many side-effects are short-lived, there is increasing awareness of the HRQOL impact of persistent effects such as peripheral neuropathy and irreversible hair loss, studied under the banner of survivorship research [32].

The role of chemotherapy in causing psychological distress is both biological and psychosocial. Chemotherapy drugs can cause or contribute to depressed mood in some cancer patients, as some drugs affect hormone function, with potential adverse mood and cognitive side-effects (e.g. medically induced menopause after oophorectomy or androgen ablation in prostate cancer treatment) [33]. Findings vary regarding the prevalence of depression and anxiety in patients with cancer undergoing chemotherapy. For example, reported estimates range from 4% to 47% in women with breast [34] or ovarian cancer [35]. Variation between estimates is likely due to different instruments and cut-points used [36]. Depression and anxiety are sometimes more common when chemotherapy is added to other treatments, and different drug regimens have also

been associated with different rates of depression [37]. Conversely, psychological distress has been found to be greater in patients who drop out of chemotherapy [38], suggesting a psychological benefit associated with undertaking treatment.

## Radiotherapy

Fatigue is frequently experienced in patients undergoing radiotherapy, and it may limit or prevent adherence and continuity of radiotherapy and reduce HRQOL. Other possible symptoms of radiotherapy include appetite loss, skin toxicity, pain, nausea and diarrhoea [39]. Longer-term effects may occur depending on the area treated, such as fertility issues from radiotherapy to the genital area or respiratory problems from radiotherapy to the lung area.

Radiotherapy is commonly used as a primary treatment for patients with head and neck cancers (HNC). Radiotherapy for HNC may be administered alone or in combination with surgery or chemotherapy. A common radiotherapy side-effect in this population is oral mucositis. This is a painful condition of the mucosa and submucosa characterised by temporary ulceration and inflammation that can lead to problems swallowing, taste changes, trouble sleeping, vocal problems, psychosocial issues and poor overall HRQOL [20]. Xerostomia is also a common side-effect, where damage to the salivary glands by radiotherapy reduces saliva production, leading to dry mouth. Xerostomia causes difficulty swallowing, speaking and eating and, in some cases, weight loss and oral infections and dental caries, which can have an impact on social functioning and HRQOL [20].

Radiotherapy has been related to favourable survival outcomes in men with prostate cancer. However, clinical trials comparing radiotherapy (brachytherapy or external beam radiotherapy) to other management options (e.g. radical prostatectomy, active surveillance, high-intensity focused ultrasound or cryotherapy), each alone or in combination (e.g. with adjuvant hormone therapy), report unique adverse event profiles with all treatment options, and higher radiotherapy doses involve more adverse events such as gastrointestinal and genitourinary toxicity [40]. Aside from mixed findings regarding urinary function, brachytherapy and radical prostatectomy were comparable in terms of HRQOL and biochemical progression-free survival while favouring brachytherapy regarding patient satisfaction and sexual function [40].

Clinical trials of breast-conserving surgery followed by radiotherapy for invasive breast cancer have shown good survival, but some have long-term toxicity from the addition of radiotherapy. The incidence of breast oedema, including breast pain, discolouration, skin thickening or rippling, ranges from 0% to 94%, and it may cause discomfort, distress and unsatisfactory cosmetic results, all of which can influence body image and sexuality [41].

## Hormonal Therapy

In men with prostate cancer, hormone treatment typically consists of androgen deprivation therapy (ADT). ADT may cause a range of side-effects that vary in their degree of morbidity and effect on HRQOL [42] including hot flushes, osteoporosis, loss of libido or impotence and psychological effects such as depression, memory difficulties or emotional lability. Hormone therapy combined with either prostatectomy or radiotherapy has been associated with significant survival benefits in patients with local or locally advanced prostate cancer. Significant local control and survival advantage may be achieved when hormone therapy is given prior to prostatectomy or radiotherapy, which may improve patients' HRQOL. However, hormone therapy is associated with significant side-effects, such as hot flushes, gynaecomastia and fatigue. The decision to use hormone therapy should, therefore, take into account the survival benefits, toxicity and cost, and the impact of long-term hormone therapy with regard to patient's HRQOL.

In breast cancer, the impact of hormonal therapy on HRQOL has had mixed results; some studies report a significant difference in HRQOL between treatment and control groups while others failed to find a difference. This may in part be due to limitations of study methods. Survival benefits may come at the cost of hot flushes, vaginal dryness, loss of interest in sex and weight gain [43], resulting in some patients discontinuing treatment. While another study concluded that hormonal therapy improved anxiety, depression, emotional, cognitive and social functions, and global HRQOL in breast cancer survivors [44].

In other tumour groups (e.g. endometrial cancer and ductal carcinoma in situ of the breast), Cochrane reviews highlight the lack of HRQOL assessment in hormone therapy trials [45] despite a validated PRO instrument available for assessing the impact of hormonal therapy on patients (the FACT-ES) [46].

### Immunotherapy

Immunotherapy works with the body's immune system to fight off remaining cancer cells by either stimulating the body's own defences or supplementing them. Some types of ovarian cancers, for example, are immunogenic, and therefore more recent clinical trials have focused on immune-therapeutic interventions in light of evidence that these offer longer survival and are more tolerable for patients. We are still learning about the impact of immunotherapies on HRQOL; however some forms have been associated with vomiting, nausea, urinary or bowel problems, fever and fatigue [47].

## The Need for Evaluating HRQOL in Patients with Cancer

The benefits and harms (e.g. symptom palliation and toxicities) of cancer treatments provide compelling arguments for incorporating the quality of patients' lives into decisions about treatment. Support for this notion has been expressed by clinical trials groups, cancer institutes, drug regulatory bodies and the pharmaceutical industry [5, 11, 12, 48, 49].

### When Is HRQOL Assessment Most Important

HRQOL assessment is especially important when prognosis is poor and treatments are associated with significant toxicity. In these instances, HRQOL is likely to be the primary endpoint. HRQOL may also be a useful primary, secondary or tertiary endpoint in situations where [19, 50]:

- A new (invasive) treatment is being evaluated.
- Different treatment modalities are being compared.
- Treatments of different intensity or duration are being compared.
- Treatments are expected to be of similar efficacy (e.g. in terms of survival), but differences in treatment trajectories and possible side-effects are expected. For example, a treatment found effective in reducing recurrence in a clinical trial may fail in the real world because it is highly toxic, reducing HRQOL and thereby compliance, hence compromising effectiveness.
- Adjuvant therapies for patients at low risk of recurrence of disease are being compared.
- Treatments differ in short-term efficacy, but the overall failure rate is high.
- Treatments may have long-term negative effects on HRQOL for survivors.
- The palliative benefits versus toxic side-effects of treatment are of interest.
- When insight into how best to provide supportive care over and above therapeutic care, when and for how long is of interest.

**Reasons for assessing HRQOL in cancer clinical trials and clinical practice** [4, 19, 51–53]

- Baseline HRQOL serves as an independent prognostic factor for survival and locoregional control.
- In some cases, HRQOL may be more sensitive and/or responsive to treatment effects than clinical measures of toxicity.
- HRQOL data may provide clinicians useful information when communicating with patients about their expectations and assist the patient and clinician in treatment decision-making through better understanding of treatment benefits and risks during the acute and survivorship phases (e.g. impact of chronic side-effects).
- Information about potential impacts on HRQOL may be one of the factors that patients consider when making decisions about treatments with their clinician.
- HRQOL helps patients make informed decisions based on what others have experienced (i.e. likely treatment effects), the efficacy and mortality associated with a particular treatment, and the possible or expected impact on HRQOL outcomes.
- PROs can be used to help identify those patients who might benefit from psychosocial interventions.
- Patients regard HRQOL as a priority and want it to be measured. As a result, recruitment rates may be higher when an HRQOL endpoint is included in clinical research.
- Measurement of HRQOL gives information about physical consequences of disease and treatments (symptom burden and decreased function); effect on a person's emotional state, feelings, coping and self-identify (psychological functioning); and a person's ability to interact with others and participate socially (work, social interaction and relationships, role functioning). This may be important in judging the effectiveness of a treatment.

## Methods of Assessing HRQOL in Cancer

A simple way of assessing HRQOL would be to ask a patient how they are feeling. However, this would likely yield very unreliable results as it would be prone to variations in both the way the question was asked and how the patient responded. A more standardised approach is needed. We do this by asking standard questions about relevant issues with a standard set of response options, in the form of a questionnaire. The questionnaire, along with the algorithm used to score patient responses into summary scores for analysis and reporting, is referred to as PRO instrument or measure.

PRO instruments draw on the psychometrics tradition and measure complex variables broken down into their component parts. Each question (item) may ask about a specific issue, for example, "do you have trouble remembering things?"; this is referred to as the "item stem". The stem will have a rating scale attached, known as "response options". The response option is usually in the form of a Likert scale, i.e. where 0 = not at all and 5 = very much so, enabling us to quantify the patients' response by attaching a numerical value to increasing levels of severity. This item may be grouped with similar items addressing a larger construct, such as cognitive functioning (often referred to as a domain or dimension), which when added together provide a scale score (or raw score) for cognitive functioning, or the scale may be comprised of only a single item. Any number of domains may be assessed in a single PRO instrument, that is, a PRO instrument may assess only one domain (unidimensional) or several domains (multidimensional). The raw scores may or may not be transformed. A common transformation is a linear transformation to an observable scale range of 0–100.

Patients usually self-complete PRO instruments, in line with the knowledge that HRQOL is subjective and so accordingly the patient should self-interpret each question. This practice also helps to reduce bias that may be introduced if questions are discussed with another individual, in line with the FDA's definition of PROs [5]. However, there are some circumstances where a researcher-administered instrument is necessary, for example, if the patient is fatigued or unable to read. Where patients are cognitively impaired or too weak or too young to self-complete, proxy assessment may be used, which will be discussed later in this chapter. As well as being quick and straightforward to use in research, instruments

have the advantage that they yield results that are readily comparable between studies. However, there are always limitations to the information that an instrument, or even a battery of instruments, can provide.

## Selecting a HRQOL Instrument

The large number of available HRQOL instruments makes it difficult for researchers to select one, particularly if more than one could be suitable. In brief, researchers should consult clinicians, patients and the literature to determine which issues are appropriate to the particular research and treatment context. They should then consult databases such as PROQOLID [54], which catalogue a large range of PRO instruments, to identify potentially suitable instruments assessing the domains of importance. These instruments should be reviewed to determine whether the questions address the issues in a meaningful way (content and face validity). The scoring system should be reviewed to determine whether the instrument produces a score for the issue(s) of importance to the research study. The literature should also be consulted to determine whether the instruments' validation studies were methodologically sound (refer to the section on what makes a good instrument described in this chapter) or whether more validation work should be done. Also, consider whether clinically important difference criteria or cut-offs have been established to assist with interpretation of the data. A pilot study in the population of interest can be a useful final step to assess the suitability of the instrument.

**Key questions to consider when selecting a PRO instrument**

1. Is the intended use for research or in clinical practice?
2. Which PROs are important to the particular research and treatment context?
3. Does the instrument cover all the PROs that matter in a given clinical context?
4. Does the instrument have evidence for the psychometric properties: validity, reliability, responsiveness, generalisability and interpretation?
5. Have clinically important difference criteria or cut-offs been established?

## Types of HRQOL Instruments

PROs may be generic, disease-/condition-specific, treatment-specific, symptom-specific and preference-based.

Generic instruments are designed to measure a range of constructs that can be applied across multiple diseases, outcomes, treatments/healthcare programmes and populations, as well as used with healthy populations [55], enabling comparisons of outcomes across diseases. A commonly used generic instrument is the Medical Outcomes Study short-form (SF-36) health survey [56].

In contrast, cancer-specific instruments are used to assess the impact of cancer generally, or a specific type of cancer, on a patient's health and functioning, with the goal of detecting minimally important effects (or changes) in individuals [55]. Disease-specific instruments often have better sensitivity to detect minor changes in HRQOL than generic instruments. Additionally, in light of the fact that certain treatments are used for multiple types of cancer, and certain clinical trials may recruit patients with different types of cancer caused by similar mutations, or receiving similar types of treatment, treatment-specific instruments are often used. Examples include measures specific to EGFR inhibitors and radiotherapy.

The three (generic-, disease- and treatment-specific) approaches are not mutually exclusive; each has its strengths and weaknesses and is suitable under different circumstances. Although also used to evaluate HRQL outcomes, preference-based instruments of health are a means of estimating health state values or preferences for calculating quality-adjusted life years [57]. These tools are used in economic evaluation in clinical trials to value the benefits of treatment or healthcare against the costs (e.g. time to healing) but are beyond the scope of this chapter.

## Types of Instruments for Cancer: Core Cancer Instruments Versus Tumour-Specific Modules

There are a multitude of available instruments. The two most widely used HRQOL instruments in

cancer clinical trials are the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core module (QLQ-C30 [48]) and the Functional Assessment of Cancer Therapy-General (FACT-G [58]).

### EORTC Instruments

The QLQ-C30 is the core instrument of the EORTC's modular approach to HRQOL assessment. It includes HRQOL domains relevant to a range of cancer sites and treatment types. The EORTC conceptualised HRQOL as multidimensional with at least three basic domains: physical functioning, including symptom experience and functional status; emotional functioning; and social functioning. It is a 30-item questionnaire with nine multi-item subscales and six single items. It incorporates five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain and nausea/vomiting) and a global health status/HRQOL scale. The single items assess dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea and perceived financial impact of disease and treatment. Ratings for each item range from 1 (not at all) to 4 (very much) during the past week. The QLQ-C30 is designed to be used across cancer populations and takes about 11 min to complete [48]. It is available in more than 90 languages.

The QLQ-C30 is complemented by modules specific to particular cancers, such as lung cancer (QLQ-LC13) and breast cancer (QLQ-BR23). The core module facilitates comparison of HRQOL across cancers, and the disease-specific modules provide sensitivity for particular trials.

### FACIT Instruments

The FACT-G was developed by social scientists over a 5-year period [58]. It is the core component within the Functional Assessment of Chronic Illness Therapy Measurement System (FACIT).

First trialled in 1992, it has undergone a number of refinements. The current version (version 4; 1997) includes 27 items appropriate for use with patients with any cancer type. Questions are summarised under four primary HRQOL domains (physical well-being, social/family well-being, emotional well-being and functional well-being). As well as domain scores, the instrument also yields a total HRQOL score (i.e. domain scores added together). Ratings for each item range from 0 (not at all) to 4 (very much) and refer to patient perception over the previous 7 days. The FACT-G is available in 45 languages. In addition to the FACT-G, the FACIT suite includes cancer type (e.g. lung, breast, ovarian), treatment (e.g. bone marrow transplant, neurotoxicity from systemic chemotherapy) and symptom-specific (e.g. anorexia/cachexia, fatigue) subscales.

The FACIT approach differs slightly from the EORTC modular system, where stand-alone modules are used in conjunction with the QLQ-C30. In the FACIT system, each of these disease, treatment and symptom-specific instruments implicitly includes the FACT-G instrument. For example, the FACT-B instrument contains all 27 questions from the FACT-G plus an additional 23 questions that relate specifically to breast cancer.

## What Makes a Good Instrument?

Scientific and methodological rigorous development of a HRQOL or other PRO instrument involves careful item selection informed by literature review and expert and patient opinion [5, 59] and testing of the instruments' validity and reliability with populations of interest. When deciding whether an instrument is "good", consideration of its (1) conceptual and measurement models, (2) validity, (3) reliability, (4) responsive to change, (5) interpretability, (6) respondent and administrative burden, (7) alternative forms and (8) cultural and language adaptations may be a deciding factor. Further, an instrument should be appropriate for the given clinical context, be acceptable, be feasible and have precision, should minimise measurement error and should ensure consistency, ultimately providing a more reliable measurement than what would be obtained by informal interviews. In practice and research, only structured and psychometrically rigorous instruments should be used. Important psychometric properties include validity, reliability, sensitivity, responsiveness and interpretability.

## Validity

The *validity* of an instrument is "the degree to which the instrument measures what it purports to measure" [60]. An instrument should be validated for every intended purpose. An instrument has good *content validity* if its items cover the range of issues that are relevant to its intended use, as determined by patients, healthcare professionals and previous research [61]. The more representative the sample of items, the more likely the instrument will yield inferences that hold true in a wide range of circumstances [59]. Whether or not it produces sensible and useful results in various circumstances should be judged in an ongoing process of validation [59, 61].

*Face validity* is used as a criterion when choosing among existing instruments for a specific purpose [61], which is distinct from content validity—the latter is determined during instrument development.

*Construct validity* is the extent to which the relationships observed among variables conform with hypothesised relationships (i.e. the degree to which an instrument represents what it is intended to measure) [59, 61]. There are two main types of evidence:

Hypothesised relationships among latent variables. Evidence is generally sought by correlation of observed variables: correlations between items in the same scale, correlations between an item and items in other scales, correlations between a scale score and its constituent items and correlations among scales of one or more instruments. *Convergent validity* is supported by correlation among measures of latent variables that are hypothesised to be similar. *Discriminant validity* is supported by lack of correlation among measures of latent variables that are hypothesised to be dissimilar. Common methods of analysis include *factor analysis*, *path analysis*, *multitrait-scaling analysis* and *multitrait-multimethod analysis*.

Hypothesised relationships exist between latent variables and external criteria. For example, patients with early-stage cancer may be expected to have better HRQOL than patients with advanced cancer. This type of evidence is said to support *clinical validity* or *known-groups validity* because the groups of patients are often defined by clinical criteria. This also provides evidence of the *sensitivity* of a scale to clinically important differences. This type of validity has also been called *discriminative validity* [61].

*Criterion validity* is the extent to which a measure corresponds to an external criterion [59, 61]. *Concurrent validity* means agreement with a true value, or "gold standard", which does not exist for HRQOL. If a short version of an established instrument is being developed, the long version may be considered the standard.

*Predictive validity* concerns the ability of an instrument to predict future health status or future events (such as hospitalisation or death). Evidence from various HRQOL instruments and a range of patient groups shows that HRQOL scores predict subsequent survival, independent of other prognostic factors such as performance status and age [62].

## Reliability

The *reliability* of a scale is its ability to yield reproducible and consistent results assuming all things being equal (i.e. true change has not occurred in the variable being measured) [61]. Formal definitions of reliability involve notions of *random variation* or *measurement error*. In HRQOL assessment, random variations may include real but transient variations in health or circumstance or in the perception of health or circumstance. Measurement error may be due to scale coarseness in approximating the continuous latent variable and inconsistent use of the scale by the respondent. A way of estimating reliability is to determine the consistency of results across items on the same measure (i.e. compare scale items that measure the same construct to determine a scales' internal consistency).

In a multi-item scale, the consistency of the items as measures of the same latent variable is

called *internal consistency*. The items are treated as repeated measures of the same concept. There are many measures of internal consistency, *Cronbach's alpha coefficient* being the most commonly used [63]. Internal consistency is commonly estimated and reported with construct validity.

Another type of reliability is the reproducibility or stability of scores on a scale when the circumstances of assessment differ but the patient's HRQOL does not. The mode of administration (self-completion or interviewer-assisted, hard copy or computerised forms) may impact reliability, along with place of completion (in the clinic or at home, in person or by telephone) and time (repeated occasions). Consistency among interviewers or proxies is commonly called *inter-rater reliability*. Reproducibility across repeated measurements is commonly called *test-retest reliability*. One of the difficulties with estimating test-retest reliability for HRQOL measures is identifying the appropriate patient population and test period. The period must be long enough so respondents do not remember their responses to questions and short enough so that their HRQOL has not changed. Reproducibility is often assessed by measures of agreement: *kappa* for discrete data or the *intra-class correlation coefficient* (*ICC*) for continuous data [63].

## Responsiveness and Sensitivity

The *responsiveness* of an instrument is its ability to detect change [60]. Responsiveness is sometimes referred to as "sensitivity to change". In the context of HRQOL, *sensitivity* is the ability to discriminate different states of HRQOL, while *responsiveness* is the ability to detect change in HRQOL. These two attributes may be considered as cross-sectional and longitudinal construct validity, respectively.

For HRQOL instruments to be useful in evaluating the effects of interventions, they must be responsive to changes in health. Existing measures of responsiveness are based on two observations per person. This is appropriate for assessing responsiveness when a single dose of treatment has a pronounced effect in a relatively short time. For example, the acute effects of emetogenic chemotherapy occur within 8 days [64]. In such cases, responsiveness may be assessed by measuring HRQOL before and after treatment. There are many circumstances where treatment is given in a series of doses and change in health occurs gradually. For example, the side-effects of chemotherapy accumulate over a course of doses [65]. A measure of responsiveness based on a series of observations per patient would be appropriate in such cases. Such a measure may provide a more precise estimate of responsiveness than one based on two observations per patient. Responsiveness should be gauged relative to the *minimum clinically important change* [66] and that the appropriate reference group for estimating background noise was "stable" patients (defined as patients in need of treatment but prior to treatment).

## Interpretability and Minimally Important Difference

*Interpretability* is "the degree to which one can assign qualitative meaning – that is clinical or commonly understood connotations – to quantitative scores" [60]. Interpreting HRQOL and PRO data presents several challenges, but there are methods to overcome them [67]. While it may be tempting to resort to *statistical significance* as a criterion, in a large enough sample, small effects with no apparent clinical importance will be statistically significant. The relevance of an observed effect should be judged relative to the *minimum clinically important difference*. This was initially defined as "the smallest difference ... which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management" [66]. Other terms have emerged since [67]. While various methods are used to estimate the minimally important difference (MID), many rely on patients' global rating of change. Estimates of MIDs are increasingly appearing in the literature. For a given HRQOL scale, all available MID estimates (and their

confidence intervals) should be considered and applied judiciously to any particular clinical or research context [67].

## Measurement and Practical Issues

### Mode of Administration

The decision of how PRO instruments will be administered is often a difficult one. Researchers need to consider how and where patients will complete instruments and via what medium. Instruments can be completed by the patient independently (self-completion) or with assistance (e.g. a nurse reading questions to the patient and recording their answers; assisted completion). They may be completed at home or in the clinic, using various different mediums (e.g. paper, electronic) and devices (e.g. computers, smart phones, tablets). These considerations are referred to as the mode of administration. After years of research as to whether mode of administration leads to differences in responses, a recent meta-analysis found that when a validated PRO instrument was used, there was no difference in self-reported responses when electronic and paper-based methods were compared; however there was some difference in responses when self-completion was compared with assisted completion depending on the place of completion (i.e. clinic versus home setting). Therefore the review concluded that mixed modes of administration could be used in research if participants are self-completing PROs to improve response rates [68].

### Timing of Instrument Administration

Researchers must decide when will be the most informative time points to assess HRQOL and other PROs. In intervention studies, patients should always be assessed at baseline before intervention. Subsequent assessments should depend on what will be informative for the clinical and research context. Assessments should continue as long as is meaningful to the research question and as permitted by the study budget, but no longer than expected median survival, as beyond that point only 50% of patients will provide data [69].

### Missing Data

Missing PRO data is arguably the biggest problem for PRO assessment [70], because it is often missing for reasons related to the patient's health status and is almost inevitable in cancer trials. For example, a recent study found that patients who dropped out of a large cohort study had worse HRQOL at baseline and rapid declines in HRQOL leading up to the final HRQOL assessment [71]. Excluding such patients from analysis is very problematic because it will artificially make it seem as though HRQOL was better than was the true case [70]. Although missing data can be handled statistically, these methods are based on assumptions that cannot always be tested; therefore it is crucial that strategies for reducing avoidable missing PRO data are employed from the design stage. The problem of missing PRO data and strategies to reduce it has been detailed [70]. Key strategies include minimising the burden on the patient by ensuring that instruments are short, validated and targeted to the research population, collecting reasons for missing data throughout the trial (this information will assist statisticians when they come to analyse the data), involving a multidisciplinary team in the study design and protocol development so that any logistical issues can be identified early, and clearly reporting the potential impact of missing data so that readers can assess generalisability issues [70].

### Longitudinal HRQOL Assessment Versus Cross-Sectional

Because medical care for cancer is usually provided as a series of treatments and clinical consultations, HRQOL assessment is usually longitudinal in nature and often assessed at clinic visits for logistical ease, if these are seen to be informative time points. However, the number of assessments should be considered with the financial research costs and burden on the patient in mind.

Longitudinal designs are often essential to describe the symptomatic, functional and HRQOL effect of treatment on patients or to evaluate the change in these issues over time. In contrast, in comparative effectiveness research,

comparing PROs in two or more treatment groups can employ cross-sectional or longitudinal designs. In such cases, the extra cost to researchers of repeated HRQOL assessment, including time and effort to collect and process the data, may be offset by smaller sample requirements if repeated measurements provide more statistical power for testing hypotheses about treatment effects. This in turn depends on how much of the variation in the data is due to substantive differences between patients and how much is due to within-patient variation.

Although longitudinal studies have advantages, they pose a number of challenges for analysis and interpretation. These include complex correlation structures and multiple hypothesis tests (due to both repeated measures over time and multiple scales to assess different dimensions of HRQOL) and missing data. Sample attrition is common in longitudinal HRQOL studies. Since poor health is likely to cause both intermittent missing data and censoring (drop-out), missing HRQOL data processes are likely to be informative [70]. This is a significant problem for longitudinal HRQOL research generally and limits the data available for developing interpretations of change in HRQOL over time. A challenge for clinicians is to evaluate the clinical meaningfulness of the reported change or lack of observed change in HRQOL data. Guidelines to help clinicians critically assess and interpret longitudinal HRQOL data (or HRQOL changes over time) and use these data in treatment decision-making are available [72].

### Proxy Assessment

In populations where patients cannot self-complete PRO instruments, for example, patients with very advanced disease, brain cancers or paediatric populations, it is obviously not possible to assess HRQOL or other PROs using self-administered instruments. In such cases, proxy assessment is an option, whereby an individual (e.g. relative or health care professional) very familiar with the patient's health and treatment situation can estimate various outcomes. Proxy reports are often discouraged because studies consistently find discrepancies between patient and proxy reports when both have been assessed simultaneously. This discordance is strongest for non-observable domains or outcomes, such as pain or emotional domains, whereas discordance is smaller for observable, physical domains [15]. Proxy assessment should only be used when self-assessment is not possible. It is recommended that proxy reporters should be used consistently throughout the trial to minimise inter-rater biases, i.e. if a child's mother completes the first proxy assessment, she should complete all subsequent assessments for that patient.

## Conclusions and Recommendations

The benefits and harms (e.g. symptom palliation and toxicities) of cancer treatments provide compelling arguments for incorporating the quality of patients' lives into decisions about treatment. In recommending treatment options to their patients, clinicians need to consider the benefits and harms treatments might have on their patients' HRQOL in the short and long term. HRQOL and PROs are increasingly being used in the management of individual patients. The International Society of Quality of Life (ISOQOL) Research has produced guidelines for implementing PRO assessment in clinical practice [73].

There are several approaches to measuring HRQOL in cancer clinical research, and many instruments have been developed; some are specific to a particular disease or treatment and others are general. Choice of the right instrument(s) for a particular application is determined by the purpose of the measurement (or research objectives) and the kind of information required [74]. The challenge for researchers and clinicians is often identifying and choosing an instrument for a particular application to suit their research questions, context and constraints [4, 19]. We have provided a brief overview of the issues to consider when including HRQOL in cancer clinical trials, such as selecting a suitable instrument [74–76] and reducing missing data [70]. Importantly, HRQOL can successfully complement survival and toxicity endpoints in oncology

trials and can illustrate that small survival benefits are particularly valued if they are also associated with HRQOL benefits.

Both in clinical research and clinical practice, HRQOL research is a growing field in which evidence is constantly emerging. In this chapter we provide a brief synthesis of evidence to date and current recommendations for incorporating HRQOL in oncology research and practice. For further information and useful resources, please see websites for the Quality of Life Office, University of Sydney and ISOQOL. Information about specific instruments can be found on the Mapi Research Trust PROQOLID website.

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# Financial Toxicity

9

Pricivel Carrera and S. Yousuf Zafar

## Introduction

The treatment and care of cancer patients have been rapidly changing over the past two decades. With the concomitant improvement in treatment efficacy and drug tolerance, technological progress has improved cancer patient survival and quality-of-life. As precision or personalized medicine gathers pace, cancer patients and their advocates can look forward to a wider array of treatment modalities and chemotherapeutic possibilities. Considering the very expensive price tag that these oncological innovations come with, however, excitement about next-generation targeted therapy drugs and immunotherapy—among others—is tempered by concern regarding the affordability of treatment both at the individual and health system levels. Considering that the diagnosis of cancer is a health "shock" resulting in an increase in health expenditure, reduced functional capacity, and lost income or productivity, the potentially ruinous impact on individual cancer patients and their household's economic well-being of cancer treatment is a major concern to the supportive care in cancer community and other stakeholders [1–3]. This chapter evaluates the so-called financial toxicity of cancer treatment, which is a relatively new term for a familiar but insufficiently examined phenomenon in the treatment and care of people with cancer.

## What Is Financial Toxicity?

Although the term "financial toxicity" was first mentioned in the medical literature in 2012 by Bullock and colleagues [4] in the context of a treatment-related toxicity focusing on the cost of modern oncology drugs which patients with cancer will have to (partly) bear, Himmelstein and colleagues [5] noted 7 years earlier that cancer was the highest-cost diagnosis among individuals declaring bankruptcy for medical reasons. Bullock and colleagues [4] suggested that the conversation on costs be conceptualized as "a discussion about financial toxicity (which) may help guide some physicians, who are already skilled at counseling their patients on other treatment-related toxicities" (pp. e54–e55). In this regard, the term financial toxicity was seen as an unintended outcome—an adverse event of cancer care given the cost of treatment. Zafar and

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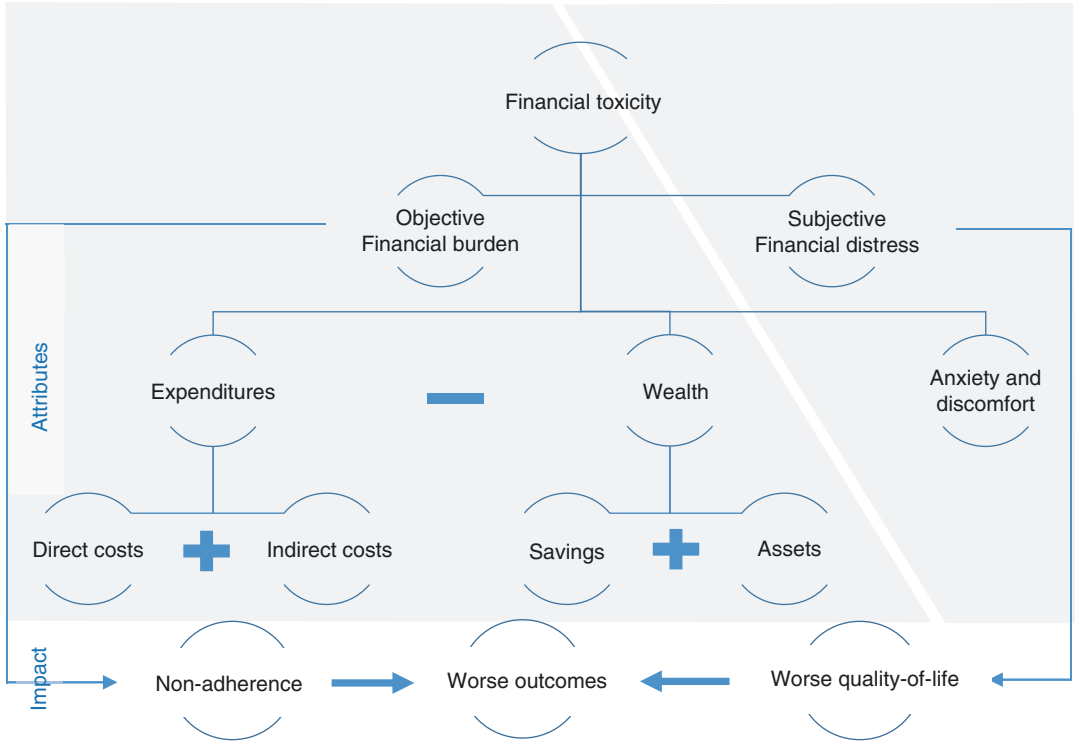


**Fig. 9.1** Financial toxicity, its attributes and impact

Abernethy [6] expounded on the concept of financial toxicity as the out-of-pocket expenses that the cancer patient with insurance bear as part of their cancer experience.

In addition to the objective financial burden faced by cancer patients, Zafar and colleagues [6, 7] suggested that financial toxicity also covers subjective distress due to the financial burden of cancer treatment. In this regard, financial toxicity is equivalent to the more widely acknowledged physical and psychological toxicities of cancer treatment. Indeed, just as the extent of the physical and psychological burden is unknown until the treatment is administered to a large population of "real-world" patients with comorbidities (that were not examined in a clinical trial), the financial burden to patients of cancer treatment has been largely opaque given the lack of mechanistic insight into these adverse effects [8].

More recently, Carrera and Olver [2] proposed the concept of financial hazard to refer to "the unintended, potential economic harm or damage of (cancer) treatment" (pp. 3399). They argued that while cost consequences of cancer treatment may be significant, the impact on household income and assets of treatment is just as important since decline if not depletion of income and assets to cover costs may affect treatment decisions and adherence. As noted by Zafar and colleagues [7] in their study of underinsured cancer patients in the USA, about half were spending their savings to help pay for their cancer care. While the financial implications of cancer treatment are unintended, they are not unanticipated in consideration of the current environment—from the prices of targeted drugs to cost-sharing arrangements under health insurance coverage [9, 10]. Based on the history of the use of the term "financial toxicity" and empirical work on the topic to date, we can conceptualize and provide mechanistic insight into the financial and economic burden of cancer treatment as illustrated in Fig. 9.1.

**Table 9.1** Statements in the COmprehensive Score for financial Toxicity (COST) for cancer patients

| Domain | COST statements for cancer patients[a] | Grading financial toxicity[b] |
|---|---|---|
| (Subjective) Financial distress | I worry about future financial problems resulting from my illness or treatment<br>I feel I have no choice about the amount of money I spend on care<br>I am frustrated that I cannot work or contribute as much as I usually do<br>I am satisfied with my current financial situation<br>I feel financially stressed<br>I am concerned about keeping my job and income, including working at home<br>My cancer or treatment has reduced my satisfaction with my present financial situation<br>I feel in control of my financial situation | What are your main concerns regarding your treatment? |
| (Objective) Financial burden | I have enough money in savings, retirement, or assets to cover the costs of my treatment<br>My out-of-pocket medical expenses are more than I thought they would be<br>I am able to meet my monthly expenses | What is the short-term, compared to the long-term, impact of your treatment on your finances? |

[a]Based on de Souza et al. [84]
[b]Based on Carrera and Olver [2] and Carrera and Ormond [9]

Financial toxicity results from both objective financial burden and subjective distress. The objective financial burden is due to the direct and indirect costs of cancer treatment which increase over time from diagnosis. This covers not just "out-of-pocket" (OOP) spending or the unreimbursed, direct costs of treatment among insured individuals and any therapy intended to prevent complications, but also indirect costs incurred resulting from treatment and auxiliary services meant to improve quality of life (QOL) [11]. This financial burden is relative to the income and assets of the household of the patient with cancer which decreases over time and may even be at risk of depletion. Indeed, catastrophic spending – a concept closely associated with health expenditures in low-income and lower middle-income countries [1], is pertinent given cancer treatment expenditures vis-à-vis ability to pay may lead to personal bankruptcy or impoverishment. Nonadherence may result due to the high expenditures associated with cancer treatment [12].

Combined with the anxiety and discomfort by the cancer patient over their cancer experience, financial distress ensues with the mounting cancer-related expenditures and reduction in wealth. Financial distress forms part of the nonfinancial costs of cancer or burden of disease. Unlike physical toxicity, the financial toxicity of cancer treatment is not borne by the cancer patient alone but by the household of the individual and may be externalized. This happens in the case of private health insurance coverage or public funding of healthcare and availability of supportive care—both from members of the household and externally. Consequently, the financial burden on the individual payment ranges from minimal to significant—due to underinsurance—and even catastrophic in the case of lack of health insurance and absence of replacement income [2, 9, 13]. This implies that while financial toxicity is universal, exposure to it differs by household circumstances and given local (i.e., national) health financing arrangements.

## Attributes of Financial Toxicity

To illustrate the magnitude of the problem, the discussion of the objective financial burden and subjective financial distress will deal with the situation of underinsurance or lack of health insurance and take the case of the USA where the absolute number of underinsured and uninsured is significant and unique among advanced economies [14, 15]. Patients without health

insurance coverage are likely to experience poor clinical outcomes due to lower rates of cancer screening, later stage at cancer diagnosis, and higher cancer-specific mortality, while those who are underinsured face similar barriers in access to healthcare [16, 17]. In the USA, government health insurance programs, such as Medicare, Medicaid, and State Children's Health Insurance Program (SCHIP), provide vulnerable populations with access but not financial protection from health expenditures. Indeed, a national survey of patients declaring bankruptcy for medical reasons found that more than 75% of them reported being insured at the onset of their illness [5].

### Objective Financial Burden

High treatment expenditures—of which drugs represent a significant percentage of direct costs—may threaten the financial stability and security of patients with cancer (and their families). Overall, patients with cancer are at 2.65 times greater risk of declaring personal bankruptcy than those without cancer [13]. Younger cancer patients had two to five times higher rates of bankruptcy than cancer patients age 65 or older who are covered by Medicare—which provides health insurance coverage for Americans aged 65 and older (as well younger people with some disabilities or end stage renal disease and amyotrophic lateral sclerosis) and have Social Security benefits [13]. According to Shankaran and colleagues [18], younger patients may have more difficulty than older individuals in adjusting to the financial pressures of cancer care for many reasons, including higher baseline household expenses and less time to accumulate assets. The delivery of targeted treatment in oncology is necessarily coupled with medical imaging, which results in the high costs of treatment.

Among solid tumor patients undergoing active treatment, up to 47% reported significant or catastrophic financial burden [19]. Based on the narratives of 252 colorectal cancer patients in the USA collected between 2008 and 2010, of which 84 identified themselves as facing financial barriers, health insurance status was mentioned by 100% of the subsample as a barrier [17]. In a selected cohort of cancer patients applying for co-payment assistance, 42% reported significant or catastrophic financial burden, and 20% of those patients reported taking less than the prescribed amount of medication for financial reasons [7]. In this cohort, self-reported financial burden was similarly associated with several other coping behaviors, including selling possessions or property, reduced spending on leisure activities, and use of savings to pay for treatment-related expenses.

Wong and colleagues [20] have found in their study regarding decision-making of cancer patients faced with trade-offs between cost, efficacy, and toxicity that when presented with hypothetical treatment scenarios, patients with lower incomes were more likely to prioritize avoidance of expensive treatments, regardless of survival or toxicity. In comparison, patients with higher incomes were found to be more likely to prioritize survival. The authors suggested that owing to cost-aversive behaviors among low-income patients, insurance plans with greater cost sharing may increase disparities in cancer care.

Using data from the LIVESTRONG 2012 survey of 4719 cancer survivors ages 18–64, Banegas and colleagues [21] found that about one-third of the survivors had gone into debt, and 3% had filed for personal bankruptcy. Of those who had gone into debt, 55% incurred financial liabilities of USD10,000 or more. Meanwhile, a systematic review of the literature on objective financial burden as a material condition measure experienced by cancer survivors by Altice and colleagues [22] found that prevalence of financial hardship varied by the measure used and population studied. Mean annual productivity loss ranged from USD380 to USD8236; 12% to 62% of survivors reported being in debt because of their treatment.

In comparison, Yabroff and colleagues [23] considered material financial hardship to involve (1) borrowing money or going into debt, (2) filing for bankruptcy, (3) being unable to cover one's share of medical care costs, or (4) making other financial sacrifices because of cancer, its treatment, and lasting effects of treatment in estimating the prevalence of financial hardship associated

with cancer in the USA among adult cancer survivors. They found that, cancer survivors age 18–64 years who were younger, female, nonwhite, and treated more recently and who had changed employment because of cancer were significantly more likely to report any material financial hardship. Gordon and colleagues [24] in their systematic review of 25 papers to determine the extent of financial toxicity among cancer survivors concluded that irrespective of how it is measured, objective financial burden is experienced by a substantial proportion of cancer survivors.

## Financial Hardship and Nonadherence

Dusetzina and colleagues [25] examined trends in imatinib expenditures from 2002 to 2011 and assessed the association between co-payment requirements for imatinib and TKI adherence. Using a propensity-score-weighted sample, they estimated the risk of discontinuation and nonadherence for patients with higher (top quartile) versus lower co-payments. Patients with higher co-payments were found to be more likely to discontinue or be nonadherent to TKIs. Medication nonadherence provides immediate cost-savings for the patient but increases the risk of various adverse outcomes. In fact, an estimated 33–69% of all hospital admissions have been attributed to nonadherence, with an annual price tag of up to $100 billion [26]. Nonadherence to imatinib and other TKIs results in disease progression and treatment resistance. Findings from multiple studies have demonstrated an association between early discontinuation of aromatase inhibitors and worse overall survival in breast cancer patients [27].

Patient preferences for and adherence to cancer treatment may be influenced by considerations regarding the impact of financial toxicity on household welfare. As noted by Altice and colleagues [22] in their systematic review of the literature on financial hardship experienced by cancer survivors between 4% and 45% of survivors did not adhere to recommended prescription medication because of cost [25]. There is ample data correlating higher out-of-pocket costs with medication nonadherence in cancer patients. In a single-center survey of 300 cancer patients, 16% of patients reported high or overwhelming financial distress, and 27% reported medication nonadherence because of financial concerns [28].

## Subjective Financial Distress

The decision to avoid or stop treatment to mitigate financial toxicity may only minimize the financial burden of treatment and need not eliminate it entirely since income and assets may continue to be adversely affected due to unemployment. Studies of cancer patients have found varying levels of self-reported financial distress, ranging from 32% to 85% [7, 29]. de Souza and colleagues [30], using a financial toxicity patient-reported outcome measure (PROM) termed COST (COmprehensive Score for financial Toxicity), reported a statistically significant correlation between the patient's financial toxicity score and health-related quality of life, as measured by the Functional Assessment of Cancer Therapy—General.

In a cohort of 233 patients with advanced cancers, the authors found a significant relationship between financial toxicity and younger age, nonwhite ethnicity, less than a college degree, unemployment, Medicaid insurance, and lower income. These findings compare with those of Fenn and colleagues [31] who found that patients reporting "a lot" of financial distress were more likely to be nonwhite, female, and younger than 61 years old, with a total annual household income of less than USD35,000 and less than a college degree. In addition to precluding treatment or engendering treatment nonadherence, high financial burden resulting from high expenditures and limited and decreasing resources saddle patients with guilt and, especially in times of economic hardship, inducing fears that about continuity of, if not the desirability of treatment [32].

Meanwhile, in a longitudinal survey of patients with nonmetastatic breast cancer, a third of patients reported a decline in financial status in the period following diagnosis, with a significant minority reporting out-of-pocket costs that exceeded USD5000 per year [33]. Finally, adult cancer survivors who were uninsured, had lower family income, and were treated more recently

were more likely to report psychological financial hardship which was defined by Yabroff and colleagues [23] as "ever worrying about paying large medical bills."

## Sources of Financial Toxicity

Akin to physical toxicity, financial toxicity from cancer treatment expenditures diminishes quality of life and impedes delivery of the highest quality care. Unlike physical toxicity, the financial burden of treatment is not borne by the cancer patient alone but by the household of the individual and may be externalized. This externalization may provide partial or full protection from objective financial burden and with it reduction in subjective financial distress given the availability of third-party payers and funding arrangements. In this regard, financial toxicity is closely related to the affordability of cancer treatment at the individual (patient) level and accessibility of cancer treatment at the health system level.

Affordability in healthcare refers to one's ability to pay for treatment without financial hardship [34]. The higher the costs of treatment (both direct and indirect) and the higher the share of costs paid out-of-pocket given one's means, the less affordable treatment is [9]. Focusing on chemotherapy, especially using targeted therapy, accessibility is dependent on the degree to which a medication is subsidized or reimbursed which impacts upon a cancer patient's out-of-pocket expenditures [35]. The reimbursement of medication involves a complex sequence of processes including but not limited to market authorization, procurement by government insurers or hospitals, and budget allocations for purchase by the public sector. The availability of a drug, as such, is sufficient but not necessary to ensure patient use given access and affordability.

In this section the main sources of financial toxicity will be explored via use cases of crizotinib, trastuzumab, and imatinib, specialty drugs used in the targeted treatment of NSCLC, breast cancer (with HER2-positive tumors), and chronic myeloid leukemia (with bcr/abl fusion genes), respectively. Both trastuzumab and imatinib are on the WHO Model List of Essential Medicines, but only trastuzumab is fully reimbursed in many countries. Crizotinib and imatinib are partially reimbursed and require significant OOP spending from patients. It is important to note that drugs present a fraction of all costs. For example, high costs are also incurred by facility fees, diagnostics, procedures, and hospitalizations.

### Prices and Pricing Strategy

The costs of developing and bringing a new pharmaceutical product to market are large, whereas the marginal costs of production are generally very small. To incentivize pharmaceutical manufacturers, they are granted patent protection to invest in research and development and bring new drugs to the market. In oncology the majority of new drug applications or biologic licensing applications are in pursuit of the US Federal Drug Administration (USFDA) and European Medicines Agency (EMA) approval for a specific patient population and indication. Not only do pharmaceutical firms have strong incentives to increase demand because of production costs, they can set prices for as high as the market can bear [36].

It has been suggested that the prices of on-patent anticancer drugs do not appear to be closely related to marginal production costs. Howard and colleagues finding that benefit- and inflation-adjusted launch prices increased by about 10% annually appeared robust to the inclusion of controls for various drug attributes (such as whether is designated priority or orphan drug) [37]. Their empirical results suggested that the launch prices of anticancer drugs, even when adjusted for inflation and survival benefits, have increased substantially over time. Similarly, Shih and colleagues [38] reported that insurance payments per patient per month for targeted oral anticancer medications more than doubled in ten years, and that the overall growth in drug prices occurred both at launch and in the years after launch. According to Moses 3rd and colleagues [14], 91% of the rise in costs since 2000 were due to price increases, with the prices of drugs and devices growing at a rate of 4% per year.

Despite the introduction of several similar drugs, for example, the price of imatinib has continued to climb since its initial approval. From a price of nearly USD30,000 when it was launched in 2001, the price of imatinib increased to just over USD90,000 in 2013 [39]. This has led to more than a hundred experts on chronic myeloid leukemia calling attention to the rapidly rising cost of cancer drugs, particularly the tyrosine kinase inhibitors. Using pharmacy claims for commercially insured individuals to examine for orally administered anticancer drugs recently approved by the USFDA, Bennette and colleagues [40] concluded that there is currently little competitive pressure in the oral anticancer drug market in the USA. They found that inflation-adjusted per patient monthly drug prices increased 5% each year during the period 2007–2013.

Affiliates of global companies and local subsidiaries have limited influence over the development of new cancer medicines, both in terms of trial design and price setting. Moreover, once a drug is approved for the initial patient population and indication, its manufacturer often seeks supplemental approvals for additional indications. Once approved by the USFDA, they are included in the product's label and collectively referred to as "labeled indications" which is an important mechanism for increasing demand. Each supplemental indication approved by the USFDA resulted in prices increasing by an additional 10% and decreasing by 2% with the USFDA's approval of a competitor drug [40]. Initially approved to treat certain adults with chronic myeloid leukemia, imatinib has since been approved for ten additional indications, including gastrointestinal stromal tumors [41] and pediatric chronic myeloid leukemia [42].

## Payment for Endpoints

Only a few drugs offer gains in overall survival (OS) which is the gold standard primary endpoint in evaluating the outcome of any drug [43]. Forty-eight new regimens approved by the USFDA between 2002 and 2014 conferred a median 2.1 month OS benefit [44]. Of the 12 drugs approved by the USFDA for various cancer indications in 2012, 9 were priced at more than USD10,000 per month, and only 3 prolonged survival—2 by less than 2 months [45]. Whether any of the current specialty drugs/targeted treatment for stage IV NSCLC offers clinically meaningful outcomes in terms of OS is subject to debate. Not surprisingly, it has been suggested that new treatments for patients may be considered innovative insofar as drug manufacturers invested R&D and brought them to market [37, 46].

Crizotinib was approved by the USFDA in the treatment of patients with known EML4-ALK–positive advanced NSCLC based on 4–5 months PFS with 11 months of use of crizotinib costing USD127,281 (in 2014 USD). Molecular testing with first-line targeted crizotinib treatment in the population with advanced nonsquamous NSCLC results in a gain of 0.011 quality-adjusted life years (QALYs), a measure of disease burden taking into account both the quality and the quantity of life lived, compared with standard care [47]. The incremental cost was Canadian USD2725 per patient, and the incremental cost-effectiveness ratio (ICER) was USD255,970 per QALY gained. First-line crizotinib therapy provided 0.379 additional QALYs, cost an additional USD95,043 compared with standard care, and produced an ICER of USD250,632 per QALY gained. Despite not meeting cost-effectiveness thresholds in many countries, news of the efficacy and effectiveness of the drug advanced its coverage.

In consideration of the difficulty of treating cancer using single agents due to the complexity of genetic and biomolecular pathways of oncogenesis, a "cocktail" approach of combining cytotoxic chemotherapies may amplify expenditures further [48]. Trastuzumab emtansine is being reimbursed at an estimated incremental cost per QALY up to GBP185,600 (EUR235,000) (in patients with HER2-positive metastatic breast cancer no longer responding to initial treatment), despite additional median survival of just under 6 months [49]. This is considerably greater than the cost per course of trastuzumab alone [50].

To be sure, defining futile treatment is increasingly becoming difficult. Cancer patients often are treated with multiple lines of therapy

until all options are exhausted. Consequently, the choice of one drug does not necessarily preclude the concurrent or subsequent demand for other similar drugs [51]. In an important multicenter study, almost 75% of 1200 patients with metastatic colorectal and lung cancers considered it likely that their cancers would be cured by chemotherapy [52]. There are few data on patients' awareness of cancer drug effectiveness or the incidence and potential severity of their side effects. Many are likely to be unaware of the 80% risk of diverse side effects, of which up to 64% are serious (grades 3–4) [53].

## Late Diagnosis and Aggressiveness of End of Life

Insurance status has been found to be a strong independent risk factor for distant-stage disease at the time of diagnosis. Uninsured female cancer patients aged 15–39 years diagnosed between 2004 and 2010 have been found to be almost twice (1.86 times) more likely to be diagnosed at a distant stage [54]. Moreover, the effect of insurance status was found to be substantially stronger for malignancies that are more amenable to early detection. Lack of insurance coverage or underinsurance and late diagnosis has also been seen among patients aged 55–74. For each cancer site, uninsured and Medicaid-insured patients had the highest proportion of American Joint Committee on Cancer stages III and IV cancers at diagnosis and those with private insurance and Medicare plus supplemental insurance the lowest [16]. Risk ratios (95% CI) for uninsured patients compared with privately insured patients were highest for the lung/bronchus, at 2.08 (1.98–2.17), and for the urinary bladder at 1.91 (1.73–2.12).

The link between late-stage diagnosis of cancer and lack of health insurance or underinsurance underlines the coping mechanism of individuals/households given the financial toxicity of cancer care. It makes economic sense ex ante but has deleterious consequences ex post. Not only do uninsured or underinsured individuals face worse health outcomes, they may also suffer from worse financial burden and increased financial distress. Notwithstanding efforts in promoting early palliative care in the past two decades and evidence to support the cost-effectiveness of such, end-of-life care remains intensive and expensive. Treatment for all patients in their last year of life accounted for more than one-quarter of Medicare spending in the USA [55].

A retrospective analysis of claims data of 28,530 patients found that the mean total cancer-related costs in the last 6 months before death were USD74,212 with hospice care covering only 4% of costs at USD3256 [56]. In comparison, inpatient and outpatient costs accounted for 55% and 41% of costs (or USD40,702 and USD30,254, respectively) with outpatient costs covering spending on chemotherapy, erythropoiesis-stimulating agents, granulocyte colony-stimulating factors, radiation, cancer-related office or emergency room visits, cancer-related hospital OP procedures, and other services with cancer diagnosis. The increase in costs in the last 6 months was found to be largely because of increased inpatient care costs which increased from USD1785 to USD20,559. Meanwhile, Hershman and colleagues [57] found that a third of bevacizumab use (USD10,000 per month) was not indicated.

Neuberg [58] called the continued aggressive care given to dying patients "desperation care" for families who cannot accept that illness has become irreversible and will only cause suffering to patients and their families. Aggressiveness of end-of-life care may be avoided and delivery of futile chemotherapy minimized with early palliative care. Cancer patients receiving either early palliative care integrated with ongoing oncology care or standard care have been found to have a better quality of life and less depression [59]. In a meta-analysis of randomized clinical trials of palliative care interventions in adults with life-limiting illness, palliative care interventions were found to be associated with improvements

in patient QOL and symptom burden [60]. Palliative care was found to be associated consistently with improvements in patient and caregiver satisfaction and lower healthcare utilization.

When the American Society of Clinical Oncology (ASCO) issued its first "Top Five" list of tests and treatments that should be questioned as part of the Choosing Wisely® campaign in 2012, the first item that was recommended was refraining from providing further cancer-directed therapy for patients with advanced solid tumor cancers and a performance status of three or four [61]. Less than four-fifths of patients with incurable cancer have been told of their prognosis [62]. In addition to patient-related and family-related barriers which discourage oncologists from discussing palliative care are oncologist-related barriers, barriers relating to the physician referring the patient to the medical oncologist, barriers relating to disease or treatment, institutional/organizational barriers, and societal/policy barriers [63]. Although physicians acknowledge that patients with incurable cancer want prognostic information and benefit from this, most struggle to provide it and experience difficulty in making reliable estimates, communicating them, and tailoring the information to the individual patient [64].

## Financial Toxicity Around the World

Strategies for dealing with financial toxicity vary by individual and health system with some systems collectivizing and assuming the bulk of costs of cancer treatment resulting in very low out-of-pocket expenditures for patients. Considering that the externalization of financial toxicity involves the redistribution of the objective financial burden of cancer treatment with potentially uneven impact across cancer patient groups, however, individual patient-level supportive care would benefit from and complemented by a collaborative approach mitigating the underlying causes of financial toxicity. Different health systems deal with the externalization of and redistribution of the financial burden of cancer treatment which we briefly explore in this section.

### Europe

The costs of cancer care in the EU are increasing at an unprecedented rate, driven by demographic changes, innovation, and consumerism within healthcare [65]. Cherny and colleagues [3] in their study on the availability and affordability of anticancer therapies found that countries with lower levels of economic development, particularly in Eastern Europe, have the most profound lack of availability, and these are largely related to the cost of targeted agents approved in the last 10 years. While adjuvant trastuzumab is widely available across Europe, usually at no cost to patients, some countries require preapproval, causing weeks of delay in its use. Moreover, newer agents for anti-HER2 therapy are not widely available or available only at full cost to patients. For example, none of the top-ranked drugs on the European Society for Medical Oncologists' Magnitude of Clinical Benefit Scale (ESMO-MCBS), namely, ipilimumab, vemurafenib, trametinib, or dabrafenib, are available in Romania [66].

There is likewise variation in terms of end-of-life care and prices across European countries with 29.4% and 41.7% of decedents dying in acute care hospitals in the Netherlands and England, respectively, while mean per capita hospital expenditures in the last 180 days of life were comparable between the Netherlands and England at USD10,936 and USD9342, respectively [67]. Since solidarity is a shared principle among health systems in Europe, such that patients are generally protected from catastrophic medical expenditures, governments have attempted to utilize health technology assessment (HTA) regarding resource allocation. Attempts to control the provision of drugs not deemed cost-effective by HTAs especially by National Institute for Health and Clinical Excellence (NICE) in England, however, have met widespread public and professional discontent.

In the case of England's Cancer Drugs Fund (CDF), which provides patients with access to cancer drugs that are not available through the National Health Service (NHS) because they were not found cost-effective, Dixon and colleagues [68] have claimed that "the approach adopted by the CDF to cost-effectiveness and prioritization has led to circumstances in which the opportunity costs of funding decisions are borne by some types of cancer patients but not others" taking funds from other cancer services (or other disease areas) without good reason to fund new cancer drugs, especially if these are not seen as cost-effective even when granting a higher cost per QALY than other medicines at the end of life. Established in 2010 and initially organized at regional level, this ring-fenced fund had spent GBP1.27 billion (EUR1.6 billion; USD1.8 billion) by 2016 without collecting data on outcomes of use of the drugs it provided and relaunched under a "managed access" system with clear entry and exit criteria [69].

In Sweden, value-based pricing has meant that no cost-effectiveness thresholds are defined, instead applying a societal perspective to consider costs and benefits of healthcare. In 2014 the country introduced a 15-year rule, whereby obligatory price reductions (7.5%) are imposed on pharmaceuticals with a market presence of over 15 years [70]. In the Netherlands, high-cost drugs are often approved, and even for reassessed drugs, which showed costs per QALY above EUR200,000, none of them have been delisted. It should be noted that oral oncolytics and other specialist drugs are considered (part of) hospital care and reimbursements of hospital care are negotiated between hospitals and health insurers [71]. Cost-effectiveness thresholds are also higher than for the NHS and based on disease severity and medical need [72]. Notwithstanding the introduction of an instrument on financing expensive medicines, following problems with reimbursement of trastuzumab, which provided "coverage with evidence development," there have been no delistings in the Netherlands resulting from negative advice based on cost-effectiveness data.

## Australia

On average, individual medical out-of-pocket expenses in Australia are higher than those in most European countries and are growing on average 6.7% annually [73]. In contrast to the comprehensive CDF, Australia has only one specific-purpose fund for cancer treatment which is the Herceptin© (trastuzumab) program for late-stage metastatic breast cancer. Trastuzumab, nonetheless, is also available for initial or continuing HER2-positive early-stage breast cancer, through the Pharmaceutical Benefits Scheme (PBS), which subsidizes the cost of listed prescription medicines in Australia. In this case, prescribers would need to specify the amount of trastuzumab required in milligrams per infusion. For drugs for which dosage is based on a patient's weight or body size, such an approach may help minimize left-over drug but need not minimize the financial burden on patients since patients have to pay dispensing fees [74].

Under the PBS Safety Net, patients receive additional PBS benefits when their annual out-of-pocket cost for prescription items exceeds a specified threshold. Formerly Complex Authority Required Drugs, Highly Specialized Drugs (HDS) are medicines used to treat chronic conditions requiring written authority approval before they can be prescribed. All eligible patients need to pay a contribution fee for each supply of PBS or Repatriation Pharmaceutical Benefits Scheme HSDs.

Research into out-of-pocket expenses is challenging in Australia because patterns of care and resource information are not routinely collected in a centralized and linked way. Gordon and colleagues [75] found that private insurance coverage did not provide patients adequate financial protection for the costs of treatment. Between the period of January 2012 and April 2013, men recently diagnosed with prostate cancer reported spending a median AUD8000 for their cancer treatment, while 75% of men spent up to AUD17,000 (2012). Twenty percent of all men

found the cost of treating their prostate cancer caused them "a great deal" of distress. On average, respondents in paid employment at diagnosis stated that they had retired 4–5 years earlier than planned.

## Challenges and Opportunities

The financial toxicity of cancer treatment is a universal challenge that needs attention and action for the benefit of the individual patient, their families, and societies at large. While cancer is the second leading cause of death in high-income countries (following cardiovascular diseases) and the third leading cause of death in low- and middle-income countries, more than half of all cancers (56.8%) and cancer deaths (64.9%) in 2012 occurred in less developed regions of the world [76]. Moreover, the global burden is expected to grow to 19.3 million new cancer cases per year by 2025, due to growth and ageing of the global population. Medical oncologists together with other members of the supportive care community, health systems, payers, and manufacturers must work to provide patient relief from the financial burden of cancer treatment in the short-term at the individual (i.e., patient) level by providing financial counseling as a part of cancer care and using tools to gauge patients' risk for financial hardship as well as long-term calling for greater cost transparency, restructuring of cost-sharing and insurance design, and eliminating low-value prescribing practices [45, 77–79].

### Individual Patients and Providers

An important step in providing supportive care in the context of financial toxicity is communication on both the financial burden of treatment and the distress related to this. While a survey of breast cancer patients found that 94% of respondents thought physicians should discuss costs of care, only 14% reported having actually had such discussions [80]. Zafar et al. surveyed cancer patients with insurance and found that 52% desired discussing their costs with oncologists, but only 19% reported having a cost discussion. The most common reason provided by patients for avoiding a cost discussion was fear of receiving lesser quality care [81]. Hunter et al. [82] found, in a study of recorded conversations between patients and physicians, cost of care was broached in a larger proportion (30%)—but still a minority—of discussions. Other obstacles that can preclude effective cost-of-care discussions between patients and physicians include uncertainty about the appropriateness of the topic, high degree of discomfort about having these discussions with patients, a lack of knowledge about a patient's socioeconomic status, and uncertainty about a patient's desire to discuss the costs of care for physicians [83].

A growing body of evidence suggests that out-of-pocket costs might be reduced directly as a result of cost discussions. A simple screening question like, "Are you having any trouble affording your healthcare?" can open the door to a cost conversation that would otherwise have been missed (see Table 9.1). Zafar et al. found that when patients discussed costs with their oncologists, those costs were lowered 57% of the time. Importantly, when costs were lowered, the vast majority of the time (75%), they were lowered without change in treatment. Physicians decreased patients' costs by referring patients to financial assistance programs and by advocating on behalf of patients with insurance companies [81]. Similarly, Hunter et al. [82] identified four strategies that lowered costs after a cost discussion took place: (1) switching to lower-cost alternative therapy or diagnostic test, (2) switching from brand name to generic drug, (3) changing dosage or frequency, and (4) stopping or withholding interventions. Hence, physicians can play an important role in reducing their patients' financial toxicity.

The conversation cannot take place, however, unless providers screen for both subjective

financial strain and objective financial burden. Shankaran et al. [78] suggest making "financial health" a routine part of clinical assessment to overcome the reluctance associated with discussing personal finances, identify patients at greatest risk for financial hardship, and prompt earlier financial assistance. In this regard, available information on the patient can be combined with the use of tools that assess financial toxicity to facilitate conversation and assistance. The COmprehensive Score for financial Toxicity (COST) measure, which has been demonstrated to be reliable and valid [84], may serve as a basis for assessing the financial burden and financial distress of cancer patients soon after cancer diagnosis since the tool was designed for and validated with advanced stage patients undergoing treatment for some time. While this tool represents important work and is readily available online (http://www.facit.org/FACITOrg/Questionnaires), it should not be seen as the only means to screen for financial toxicity.

Following Bullock and colleagues, patients' desires to discuss treatment costs should not be taken as an acquiescence to the integration of cost-saving action into all clinical decisions [4]. In a survey of breast cancer patients, almost all (96%) wanted to discuss expensive drug options, even if they were unlikely to be affordable [85]. Focusing on goals of care and the value of care delivered might not only reduce costs for patients, but likely improve outcomes, as well. Weeks et al. [52] found that a large proportion of patients with advanced cancer did not understand that their chemotherapy could not cure their cancer. The results of this study and others like it suggest that patients might make treatment decisions with incomplete or perhaps inaccurate assumptions, and those decisions might result in costs that might have been avoidable.

## Regulators and Policy-Makers

While patients and providers have an important role to play in reducing costs, regulators and policy-makers also are part of the solution, especially in regard to price transparency and use of cost-effectiveness analysis. Without knowledge of how much an intervention will cost, physicians will be challenged in assisting patients with their financial toxicity [86]. Studies suggest that making prices readily available at the point of care might reduce costs and increase competition. For example, Wu et al. [87] found in a randomized study that when patients seeking outpatient MRIs are informed about a lower-priced facility, they are willing to obtain their MRI at that less expensive facility. Over time, informing patients about MRI prices drove down prices and increased competition between radiology facilities.

Although payers and health authorities in Europe, particularly in the UK resulting from the reform of the CDF, are able to negotiate prices to meet reimbursement thresholds, these are almost exclusively confidential precluding price referencing. At the same time, a review of market access of cancer drugs in Europe has shown inconsistency in the use of cost-effectiveness analysis in decision-making and extent of pharmaceutical price regulation schemes [88]. As Siddiqui and Rajkumar [51] contend, while competition among manufacturers has been effective in controlling prices for drugs in many chronic conditions, it has largely been unsuccessful in oncology. Considering that financial toxicity is as much about promoting the welfare of the cancer patient (and their families) as it is about ensuring the sustainability of health systems, strategic and systemic solutions are needed for the longer term.

Recognizing that regulations such as the free-pricing of originator drugs in Germany and Medicare coverage of every cancer drug approved by USFDA induce high prices and distort pricing which ultimately causes financial burden and financial distress to patients, value frameworks – from the ASCO value framework to the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MBS) have been developed and are being promoted to serve as countervailing forces. By taking into account payer costs as well as OOPcosts and QOL, it is hoped that the health and economic outcomes of patients with cancer will be in the consciousness

of various stakeholders. Other health professionals and patient advocates go further by being explicit about outcomes-indexed pricing of drugs (See [45]) and refusing drugs that are more expensive but are no better than competition [89].

## Insurance Providers

While much of the attention regarding costs is often focused on manufacturers, in recent years, payers have played a growing role in financial toxicity. Much of this has occurred via cost sharing or the shifting of a portion of healthcare costs to patients. Health insurance coverage may provide protection from high costs of treatment but may not be sufficient given user fees. In the USA, cost sharing was popularized in the 1980s, after a large, randomized study found that patients who pay a portion of their medical bill are less likely to use low-value interventions [90]. Over the past decade, cost sharing has increased: in the USA, worker contribution to premiums has increased by 200%, deductibles have doubled, and the proportion of plans with multi-tiered formularies have increased [91]. As described above, cost sharing can have a tremendous impact on adherence to cancer therapy, even when the absolute amount is relatively modest (less than USD100 per month) [25, 27, 92].

One potential solution to the harms of cost sharing is in value-based insurance design, which differs from standard insurance design in that it varies cost sharing by the value of the intervention [93]. Again, imatinib for chronic leukemia serves as a good example of an intervention that would benefit from value-based insurance design. Since imatinib is a high-value intervention, it would have no cost sharing for patients under the auspices of value-based insurance design. This example is particularly important since evidence suggests that even modest co-payments for imatinib can reduce adherence to this potentially lifesaving drug [25]. The expense for subsidized cost sharing for high-value interventions like imatinib is balanced with income from high-cost sharing placed on low-value interventions [93].

When patients face large OOP costs for cancer treatment, they can be extended valuable information in reducing their liabilities. Patients with private insurance in the US can apply for aid from drug manufacturers' or charitable foundations' co-pay assistance programs, which offset OOP costs [94]. European patients can avail themselves of drugs via compassionate-use programs [95]. Co-pay assistance, compassionate use, and coupon programs, are short-term solutions which help keep drug prices high by lowering the elasticity of demand [96]. Indeed, not only are manufacturers able to set higher prices, the nature of the market for cancer drugs allow them to keep prices high even with the entry of generics and biosimilars [37]. However, without a short term replacement for these programs at hand, oncologists often have no other option to reduce patients drug-related financial burden.

## Manufacturers

No conversation on reducing financial toxicity is complete without addressing the role of drug manufacturers. Pricing practices are discussed in detail in the section "Sources of Financial Toxicity." In summary, prices have increased substantially over the past few decades. Howard et al. found that increases in drug prices have been above and beyond that which would be expected by inflation and improved benefit. Indeed, in many cases, new drug prices are based on the prices of those drugs' predecessors [37]. Additionally, Mailankody and Prasad [97] found very little correlation between new drug prices and relative improvement in outcomes, suggesting that pricing is not based on value but rather by what the market will bear. With these unsustainable pricing practices in mind, drug manufacturers have an opportunity to consider value-based pricing or indication-based pricing as a means to reduce prices while maintaining profits [45, 98].

Drug manufacturers may focus on PFS for practical reasons. Trials designed to detect differences in PFS are shorter (progression precedes death) and require a smaller sample size because

the variation PFS is typically lower than the variation in OS. Progression-free survival and similar measures other than OS, however, are not reliable surrogates for OS in general [99, 100] and specifically in non-curative settings [3]. The usefulness of PFS as a surrogate for OS may depend, in metastatic or advanced cases, on cancer type [97]. Additionally, some drugs have secured USFDA approval without much evidence of clinically proven benefit. Rupp and Zuckerman found that, of 18 cancer drugs that did not demonstrate improvement in OS but still obtained approval by the USFDA from 2008 to 2012, only one drug had data showing improvement in quality of life [101]. In both OS and PFS, unless pricing and pricing strategies are linked to meaningful clinical outcomes, patients may only benefit from innovative treatment insofar as they are available and accessible but not affordable [39, 44].

In summary, the mechanistic insight into financial toxicity in this chapter is hoped to promote further discussion and collective action toward the reduction or prevention of financial burden and financial distress faced by patients with cancer (and their loved ones). This includes its prominent role in the supportive care provided to patients. This will help realize the vision of the Institute of Medicine for care for individuals near the end of life that is "compassionate, affordable, sustainable, and of the best quality possible" [102].

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# 10 Integrative Oncology: The Role of Complementary Medicine in Supportive Cancer Care

Gary E. Deng and Shelly Latte-Naor

## Introduction

### Integrative Oncology: History and Current Applications

> *"There are many definitions of "integrative" health care, but all involve bringing conventional and complementary approaches together in a coordinated way."*

### National Center for Complementary and Integrative Health

Integrative oncology (IO), as it is implemented in most National Cancer Institute (NCI)-designated comprehensive cancer centers, refers to the practice of utilizing complementary health modalities in conjunction with conventional medicine. IO serves to optimize supportive cancer care by offering non-pharmacologic approaches to symptoms of cancer and adverse effects of its treatment. In survivorship, the practice of IO is focused on improving the quality of life (QOL), optimal recovery, as well as promoting lifestyle changes that may reduce recurrence risks for some cancers.

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The practice of IO stands is in contrast to the concept of "alternative medicine" where conventional treatment is often rejected based on unsubstantiated theories.

Best available evidence forms the basis of the IO approach and practitioners prioritize minimizing risks of adverse effects and drug interactions when utilizing IO modalities. The commitment to rigorous scientific practice and critical use of IO methods in cancer care was strongly underlined by the foundation of the Society for Integrative Oncology (SIO) in 2003 and the release of the first set of general clinical practice guidelines in 2009, followed by two other cancer-specific guidelines thereafter [1–3].

Despite this clear philosophical and functional distinction between alternative and integrative medicine, consistent with common usage, the term "complementary and alternative medicine" (CAM) will be used here as a synonym for integrative medicine.

The widespread availability and high prevalence of CAM use stand in sharp contrast to the paucity of reliable public information on the topic and the hesitance of health-care providers to counsel on the use of CAM modalities. This chasm can be bridged by well-trained IO practitioners that can navigate the safe use of complementary methods in the context of cancer treatment. This need has been recognized and addressed with the implementation of specialized IO centers in most NCI-


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designated cancer centers and other health-care institutions throughout the country. Additionally, the awareness about the benefits of IO among independent practitioners is increasing rapidly.

## Prevalence of Use and Patient Considerations

Based on data from the 2007 National Health Interview Survey, it was estimated that 38% of US adults used CAM, spending $33.9 billion out of pocket on visits to CAM practitioners and purchases of CAM products, classes, and materials [4].

Cancer patients and survivors represented the largest group among users of CAM, with 65% reporting lifetime use of CAM. An analysis of the 2012 National Health Interview Survey (NHIS) found that approximately 79 % of cancer survivors reported using at least one nutritional supplement and/or CAM modality in the past year [5].

The decision to turn toward complementary or alternative medicine is influenced by a variety of social, demographic, cultural, as well as disease-related factors [6]. Patients may find that CAM aligns with their philosophy or the belief system they hold in regard to their illness. CAM use may be encouraged by the patient's perceived risk or benefit of conventional care, their individual experience with providers, and their expectations in regard to CAM use [6]. Actively making treatment decisions by choosing CAM may increase patients' sense of autonomy and self-empowerment [7].

## Benefits of a Lifestyle-Guided Approach to Supportive Care

A multimodal approach to supportive care, which addresses physical, nutritional, mental, emotional, and spiritual aspects of well-being, beyond the targeted efficiency of conventional care, is increasingly sought out by patients.

The individual, patient-centered attention such an approach delivers, creates a welcome contrast to the frequently fast-paced and highly specialized environment of cancer care. Targeting lifestyle choices and behavior modifications such as dietary patterns and physical activity is gaining significance in supportive cancer care but also carries numerous health benefits that span beyond the realm of cancer-related issues, e.g., directly supporting cardiovascular and mental health [8].

## Caveats

Given the widespread and often indiscriminate, poorly informed use of CAM by cancer patients, increasing attention by health-care providers is called for.

The potential for adverse effects is especially prominent in the vulnerable cancer population. Furthermore, the unsupervised use of CAM can lead to drug interactions when used in conjunction with conventional treatment [9].

Meanwhile, many health-care providers do not feel qualified to provide guidance in CAM use and are understandably cautious about many complementary modalities. Cancer patients are frequently hesitant to volunteer information about their CAM use for fear of being dismissed or shamed for their choices [10].

A perceived polarization between the patient's belief system and conventional care can strain the patient-doctor relationship and potentially lead to alienation and abandonment of lifesaving treatment.

Therefore it seems pertinent to foster open, nonjudgmental communication about CAM use between patients and health-care providers as well as promoting high-quality information about the safe use of CAM.

# Modalities

## Introduction

The following sections will introduce the most utilized forms of integrative oncology (IO) and their role in supportive cancer care. This overview aims to familiarize practitioners with the theoretical framework and clinical use of commonly used IO modalities in order to foster confidence within collaborations and improve interdisciplinary communication.

It is important to point out that there are no nationally standardized credentialing guidelines for the various complementary modalities. Credentialing requirements vary on a state-by-state basis and are unique to each modality.

The mentioned modalities are not encompassing all IO-related therapies but focus on the most commonly used ones: acupuncture and Traditional Chinese Medicine (TCM), several mind-body therapies, movement therapies such as yoga and Tai Chi, music and art therapies, massage, and natural products.

## Traditional Chinese Medicine and Acupuncture

### Theoretical Background

The foundation of Traditional Chinese Medicine (TCM) is thought to have emerged in ancient China and dates back over 2500 years. The overall prevalence of TCM use in the USA is unknown; however the predominant use of TCM is in the form of acupuncture.

In a recent population-based study, acupuncture was used by over 10% of cancer survivors across the cancer spectrum [11].

TCM represents a medical system, featuring a theoretical framework for pathophysiology, diagnostic approaches, and treatments that evolved independently and is distinct from Western medical systems. The key elements of TCM are based on Taoist philosophy and aim to harmonize different bodily functions, ultimately balancing energy flow. Life energy, called Qi and its unobstructed flow along meridians in the body, is seen as essential for optimal health and well-being.

Treatment modalities include acupuncture, Tui Na (massage), herbal medicine, dietary modifications, and movement practices such as Qi Gong. Rather than fixed treatment protocols, interventions are highly personalized and adjustable to a patient's constitution and momentary condition.

Acupuncture is a technique in which needles are inserted in designated points along the energy meridians. Although randomized controlled trials are beginning to document the benefits of acupuncture for various conditions, its theoretical framework remains poorly understood in the West. The placebo effect has been consistently documented to play a large role in the context of acupuncture treatment, but other theories include the stimulation of neurotransmitters and endorphins through needle insertion as well as modification of immune markers [12, 13] and the mechanical effect on connective tissues [14].

### Evidence and Current Applications

The Clinical Practice Guidelines on the use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer as well as the guidelines of Complementary Therapies and Integrative Medicine in Lung Cancer, published by the Society of Integrative Oncology in 2014 [1, 2], endorse acupuncture, electroacupuncture, and acupressure as treatment add-on options for several indications.

One of the recommendations points to the use of electroacupuncture and acupressure for chemotherapy-induced nausea and vomiting [1, 2]. Furthermore, acupuncture is supported as an adjunct treatment of the following conditions: anxiety, depressed mood, fatigue, and quality of life measures may be addressed with acupuncture in breast cancer patients and survivors [1]. Acupuncture may also be considered for the alleviation of vasomotor symptoms related to antiandrogen therapy or menopause and as a non-pharmacologic approach for aromatase inhibitor-associated musculoskeletal symptoms [1].

Contraindications to needling in the cancer population include increased bleeding risk due to thrombocytopenia and coagulation disorders, increased risk of infection due to low neutrophil counts, and local considerations such as avoidance of needling in tumor tissue or damaged skin after radiation or surgery [15].

A 2015 Cochrane review found inconclusive evidence for the use of acupuncture in cancer-related pain. Pain in cancer patients may be due to conditions unrelated to cancer, tumor growth, bone metastases, or cancer treatment. Pooling of data was largely precluded due to heterogeneity of methodologies, cancer populations, and tech-

niques used in the included studies [16]. Likewise a recent meta-analysis and systemic review, pooling data from 13 RCTs with 969 patients across the cancer spectrum [17], found inconclusive evidence for the use of acupuncture for treatment of cancer-related pain; however, despite lack of high-quality evidence, existing studies do warrant consideration of acupuncture for pain control. Several randomized controlled trials indicate that acupuncture may reduce pain scores and potentially provide quicker and longer-lasting analgesic effects in cancer patients when compared with conventional medicine. Particularly when conventional pain management is unsatisfactory or burdens the patient with adverse effects, acupuncture may allow for a low-risk, non-pharmacologic adjunct treatment [18, 19].

Another promising indication for acupuncture lies in the treatment of aromatase inhibitor-related arthralgia in breast cancer. Although the evidence is still largely inconclusive, lacking larger sample size studies and longer follow-up periods, a recent meta-analysis showed trends toward reduced pain and stiffness following acupuncture treatments and points toward acupuncture as a safe option for this often treatment-limiting symptom [20–22].

Regarding general pain conditions, such as musculoskeletal pain and headache, a meta-analysis published by *The Journal of the American Medical Association* found that acupuncture was associated with improved pain outcomes compared with sham-acupuncture and no-acupuncture controls [23]. The Joint Commission includes acupuncture as one of the non-pharmacologic options for comprehensive pain management [24].

Current evidence suggests that acupuncture represents an adjuvant option for the management of fatigue and improving quality of life in cancer patients, although conclusive data are still lacking [17]. The effectiveness of acupuncture in treating cancer-related anorexia, constipation, paresthesia and dysesthesia, insomnia, and limb edema remains unclear.

Furthermore, acupuncture was found to be beneficial for treatment of radiation-induced xerostomia in several trials although definitive high-quality evidence is still lacking [25–28].

Studies show inconclusive results on the benefit of acupuncture and electroacupuncture in the treatment of chemotherapy-induced neuropathy (CIN). More research is in progress to assess the use of acupuncture and related practices for this common and difficult to treat entity [29, 30].

The use of herbal supplements, Tai Chi, and Qi Gong, although part of TCM, is discussed in other parts of this chapter.

**Summary**

- Consider acupressure and acupuncture for chemotherapy-induced nausea and vomiting in conjunction with pharmacologic treatment.
- Acupuncture may present a low-risk, non-pharmacologic treatment option for mood disorders and quality of life enhancement.
- Consider acupuncture as a safe adjunct treatment for pain conditions and hot flashes.
- Consider a trial of acupuncture for difficult to treat symptoms where conventional treatment often remains unsatisfactory, such as aromatase inhibitor-associated musculoskeletal symptoms or chemotherapy-induced neuropathy.
- Acupuncture can be considered in the treatment of xerostomia after radiation therapy.

## Mind-Body Medicine

### Theoretical Background

Patients and caregivers, whose lives have been touched by cancer, deal with enormous stressors over the course of their diagnosis, treatment through survivorship, or end-of-life care. The implications of the psychosocial burden associated with cancer are well documented, showing significant effects on well-being and quality of life and potentially on clinical outcomes. While the role of stress in cancer remains controversial,

there is evidence to suggest that chronic stress may play a role in disease progression [31, 32] and may contribute to overall mortality [33, 34]. The underlying mechanisms for these effects are suspected to involve chronic activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. The physiologic impact associated with these changes are implicated to enhance angiogenesis and stimulate cancer invasion, inflammation, and immune dysregulation [31, 35].

There is substantial evidence showing the negative consequences of sustained stress on overall health and well-being through psychological, behavioral, and physiologic changes [35, 36]. Beyond the immediate impact on quality of life and other health measures, cancer-related stress can impact the future health of the patient and influence comorbid conditions [37, 38]. Thus, the connection between psychosocial and physiologic components of well-being, namely, the mind-body connection, is an important aspect of cancer care.

The role of the mind, emotions, and behaviors in health and well-being is central to many traditional medicine systems. Some mind-body modalities are based on these ancient systems, such as meditation, yoga, Tai Chi, Qi Gong, relaxation techniques, and guided imagery; others are based on more recent systems, such as clinical hypnosis and biofeedback. Some of these modalities are discussed in the following paragraphs; others will be addressed separately.

As research supporting the benefit of some of these modalities is emerging and documenting their safety and cost-effectiveness, they are quickly becoming part of mainstream care. Mind-body practices have been found to improve QOL, combat harmful effects of stress, and create fundamental changes in the way the brain functions [39–41]. Mind-body therapies are also emerging as a non-pharmacologic adjunct treatment option for chronic pain [42] and insomnia [43] and are implicated with beneficial effects on telomere length [44] and cellular immunity [45, 46].

The choice between the different mind-body modalities should primarily take patient preference and symptoms into account. Recommendations should be guided by evidence and consider the involved time and financial commitment for the patient.

- Meditation- and Mindfulness-Based Interventions

Mindfulness-based Stress Reduction (MBSR) is the best-researched mind-body intervention both in the cancer setting and in other medical conditions. A large body of literature documents the effects of MBSR and related interventions on several outcomes, such as quality of life, depression and mood disturbance, pain, and stress symptoms.

A practice founded in Buddhism, mindfulness describes a state of nonjudgmental present-moment awareness. In the practice of mindfulness meditation, arising thoughts, emotions, and physical sensations are observed with open, relaxed attention. Mindfulness-based Stress Reduction is an 8-week curriculum that was conceived by Jon Kabat Zinn in 1979. Having emerged as a health-care intervention, it offers a secular framework for the practice and study of meditation, mindful movement, and stress management in a group setting [47, 48].

The majority of the large randomized controlled trials of MBSR or modified interventions based on MBSR have been done in breast cancer patients. The *Journal of Clinical Oncology* published a randomized controlled trial in 2016 in which 322 breast cancer survivors were randomized to either a modified MBSR group for breast cancer (MBSR-BC) or usual care. The authors found that the 6-week MBSR-BC program significantly improved a broad range of physical and psychological symptoms, and the beneficial effect was present at 6 and some at 12 weeks after the intervention. There was immediate and sustained improvement in fear of recurrence in the MBSR-BC group through the study period. Significant improvement in anxiety and fatigue was also observed.

A mindfulness-based cancer recovery program has been demonstrated to improve quality of life measures and sleep quality and reduce stress symptoms in breast cancer patients [41, 49, 50].

Two recently published, large randomized controlled trials demonstrate that MBSR and mindfulness medication reduce lower back pain and thereby put these modalities on the map as safe and effective potential adjunct treatments for other pain categories [42, 51]. Thus the significant benefit of MBSR and related interventions is that they are likely to address and alleviate a range of symptoms concurrently.

The Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer endorse meditation and stress reduction for the treatment of anxiety and depression and quality of life improvement [1].

- Yoga

Yoga is a movement-based mind-body practice that aims to "yoke" or join the mind and body. There are several major schools and traditions, representing different styles of yoga. Among the several schools of yoga originating in India or Tibet, Hatha yoga practices are most common in the West. Beyond physical yoga postures, the practice of yoga often involves breathing techniques, meditation, chanting, and study of philosophical texts and rules of conduct.

Several large meta-analyses and review articles summarize the evidence of the benefit of yoga on quality of life and emotional health in cancer patients and survivors [40, 52, 53]. A randomized controlled trial evaluated a 12-week Iyengar yoga intervention for breast cancer survivors with persistent posttreatment fatigue and found significant improvements in fatigue and vigor [54]. Furthermore, yoga has been found to potentially impact biological markers which are thought to be related to cancer-related fatigue. Several studies demonstrated lower inflammatory markers (IL-6, TNF-α, and IL-1β) and reduced activity of the pro-inflammatory transcription factor nuclear factor kappa B in yoga participants, associated with reduced fatigue [55, 56]. Similarly, stress-related markers, such as serum cortisol, were found to be positively affected by yoga practice, correlating with improvement in quality of life measures and physical functioning [57]. These benefits of yoga practice have been shown to exceed the effects of regular stretching exercises [57]. Additionally there is emerging evidence of the benefits of yoga practice on sleep quality. A multicenter trial involving 410 cancer survivors found improved sleep quality as measured by the Pittsburgh Sleep Quality Index and reduction in use of sleep medications after a 4-week, biweekly yoga intervention, consisting of Hatha and restorative postures as well as breathing exercises and meditation [58].

A randomized controlled trial demonstrated a reduction in menopausal symptoms for breast cancer survivors undergoing a 12-week program of yoga, combined with meditation. The intervention has been shown to decrease reported somato-vegetative, psychological, and urogenital menopausal symptoms which persisted through the 3-month follow-up period [59].

- Tai Chi

Tai Chi is a century-old movement practice, originating in China likely over 400 years ago. Originally based on martial arts movements, the practice evolved to be characterized by flowing movement sequences coordinated with the breath and focused attention. Tai Chi, when practiced for restorative purposes, is embedded in the framework of Qi Gong practices, which also include meditation, energy work, and self-massage.

As a safe form of exercise, Tai Chi and Qi Gong have been found to be of particular benefit when encouraging debilitated and elderly patients to resume physical activity. As such Tai Chi has been found to improve balance and reduce risk for falls in a systematic review [60]. A randomized trial, comparing physical therapy to Tai Chi for osteoarthritis of the knee, found that both groups had similar clinically significant improvement, while the Tai Chi group also showed improvements in depression and quality of life scores [61].

The slow-moving, low-impact movement forms may be ideal for weakened or fatigued cancer patients who seek to engage in safe exercise. In the cancer population, Tai Chi has been found to be effective for managing cancer-related fatigue in patients with lung cancer undergoing chemotherapy in a recently published randomized controlled trial [62]. There is also evidence that Tai Chi may help increase lung capacity and lower BMI in breast cancer patients [63].

- Guided Imagery

Guided imagery has been practiced in the health-care setting since the 1970s. Visualizations are inherent to many contemplative traditions but are now evaluated for clinical use in several formats. The technique involves a mental imaginary journey, guided by a practitioner live or via recordings. The practitioner's narrative invokes imagery that engages all senses and vividly creates imaginary scenarios that are soothing and reassuring. The imagery is thereby tailored to the patient's symptoms and clinical context, such as detailed visualizations of successful treatments or procedures and gradual healing of wounds.

Guided imagery has been successfully implemented for presurgical relief of anxiety and has been found to decrease perioperative blood loss and pain [46, 64]. However rather than targeting specific symptoms, guided imagery poses a safe and resource friendly modality to address a range of symptoms.

A randomized controlled trial of 208 breast and prostate cancer patients undergoing chemotherapy found that a combination of guided imagery and progressive muscle relaxation can improve a cluster of chemotherapy-associated symptoms such as pain, fatigue, and nausea and improve quality of life measures [65].

Several randomized controlled trials demonstrated an immunostimulatory effect of guided imagery [45, 46, 66]. One study demonstrated an increase in immune markers in 80 patients with locally advanced breast cancer. Patients that underwent a guided imagery intervention showed marked increase in parameters of cell-mediated immunity and cytotoxicity, such as activated T cells and regulatory cytokines [45]. The extent of the observed immunologic changes correlated with the self-reported guided imagery practice frequency; however, the clinical implications of these findings are not yet established.

- Clinical Hypnosis and Self-Hypnosis

According to the American Society of Clinical Hypnosis (ASCH), the term hypnosis refers to "a state of inner absorption, concentration and focused attention" [67]. This state is then used by practitioners to make therapeutic suggestions that can be used, for example, for symptom control or behavior modification. Although practices which utilize altered mind states for therapeutic purposes have been described since ancient times, the practice of clinical hypnosis dates back about 100 years and has since been scientifically controversial.

Among many dubious schools and credentialing institutions, only ASCH provides a standardized training and certification process for clinical hypnotherapists.

Similar to guided imagery, hypnosis has been frequently evaluated for anxiety relief in relation to medical procedures [68]. Pre- or periprocedural hypnosis was found to decrease anxiety and pain in a woman undergoing breast biopsy, without increasing procedure time [69, 70]. Other uses have been evaluated in the context of cancer: hypnosis reduced perceived hot flashes in breast cancer survivors and was found to reduce anxiety and depression and improved sleep in one randomized trial [71]. The beneficial effects on the management of hot flashes were later confirmed in a postmenopausal woman [72]. A recently published review documents the beneficial effects of hypnosis on pain and distress in the breast cancer population [73].

**Summary**

- There is good evidence in breast cancer patients for the use of meditation, particularly MBSR for anxiety, depression, and quality of life improvement.
- Gentle yoga can improve cancer-related fatigue and improve sleep quality.
- Tai Chi can provide a safe, low-impact exercise option and may improve balance in elderly or physically debilitated patients.
- Guided imagery provides a convenient non-pharmacologic tool to addressing periprocedural anxiety and stress.
- Clinical hypnosis should be considered as an adjunct treatment for hot flashes.

- Music and Art Therapies
  - Theoretical Background

Music and art therapies are based on the clinical and evidence-based use of music and art interventions within a therapeutic relationship with the aim of accomplishing individualized treatment goals. According to the American Art Therapy Association, art therapy is a mental health profession in which clients, facilitated by the art therapist, use art media, the creative process, and the resulting artwork to explore their feelings, reconcile emotional conflicts, foster self-awareness, manage behavior and addictions, develop social skills, improve reality orientation, reduce anxiety, and increase self-esteem [74].

- Clinical Applications

Creative psychological interventions (CPIs) are being used across the cancer spectrum and in all disease stages for the management of treatment-related symptoms and aim to support psychological readjustment to the loss, change, and uncertainty of cancer treatment and survivorship [75]. While high-quality research in this area is still lacking, these modalities have become highly utilized supportive treatments, especially for hospitalized patients. A systematic Cochrane review concluded that music interventions may have beneficial effects on anxiety, pain, fatigue, and QOL in people with cancer and found that music may have a small effect on heart rate, respiratory rate, and blood pressure [76]. Music therapy interventions have been shown to reduce anxiety and recovery time when used perioperatively in patients undergoing breast surgery for confirmed or suspected breast cancer [77].

- A recent review article evaluated the effect of different CPIs on psychological outcomes for adult cancer patients. Considering the evidence of ten randomized controlled trials across the CPI spectrum, including music, art, and dance therapies, these interventions showed benefit in adult cancer patients with respect to anxiety and depression, quality of life, coping, stress, anger, and mood. There was no difference observed to suggest that any one type of CPI was superior in their effects [78]. In children with leukemia, art therapy has shown to be beneficial in supporting children and parents during painful medical procedures [79].

**Summary**

- Consider creative psychological interventions as a supportive measure, particularly in the context of hospitalization and exposure to medical procedures.

- Massage and Other Touch Therapies
- Massage Therapy
  - Theoretical Background

Massage therapy encompasses a variety of techniques and styles that use touch, kneading, stoking, and other physical manipulation of muscles and connective tissues, with the goal to release tension, alleviate pain, improve circulation, and achieve relaxation. The use of massage has been described in many ancient cultures, and accordingly there are different massage and bodywork traditions present until today, such as Abhyanga with roots in India or the Japanese bodywork form shiatsu. Swedish massage is most prevalent in the West and is characterized by a variety of stroke techniques that are geared toward easing muscle tension and pain.

- Clinical Applications

The safety of massage therapy has been assessed in the cancer population and found to have an overall low risk for adverse effects. Some caveats include the risk for bleeding and hematomas in patients with cytopenias and patients taking systemic anticoagulation or massage of friable tumor tissues, the documented risk of dislodging vascular thrombi, the risk of fractures due to metastatic bone disease, and a heightened risk for skin infection in areas affected by radiation or surgical wounds [80]. With these caveats in mind, there are several potential roles for therapeutic massage and other forms of bodywork in the cancer setting.

- Recent data reviews found no conclusive or only weak evidence for the benefits of massage in the cancer setting and pointed to the paucity of adequately powered studies with good quality study designs in this area [81,

82]. Despite the lack of definitive data, massage stands out as one of the most popular and highly utilized IO therapies.

- A randomized controlled trial of 380 patients with advanced cancer showed that both a series of six 30-minute massage sessions and simple-touch sessions over 2 weeks reduced pain and improved mood. Massage was significantly superior for both immediate pain and mood, but not for sustained pain, worst pain, QOL, symptom distress, or analgesic medication use [83]. When delivered during chemotherapy, therapeutic massage may reduce self-rated pain, fatigue, nausea, and anxiety [84]. In addition to chemotherapy-related symptoms, postsurgical cancer pain may respond to massage therapy [85, 86]. Among the different massage techniques, foot reflexology is thought to be particularly beneficial in the cancer setting [86]. Focusing the massage intervention on the feet may allow for its application in various health-care settings and bypass areas of the body where surgical or radiation scars may limit the treatment.
- Manual lymphatic drainage (MLD) is a commonly used adjunct treatment for patients at risk for cancer-related lymphedema. In the setting of breast cancer, the prevention and treatment of debilitating upper extremity lymphedema are commonly addressed with a combination of MLD, compression sleeves, and physical therapy. The benefit of MLD is observed particularly for mild to moderate breast cancer-related lymphedema [87, 88]. Massage therapy may also temporarily alleviate anxiety and stress [89, 90].

**Summary**

- Incorporate MLD for prevention and treatment of breast cancer-related lymphedema.
- Massage can be considered for alleviation of anxiety and stress as well as for chemotherapy-related symptoms or postsurgical pain.

- Nutrition, Natural Products, and Supplement Use
  - Nutritional Guidance

At most medical institutions, trained dietitians address nutritional concerns and treatment-related dietary impairments for patients undergoing cancer treatment. Nonetheless, patients at all disease stages are left with the question whether they can modify their cancer risk with the way they eat. Many patients are drawn to pursue popular diets, which frequently get promoted as curative regimens for cancer. Some of these touted diets are harmless but lack a scientific base, e.g., the "alkaline diet" [91]. Other diets are severely restrictive and may be considered hazardous to the patient (e.g., Gerson therapy)—particularly when paired with a philosophy that rejects conventional care [92].

- When discussing nutrition with cancer patients, a topic frequently raised is the utilization of nutritional and herbal supplements. A general emphasis should be made on obtaining all nutrients from a well-balanced, whole foods diet. In this chapter we will discuss some of the most common caveats and considerations in regard to the use of natural products in the cancer setting.
- Patients can be referred to the American Cancer Society Guidelines for Nutrition and Physical Activity:
- http://www.cancer.org/healthy/informationforhealthcareprofessionals/acsguidelines/nupaguidelinesforcancersurvivors/.
  - Drug Interactions

According to a survey published in the *Journal of Clinical Oncology*, 64–81% of cancer survivors reported using dietary supplements [93]. Lack of reliable information, widespread availability, and popular, unsuspecting use of these supplements demand the attention of the medical community. Particularly in the cancer setting, the concern for herb-drug interactions often drives an aversive mind-set toward supplement use among health-care providers.

Detrimental herb-drug interactions may occur, and concurrent use of supplements such as complex botanical agents during surgery, chemotherapy, or radiation therapy can be problematic [94, 95].

To address this concern, several common patterns of interactions need to be considered when evaluating a particular supplement: induction or inhibition of the cytochrome P450 system, impairment of coagulation, or direct toxic effects [9, 96–98].

Many herbs, such as St. John's wort, interfere with cytochrome P450 enzymes. Reduced plasma levels of SN38, an active metabolite of irinotecan, have been reported following simultaneous use [99]. Such metabolic interactions preclude St. John's wort for patients on medications metabolized by cytochrome P450 3A4. Black cohosh was equally found to be a strong inhibitor of both CYP450- and carboxylesterase-mediated biotransformation of tamoxifen and irinotecan, respectively, to their active metabolites, potentially reducing their clinical efficacy [100].

Other supplements such as vitamin E, fish oil, ginkgo biloba, feverfew, and ginger may have adverse effects in perioperative use such as increased bleeding tendency, when taken in a large enough amounts. Garlic, in high concentrations, is also known to decrease platelet aggregation and potentially elevate international normalized ratio values and should not be used with anticoagulants or in patients with platelet dysfunction [101].

Green tea extract is implicated with causing hepatotoxicity [102]. Based on a case report, there may be a potential for liver toxicity with the concomitant use of *Panax* ginseng and imatinib [103]. Excessive use of vitamin A supplements may result in liver injury as well [102].

Other mechanisms by which supplement-drug interactions may occur are by induction and inhibition of P-glycoprotein, e.g., by herbal compounds such as piperine, curcuminoids, or resveratrol [104].

Natural products with phytoestrogenic activity pose a concern for patients with hormone-sensitive tumors, as in the case of estrogen receptor-positive breast cancers. Isoflavones, such as those obtained from soy products and lignans, such as those present on seeds and grains, are the most common phytoestrogens. While moderate culinary use is not harmful and may even be beneficial, dietary supplements containing large amounts of phytoestrogens should be avoided in the case of hormone-sensitive cancers. They include red clover, kudzu, fo-ti, wild yam, dong quai, chaste berry, and licorice [105–108].

Although many herbs have documented benefits, caution is warranted in the context of cancer treatment. The conversation about supplement use should be initiated by health-care providers in order to discourage self-treatment. Patients interested in taking natural products which show a health benefit in preliminary studies should do so under close medical monitoring and under the guidance of IO practitioners.

More information in relation to possible drug-herb interaction can be found here:

https://naturalmedicines.therapeuticresearch.com/https://www.nih.gov/

https://toxnet.nlm.nih.gov/

## Quality

- One of the greatest concerns regarding both therapeutic use and scientific evaluation of botanical agents is quality. Contamination and adulteration of dietary supplements are important considerations, since product inconsistencies and contamination have been reported on many occasions. Such factors can deeply impact the safety and efficacy of treatments [109, 110]. Botanical products have to be evaluated for their levels of contaminants, such as pesticides, heavy metals, aflatoxins, and microorganisms to ensure quality and safety. It is noteworthy that legislation generally does not oblige manufacturers to repeat such analyses prior to the use of raw materials from botanical or animal origin; rather a one-time certificate of analysis suffices to comply with legal requirements.
- The strict labeling of plant parts, preparation (extract vs. crude herb), and standardization for active ingredients is not common practice but is essential for health-care providers and researchers alike. A prominent example that highlights the pharmacokinetic aspects of natural product use is turmeric. Both the revered

spice and its best researched active ingredient curcumin are poorly absorbed in their natural form. Bioavailability can be dramatically enhanced by the formulation of the curcumin product such as the use of liposomal encapsulation or the addition of piperine [111].

- Natural Products Under Investigation
- This section includes examples for natural products that have been studied in specific oncologic contexts, based on preliminary clinical data and preclinical data.
  - Coriolus Versicolor

Coriolus versicolor is a medicinal mushroom of the basidiomycetes class, commonly used in Traditional Chinese Medicine. Polysaccharide-K (PSK), a Japanese proprietary product derived from coriolus, was found to have immunostimulatory properties and has been evaluated as an adjuvant treatment for gastric and colorectal cancers. Used in conjunction with chemotherapy, it has been shown to improve survival [112–115]. Based on a recent review on the use of PSK in lung cancer patients, it may improve immune function, reduce tumor-associated symptoms, and extend survival [116].

– Curcumin

Curcumin is one the best studied active compounds in the popular spice turmeric. Preclinical and clinical studies demonstrate anti-inflammatory and antiproliferative properties of this herb. In a phase-two clinical trial in patients with advanced pancreatic cancer, curcumin was found to have clinically relevant biological activity in some patients and was well tolerated [117].

– Epigallocatechin Gallate (EGCG)

EGCG is the active constituent in green tea, which accounts for 40% of the total polyphenol content. As part of a phase-two clinical trial on 42 patients with Rai stage 0 to II chronic lymphocytic leukemia, daily intake of ECGC leads to a decrease in lymphadenopathy and absolute neutrophil count [118].

– Probiotics

The term probiotics refers to a number of living microorganisms, which are implicated in a variety of health effects, such as prevention of *Clostridium difficile*-associated diarrhea [119]. In cancer patients, the use of probiotics may reduce the severity and frequency of treatment-associated diarrhea and the need for anti-diarrheal medication [120].

– Omega-3 Fatty Acids

Omega-3 fatty acids are often supplied by fish consumption and fish oil supplementation. In non-small cell lung cancer patients, supplementation with fish oil may help to maintain weight and muscle mass during chemotherapy while enhancing the effects of chemotherapy and improving survival [121, 122].

## Herbal Combinations

Studying preparations with multiple herbal components is more challenging [123]. However there are examples of properly done studies.

In a double-blind, randomized, placebo-controlled trial, a preparation containing green tea extract, pomegranate, turmeric, and broccoli extract was given to prostate cancer patients. A favorable effect on PSA progression was observed both in patients on active surveillance and those experiencing a PSA increase after radiotherapy [124]. The median rise in PSA was significantly smaller in the supplement group than in the placebo group.

A four-herb formulation was studied in phase 1 and 2 trials of digestive tract cancer and found to be well tolerated [125, 126]. A 12-herb formulation was studied in lung cancer patients and found to not affect the pharmacokinetics of docetaxel [127].

Resources for further inquiry about natural products, related research, and common use can be obtained via the National Center for Complementary and Integrative Health, the Memorial Sloan Kettering Cancer Center, and the Natural Medicines Comprehensive Database.

https://nccih.nih.gov/health/herbsataglance.htm

https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs

http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND

**In Clinical Practice**

- Actively encourage an open communication with cancer patients and survivors about the use of natural products.
- The possibility of herb-drug interactions has to be addressed on a case-by-case basis—when in doubt, err on the safe side.

## Summary

The American Society of Clinical Oncology includes integrative therapies in their updated 2016 Practice Guidelines for management of chronic pain in cancer survivors. Modalities such as acupuncture, massage, hypnosis, and meditation are recommended as adjunct treatments for chronic pain conditions (persistent longer than 3 months) in adult cancer patients and survivors, irrespective of the cause [128]. Other evidence-based integrative oncology clinical practice guidelines have been developed and published over the years [1–3]. Complementary therapies are increasingly being incorporated into the clinical care for pain and other clinical scenarios, such as vasomotor symptoms or mood disorder. Noninvasive therapies with favorable risk-benefit profiles can be safely used to target cancer-related symptoms.

Fostering open, non-stigmatizing communication about complementary therapy use and educating the patient to the dangers of unsupervised treatment with natural products, while monitoring their use carefully, can ensure optimal integrity in disease management. This dual approach to complementary modalities can help alleviate the underlying psychological and physical symptoms that many patients with cancer experience, whereby supporting, as opposed to hindering the standard of care [129].

Straddling the challenges of conventional cancer treatment and the fast-evolving knowledge of integrative therapies requires well-trained and experienced clinicians, who are dedicated to the field. At major cancer centers that have an integrative medicine service, IO physician specialists paired with providers of integrative modalities can ensure high-quality, safe use, and seamless integration of IO and conventional care. IO is beneficial for cancer patients in the inpatient and outpatient setting and should be part of a multidisciplinary approach of quality comprehensive cancer care.

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# Part III

# Cardiovascular

# 11 Victims of Our Own Success: Cardiac Toxicities from Conventional and Emerging Cancer Therapies

Haider H. Samawi and Winson Y. Cheung

## Introduction

Cancer and cardiovascular disease are by far the two leading causes of death in the developed countries. Modern developments in diagnostic and treatment strategies within all aspects of cancer management—medical, surgical, and radiation oncology—mean that an increasing number of patients who are diagnosed with cancer today will live to become long-term cancer survivors. The majority of these individuals would have received some form of anticancer treatment during the course of their illness as a means to control their cancer or manage their symptoms. Because many systemic therapeutic agents as well as radiation techniques can be associated with acute, early, or late cardiac toxicities, a significant number of patients with a prior history of cancer are at risk of developing cardiovascular complications. Manifestations are diverse and can span the full spectrum of cardiac diseases such as cardiac arrhythmias, cardiomyopathies, and ischemic heart diseases. In addition to worsening overall quality of life, these conditions are not infrequently irreversible or fatal; therefore, they highlight the importance for members of the cancer care team to share a basic awareness of the potential risk factors, causes, and management of these various cardiac toxicities. Additionally, recent advances in basic and translational cancer research have led to an explosion in the use of mechanistically based therapies many of which have been shown to cause cardiovascular complications.

Cancer survivors who develop cardiac dysfunction as a result of their treatment could face devastating consequences and worse survival [1]. Consequently, early identification, monitoring, and prevention are essential to minimize irreversible damage. Chemotherapy-related cachexia, emesis, and myelosuppression are dose-limiting toxicities which in the past have prevented the administration of chemotherapy doses that are sufficiently high enough to cause cardiac toxicities. Over the last decade, however, advances in symptom control and supportive care measures, including the frequent use of 5-$HT_3$ antagonists (e.g., ondansetron, granisetron) and granulocyte colony-stimulating factors, have not only improved patient tolerability toward chemotherapy, but they have also allowed clinicians to deliver more intensive and prolonged courses of treatment in an effort to maximize cancer control. With the uptake of more aggressive systemic treatment regimens, cardiac complications are increasingly recognized in a growing population of cancer patients and survivors. The more widespread availability of imaging facilities coupled with recent improvements in radiographic modalities has further resulted in the detection of more

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subclinical cardiac abnormalities. Conversely, newer radiation techniques are designed to limit unnecessary exposure to vital organs, such as the heart. Such efforts have decreased the incidence of radiation-related cardiac dysfunction, but some degree of risk remains.

At the cellular level, the effect of antineoplastic drugs on cardiomyocytes has been divided into two main categories: type I cardiotoxicity, as seen with anthracyclines, is characterized by structural changes in cardiomyocytes leading to apoptosis and death. This process is dose dependent and irreversible. Conversely, in type II cardiotoxicity, myocardial dysfunction and loss of contractility (stunning) occur with minimal structural changes. Classically seen with trastuzumab, type II injury is not dose dependent and is often reversible with discontinuation of the drug. Cardiac toxicities have traditionally been classified as "acute" (e.g., those that occur during or immediately after chemotherapy administration), "early" (typically within the first year after treatment), or "late/delayed" (e.g., years to decades after chemotherapy or radiation exposure). Recent evidence suggests, at least with anthracyclines, that cardiotoxicity represents a continuum that begins with subclinical decline in LVEF that can progress to symptomatic heart failure [2, 3]. As clinicians develop a higher vigilance for the risk of treatment-related cardiac toxicities, a variety of strategies have been employed to minimize this serious risk without unnecessarily compromising treatment efficacy. These various strategies include modifying the schedule of drug administration or radiation exposure, altering the actual drug molecule or the vehicle for drug delivery, or using adjunctive "cardioprotective" agents during active treatment. Unfortunately, none of these approaches have proven to be completely successful, thereby underscoring the ongoing need to closely monitor patients who are either currently receiving or have previously received potentially cardiotoxic agents.

In this chapter, the cardiotoxicity profiles of several pertinent, commonly used classes of anticancer agents, including anthracyclines (e.g., doxorubicin, epirubicin), molecularly targeted drugs (e.g., trastuzumab), and radiotherapy will be introduced and discussed. There will be an emphasis on anthracyclines since they are the most frequently implicated agents for cancer treatment-related cardiac dysfunction. Potential cardiovascular side effects of hormonal anticancer treatments are beyond the scope of this review.

## Anthracyclines

### Background

A class of chemotherapy drugs widely used in oncology to treat a variety of solid tumors and hematologic malignancies, anthracyclines exert their cytocidal activity by several mechanisms including inhibition of DNA and RNA synthesis by directly binding to the DNA of replicating cells, impairing DNA repair by inhibition of the enzyme topoisomerase II and generation of cytotoxic free radicals. Because cancer cells are rapidly proliferating, these various actions of anthracyclines can confer effective antitumor activity. The exact mechanisms by which anthracyclines contribute to cardiac dysfunction and myocardial damage are not entirely understood and might differ from its anticancer effects, particularly since myocytes of the heart are not actively replicating. One possible mechanism for their cardiotoxicity is that anthracyclines cause an increase in the generation of reactive oxygen species as well as a decrease in endogenous levels of antioxidant enzymes that are normally responsible for scavenging oxygen free radicals throughout the body. This can lead to an increase in oxidative stress, which may then result in irreversible myocardial damage [4, 5]. More recent evidence suggests that anthracyclines form a complex with the topoisomerase II beta enzyme present in cardiomyocytes leading to DNA double-strand breakage and cell death [6].

### Risk Factors

Several clinical factors have been identified that predispose individuals to an elevated risk of developing anthracycline-induced cardiac toxici-

ties such as dose of the drug, age, female gender, prior mediastinal radiation, use of other cardiotoxic agents, and preexisting cardiac conditions. One of the strongest and most reliable predictors is the cumulative dose of anthracycline drug delivered. With doxorubicin, for example, a combined analysis of three prospective trials showed that congestive heart failure (CHF) occurred in 5%, 26%, and 48% of patients who have received a cumulative dose of 400 mg/m$^2$, 550 mg/m$^2$, and 700 mg/m$^2$, receptively [7]. Based on these observations, it is recommended that the cumulative dose of doxorubicin not exceed 400–500 mg/m$^2$. While for epirubicin, the maximal cumulative dose is set at 900 mg/m$^2$. While these cumulative dose thresholds serve as a general guideline for clinicians and patients, treatments should be individualized. With the availability of noninvasive surveillance techniques, such as echocardiograms and MUGA scans that can assess cardiac function, therapy should be stopped at much lower cumulative doses if there is early evidence of cardiac dysfunction. Conversely, treatment to higher cumulative doses may also be considered if there are no signs of cardiac toxicities and anthracyclines are clinically indicated for maintaining tumor control.

Extremes of age is another well-established risk factor. Children have been consistently shown to develop cardiac toxicities at much lower cumulative doses than in adults. A similar relationship is observed in older patients, many of whom have preexisting hypertension or heart conditions. The precise reasons for this age-related association are unclear, but it is possible that the very young and very old age groups have less functional cardiac reserve to accommodate the strain that anthracyclines place on myocytes [8]. In a similar manner, a prior history of radiotherapy also increases susceptibility to cardiotoxic effects, possibly because of diminished cardiac reserve caused by previous radiation exposure. This is particularly evident for those who have received mediastinal or chest wall irradiation. Such exposures probably introduce moderate degrees of damage to the cardiac endothelium and coronary blood vessels, and subsequent treatment with anthracyclines results in further insults to the heart [9]. Likewise, the use of cardiotoxic nonanthracycline agents in combination with anthracyclines often poses a synergistic toxic effect. One common example would be the concurrent or sequential administration of taxanes and trastuzumab, both of which are cardiotoxic, along with anthracyclines for the management of both early- and advanced-stage breast cancers [10, 11].

The risk of cardiac toxicity after anthracycline exposure is variable between different individuals suggesting that genetic disposition is in play. Polymorphism in genes encoding several proteins involved in tissue remodeling, protection from oxidative damage, and drug efflux have been suggested [4, 12].

## Clinical Manifestations

The clinical presentation, the severity of dysfunction, as well as the onset of cardiac toxicities are highly variable. Acute toxicities may present as rhythm disturbances (such as atrial fibrillation), constitutional symptoms from pericarditis or myocarditis, chest discomfort due to cardiac ischemia, or dyspnea as a result of heart failure. Fortunately, early cardiac events are rare, and many are actually subclinical in nature with minimal sequelae. Therefore, formal cardiac monitoring is usually not warranted during the initial administration of anthracyclines, unless there are pertinent findings on patient history, physical examination, or recent cardiac tests that suggest a heightened risk for complications. While acute cardiac dysfunction may occur, the peak time for the appearance of cardiac toxicities is typically about 3–6 months after the last anthracycline dose, at which point serial monitoring of cardiac function should be considered. If early symptoms and signs of possible cardiomyopathy are left undetected or untreated, mortality can exceed 50% [13].

Chronic cardiac toxicity is most commonly seen within the first year following chemotherapy and ranges from asymptomatic left ventricular (LV) dysfunction to CHF. In one prospective study, the vast majority of LV dysfunction (98%)

occurred within the first year[2]. Nonetheless, the onset of cardiac dysfunction can rarely occur more than 10 years after the last dose of anthracycline administered, as evidenced by cases of serious heart failure found among long-term childhood cancer survivors, who were previously treated with high doses of anthracyclines as part of their chemotherapy regimens. In most of these situations, the cardiac abnormality presents as nonischemic dilated cardiomyopathy. Interestingly, the risk of such late cardiac problems appears to be lower among young women with early-stage breast cancers who have received only a short, adjuvant course of anthracycline-based chemotherapy, with the proviso that the cumulative dose did not exceed 300 mg/m$^2$ [9]. This finding further emphasizes the strong dose–response pattern that exists between the cumulative dose administered and the risk of cardiac toxicities. One important consideration remains: when compared to those receiving chemotherapy without anthracyclines or those not given any chemotherapy at all, the overall cardiac risk remains higher in patients who have previously been treated with any anthracyclines, irrespective of dose.

## Minimizing the Risk

First and foremost, to minimize the risk, limit the lifetime cumulative dose as described above. Several other approaches have been introduced to potentially lower the risk of anthracycline-induced cardiac toxicities, including (1) altering the mode of drug administration, (2) encapsulating the anthracycline drug molecule within liposomes, and (3) using adjunctive "cardioprotective" agents during treatment. Along with these strategies, intensive and serial monitoring with noninvasive cardiac imaging techniques has also been advocated to detect the earliest possible evidence of cardiotoxicity, at which point prompt and necessary measures can be taken to prevent the development of more severe forms of cardiac dysfunction.

A continuous infusion of anthracycline over the course of 48–96 h may lower the incidence of cardiotoxicity. This potential benefit has been suggested based on small observational studies, which showed that patients treated with prolonged infusions of anthracyclines were less likely to develop heart problems, defined as >10% reduction in left ventricular ejection fraction, when compared to those who received the conventional bolus treatment [14]. Infusional delivery, however, is less practical and resource intensive and might be associated with worse outcomes. For these reasons, anthracyclines are still typically administered by the bolus route.

There are also ongoing efforts aimed at modifying the anthracycline molecule to minimize cardiotoxic effects, while maintaining its antitumor efficacy. A prime example of this strategy is the incorporation of anthracyclines into liposomes, which has been shown in studies to have a similar efficacy as free, unbound anthracyclines. In addition, this formulation is appealing because it lowers the incidence of cardiac dysfunction and also permits substantially higher cumulative doses to be delivered [15].

Finally, the use of adjunctive cardioprotective agents, such as dexrazoxane, in conjunction with anthracyclines may reduce cardiotoxicity. Dexrazoxane is an EDTA-like chelator [16] believed to prevent cardiac damage by binding to iron stores that are released from intracellular storage during oxidative stress. It has been shown in randomized controlled trials to reduce the incidence of anthracycline-associated heart failure and subclinical cardiac toxicity [17, 18]. While this cardioprotective agent can be helpful, it is imperfect due to concerns about its potential to interfere with cancer therapy, its apparent association with lower treatment response rates, and its possible exacerbation of anthracycline-induced myelosuppression [19]. Unfortunately, data in these areas have been inconsistent; thus, it is currently unclear whether the benefits of dexrazoxane truly outweigh its risks. At the present time, the American Society of Clinical Oncology endorses the use of dexrazoxane only for patients who have received a cumulative dose of doxorubicin ≥300 mg/m$^2$ or an equivalent dose of epirubicin for the treatment of metastatic disease. Given its potential detrimental impact on antitu-

mor efficacy as well as on myelosuppression, dexrazoxane is not recommended for use in the adjuvant setting when the goal of therapy is cure. The use of dexrazoxane does not entirely eliminate the risk of cardiotoxicity. As such, patients who receive dexrazoxane should continue on regular cardiac monitoring.

Preliminary research points toward a possible benefit of concurrently administering β-blockers and ACE inhibitors with anthracyclines as a primary preventive measure against cardiotoxicity. In some of these prior studies, the prophylactic use of β-blockers, ACE inhibitors, or both was associated with better preservation of left ventricular ejection fraction [20–22]. Definitive conclusions, however, are difficult to draw as data in this regard have been based on retrospective analyses or small randomized trials. Whether benefit from prophylactic use of these agents is clinically meaningful remains to be seen.

## Cardiac Monitoring

Serial noninvasive cardiac monitoring continues to be an essential component in the ongoing management of anthracycline-treated patients so that the earliest possible evidence of cardiotoxicity can be detected. A variety of monitoring techniques that mostly rely on measuring changes in LV ejection fraction have been employed; and guidelines have been developed for monitoring and drug discontinuation by expert groups. One set of proposed guidelines is shown in Table 11.1. These guidelines are mostly based on consensus rather than evidence. Echocardiography is perhaps the most frequently used noninvasive strategy for evaluating left ventricular ejection fraction. This modality is currently endorsed by the American College of Cardiology for monitoring anthracycline-induced cardiotoxicity. Owing to its widespread availability and its lack of radiation exposure, echocardiograms remain a popular standard. Disadvantages, however, include its poor reproducibility and variability in interpretation among clinicians. In addition, it can be occasionally difficult to accurately quantify the global ventricular function.

**Table 11.1** Recommendations for cardiac monitoring in patients receiving anthracyclines

| |
|---|
| A baseline assessment of left ventricular ejection fraction is recommended before starting treatment with an anthracycline |
| Anthracyclines should not be administered if left ventricular ejection fraction is less than 30% |
| If ejection fraction is between 30 and 50%, ejection fraction should be reevaluated prior to each dose of anthracycline |
| Anthracyclines should be discontinued if there is cardiotoxicity, defined as an absolute decrease in ejection fraction by greater than 10% or a final ejection fraction of less than 30% |
| Serial reassessments of ejection fraction should be performed once the cumulative dose threshold has been reached and even sooner in patients with known heart disease, radiation exposure, or abnormal electrocardiographic results |

Radionuclide imaging, using multi-gated cardiac blood pool imaging (MUGA scan), has become a common technique for monitoring cardiac dysfunction because it provides results that are highly reproducible making it ideal for serial measurements. It also can detect subtle changes in systolic and diastolic function. As a result of such early detection, some cardiac abnormalities may be potentially reversible. Disadvantages of MUGA scans, however, include limited ability to assess structural cardiac abnormalities (such as valvular heart disease), small radiation exposure, and the need for intravenous access.

There is also an emerging interest in exploring newer approaches to cardiac monitoring. Cardiac magnetic resonance (CMR) imaging, for instance, may be particularly useful when other imaging modalities yield suboptimal images. CMR can also demonstrate subclinical changes such as myocardial edema prior to the onset of LV dysfunction [23]. Alternately, there is ongoing research to clarify the role of cardiac biomarkers, such as troponin and natriuretic peptide. The hypothesis is that these biomarkers may provide earlier signs of cardiac damage than any standard imaging techniques. In preliminary studies, elevations in troponin and natriuretic peptide were associated with the severity of myocardial damage secondary to anthracyclines, correlated with the degree of decrease in left ventricular

ejection fraction, and were predictive of subsequent cardiac-related morbidity and mortality [24]. Whether early elevations in these biomarkers predict any protective benefit from the prophylactic use of conventional therapeutic agents for heart failure, such as β-blockers and ACE inhibitors, is uncertain. Overall, these early data are promising for identifying early anthracycline-related cardiotoxicity, but there is insufficient evidence to support their routine use at the present time.

Finally, it is important to recognize that the "gold standard" of assessing anthracycline cardiotoxicity is the endomyocardial biopsy since this method allows for direct evaluation of both the presence and the degree of cardiac damage [25]. Characteristic features of chemotherapy-related injury include depletion of myofibrillary bundles, evidence of myofibrillar lysis, mitochondrial disruption, and intramyocyte vacuolization. Understandably, this procedure is invasive and itself carries the risk of complications, such as arrhythmias and bleeding. Furthermore, the interpretation of the biopsy specimens requires special expertise in histology and pathology. For these reasons, endomyocardial biopsy has typically been reserved for patients in whom a definitive diagnosis is required or for those in whom noninvasive imaging modalities fail to provide adequate information regarding the cardiac functional status.

## Prognosis and Management

The short- and long-term prognosis of individuals affected by anthracycline-induced cardiac toxicities appears to depend heavily on the severity and stage of cardiac symptoms at the time when dysfunction is initially diagnosed. This observation further underscores the importance of prompt and early detection. Patients who manifest with clinical symptoms at diagnosis have a worse outcome when compared with those who present with an asymptomatic decrease in left ventricular ejection fraction. In a prospective study of 2625 women treated with anthracyclines for a variety of solid tumors, 226 (9%) developed cardiac toxicity of whom full or partial recovery of LVEF was observed in 82% of cases after prompt initiation of enalapril, either alone or in conjunction with a β-blocker [2]. These data indicate significant potential for reversibility with early detection and treatment and challenge the concept of irreversible myocardial damage. However, the potential for spontaneous recovery in asymptomatic patients is unclear.

Currently, anthracycline-associated cardiac dysfunction is treated in a similar fashion to other causes of LV dysfunction with the use of medical therapy, such as β-blockers and ACE inhibitors. At least one study suggests that ACE inhibitors should be considered as first-line treatment for both asymptomatic left ventricular dysfunction and symptomatic heart failure. In this small series of women with metastatic breast cancer who received epirubicin, 7 of 8 women treated with ACE inhibitors had an increase in ejection fraction ≥15% whereas only 1 of 33 women without ACE inhibitor therapy demonstrated a similar response [26]. Until more evidence becomes available, medical management of chemotherapy-related heart failure should incorporate the use of these medications. To this end, most experts also concur that for patients in whom anthracycline-induced cardiotoxicity is refractory to standard medical therapy, interventions such as cardiac resynchronization therapy should at the very least be considered in the appropriate setting.

## HER-2-Targeted Therapy

### Trastuzumab

#### Background

Trastuzumab is a humanized monoclonal antibody that targets the human epidermal growth factor receptor-2 (HER-2), a receptor tyrosine kinase that is overexpressed in up to 25% of breast cancer patients. Binding of trastuzumab to the extracellular domain of HER-2 results in inhibition of downstream signal transduction, thereby resulting in cellular growth inhibition. This molecularly targeted agent has led to dramatic improvement in outcomes and has become a crit-

ical component in the management of both adjuvant and metastatic HER-2-positive breast cancer. These benefits must be carefully weighed against the added risk of cardiac toxicities from trastuzumab treatment.

The precise mechanisms underlying trastuzumab-associated cardiac dysfunction are as yet unclear. Of note, considering that many patients who receive trastuzumab have also been previously treated with anthracyclines, it was once postulated that potentiation of prior anthracycline-induced cardiac damage was the most responsible factor. However, histopathological studies from endomyocardial biopsy specimens from individuals with trastuzumab-related cardiac dysfunction have refuted this hypothesis, since anthracycline-based structural changes were not always observed. Moreover, trastuzumab dysfunction can develop even in the setting of anthracycline-naïve patients. Preliminary studies indicate that trastuzumab cardiotoxicity may be directly related to HER-2 blockade (on-target toxicity) [27]. Early animal models, for instance, suggest that HER-2 signaling is an important step in embryonic cardiac development. It also participates in protecting the heart from potential cardiotoxins where studies show that HER-2 gene knockout mice are more likely to develop dilated cardiomyopathy and their myocytes demonstrate increased susceptibility to anthracycline-induced cell death [28]. In further support, serum HER-2 levels appear to be increased in patients with chronic heart failure with levels correlating inversely with left ventricular function [29].

The following section briefly reviews the clinical manifestations of trastuzumab cardiotoxicity, the guidelines for monitoring cardiac function during treatment, and the management of patients who experience cardiotoxicity as a result of trastuzumab exposure.

## Risk Factors

The overall incidence of cardiac dysfunction in trastuzumab-treated patients ranges between 3% and 19%, while the incidence of symptomatic heart failure is 2–4%. Cardiac toxicity is modest when trastuzumab is used alone, but the rate becomes significantly higher among individuals who receive trastuzumab concurrently with other potentially cardiotoxic agents, especially anthracyclines [30]. In the pivotal phase III trial that evaluated the benefit of adding trastuzumab to conventional cytotoxic chemotherapy for metastatic breast cancer, the incidence of *any* cardiac dysfunction was 27% for trastuzumab plus doxorubicin and cyclophosphamide (AC) vs. 8% for AC alone and 13% for trastuzumab plus paclitaxel vs. 1% for paclitaxel alone. As expected, the incidence of *severe* heart failure, consisting of either class III or IV symptoms, was substantially lower: 16% with trastuzumab plus AC vs. 4% for AC alone and 2% with trastuzumab plus paclitaxel vs. 1% for paclitaxel alone [11]. These findings resulted in the recommendation that concurrent delivery of anthracyclines and trastuzumab be generally avoided or used with great caution in favor of sequential therapy because of the increased risk of cardiotoxicity associated with concurrent administration. Subsequent trials employing frequent cardiac monitoring showed lower incidence of LV dysfunction and symptomatic heart failure with trastuzumab use in combination with anthracyclines and to much lower extent with the use of taxanes. The precise mechanisms underlying the additive cardiotoxicity of anthracyclines and trastuzumab are unclear, but upregulation of HER-2 blockade by anthracyclines is thought to be at least partially responsible for this synergistic effect.

Aside from concurrent anthracycline use, additional risk factors have been proposed to identify individuals with a higher likelihood of developing trastuzumab-related cardiotoxicity including older age, preexisting LV dysfunction, use of antihypertensive medications, higher body weight, prior chest radiation, and prior therapy with anthracyclines.

## Clinical Manifestations

Unlike the adverse events observed with anthracyclines, trastuzumab-related cardiac toxicities tend to manifest as asymptomatic reductions in ejection fraction as opposed to overt heart failure. In further contrast, trastuzumab-associated cardiac disease is not dependent on the cumulative

dose of drug administered. It is commonly reversible with treatment cessation and frequently amenable to treatment rechallenge if cardiac function recovers after a planned treatment break.

Because of these differences, chemotherapy-related cardiac abnormalities are categorized by some experts into type I and type II dysfunction [31]. The former "type I" refers to anthracycline-associated injury, which results in permanent myocyte destruction and clinical heart failure. Conversely, the latter "type II" refers to trastuzumab-associated damage, which is more often associated with transient loss of cardiac contractility and less likely to involve myocyte death or clinical heart failure. Owing to its somewhat transient nature, this form of dysfunction may be reversible.

## Minimizing the Risk

At least in the adjuvant setting, several approaches have been proposed as potential ways to lower the risk of trastuzumab-related cardiotoxicity. First, attempts at shortening the duration of trastuzumab treatment were examined in clinical trials. Most adjuvant breast cancer trials involving trastuzumab have administered the agent over the course of 12 months. In the FinHer trial, an anthracycline- and taxane-containing regimen was compared to the same chemotherapy regimen plus a 9-week course of trastuzumab [32]. The trastuzumab arm showed a 35% improvement in distant disease-free survival (DFS), albeit nonsignificant. No cardiac dysfunction was observed in the trastuzumab study arm, suggesting that a decrease in the duration of exposure to trastuzumab may confer substantially less cardiac risk. However, the large phase III trial PHARE that involved 3384 patients failed to demonstrate non-inferiority with a shorter 6-month duration of trastuzumab compared with 12 months [33]. Therefore, despite more cardiac events, the currently recommended duration of adjuvant trastuzumab remains 12 months.

Another method is integrating trastuzumab into nonanthracycline-containing adjuvant regimens. One example consists of docetaxel and carboplatin, plus trastuzumab (TCH). Indeed, results from the BCIRG 006 trial, in which one of the three arms utilized the nonanthracycline-containing TCH adjuvant chemotherapy regimen, are promising with respect to lowering cardiac risk [34]. However, the anthracycline-containing regimen showed a nonsignificant trend toward improvement in survival. Until further evidence, anthracycline-based chemotherapy in combination with trastuzumab is preferred for locally advanced HER-2-positive breast cancer with larger tumors or involvement of locoregional lymph nodes. TCH is an acceptable alternative in select patients with small tumors.

As outlined previously, concurrent administration of trastuzumab with anthracyclines conferred a high rate of cardiac events and should be avoided.

## Cardiac Monitoring

Heart function should be evaluated prior to the instigation of trastuzumab therapy as well as regularly during treatment. Patients with a normal baseline ejection fraction based on imaging, and neither symptoms nor signs of heart failure on history and physical examination, respectively, should be considered eligible for trastuzumab therapy. Patients with LVEF 40–50% may be considered on a case-by-case basis and warrant careful monitoring. While the following are not contraindications to therapy, special caution should be taken when patients with a prior history of hypertension, coronary artery disease, and valvular heart disease are receiving trastuzumab.

Currently, there are no universal recommendations on the optimal methods or schedules for monitoring patients for trastuzumab cardiotoxicity. However, clinical guidelines have been proposed by expert groups and major organizations. Expert consensus by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [35] recommends a baseline assessment with history and physical examination and a cardiac imaging test. Additionally, measurement of troponin level is desirable. Patients should also undergo follow-up cardiac imaging every 3 months while on trastuzumab therapy.

Likewise, guidelines for the management of cardiac complications during trastuzumab therapy have been developed. A set of proposed guidelines is outlined in Table 11.2.

**Table 11.2** Recommendations for trastuzumab adjustments based on changes in left ventricular ejection fraction during cardiac monitoring[a]

| |
|---|
| *Asymptomatic patients* |
| If LVEF decreases by less than 10%, continue with trastuzumab. IF LVEF is more than 5 points below LLN, repeat LVEF assessment in 4 weeks[b] |
| If LVEF decreases by 10–15% but is still above LLN, continue with trastuzumab; otherwise, hold trastuzumab and repeat ejection fraction assessment in 4 weeks[b] |
| If LVEF decreases by more than 15%, hold trastuzumab and repeat ejection fraction assessment in 4 weeks |
| Once held, trastuzumab can be resumed if the overall ejection returns to more than 50%; otherwise, trastuzumab should be stopped<br>After two holds, permanent discontinuation of trastuzumab should be considered |
| *Symptomatic patients* |
| Trastuzumab should be discontinued, and appropriate therapy and referral to cardiology should be instituted |

*LLN* Lower limit of normal
[a]Modified from National Surgical Adjuvant Breast and Bowel Project B-31 trial protocol [36, 37]
[b]Consider referral to cardiology and initiation of therapy in all patients with LVEF below LLN

### Prognosis and Management

In contrast to anthracyclines, data indicate that trastuzumab-related cardiac toxicities are frequently reversible in the majority of cases. Moreover, early evidence suggests that reintroduction of trastuzumab appears to be safe as long as cardiac abnormalities that develop while receiving the drug have resolved. In the phase III trial by Slamon et al., for instance, 33 patients continued trastuzumab for a median of 26 weeks despite developing an asymptomatic decline in ejection fraction. The cardiac status of 85% improved or remained the same, while symptoms were reversible for 75% of those who received standard medical therapy for heart failure [11]. Similarly, in a retrospective review from MD Anderson Cancer Center, the majority of those who stopped trastuzumab after developing symptomatic heart failure recovered with appropriate medical therapy, which consisted of β-blockers and ACE inhibitors [38]. While recovery was not universal, treatment was reinitiated in more than half of patients who interrupted trastuzumab for either an asymptomatic or symptomatic cardiac event, of whom most remained free of subsequent cardiac problems.

### Other HER-2-Targeted Agents

A number of HER-2-targeted agents are now approved for the treatment of HER-2-positive breast cancer such as lapatinib, pertuzumab, and ado-trastuzumab emtansine (T-DM1). Each has a unique mechanism of action that differs from trastuzumab. Preliminary results from clinical trials have suggested that these agents have a favorable cardiac safety profile compared to trastuzumab. For example, in a pooled analysis of over 3600 patients using lapatinib, an oral small molecule tyrosine kinase inhibitor that affects both HER-2 and epidermal growth factor receptor (EGFR), cardiac events occurred in only 1.6% of patients, and mostly were asymptomatic declines in LV function [39]. Similarly, only 1.7% had a cardiac event in a phase III trial using T-DM1 which is an antibody-drug conjugate composed of trastuzumab linked to an antimitotic agent [40]. Nonetheless, these trials included highly selected patients, and the experience with these agents has been less extensive.

More recently, combining trastuzumab with other HER-2-targeted therapy was associated with improved outcomes. In the Cleopatra trial, combining pertuzumab with trastuzumab and docetaxel for first-line treatment in women with metastatic HER-2-positive breast cancer has resulted in an impressive 15-month improvement in OS establishing this regimen as the new standard in this setting. This combination was not associated with significantly worse cardiac toxicity.

Similar to trastuzumab, cardiac monitoring with use of these agents is recommended at baseline and at regular intervals.

## Radiation Therapy

### Background

Radiation therapy, which can be applied either by itself or in combination with systemic treatment agents, has contributed to significant improvements in the survival of patients with specific cancers, including the breast, Hodgkin disease, as well as malignancies involving the thorax (e.g.,

lung, esophagus). Such advances have resulted in a higher prevalence of cancer survivors, who are now at increased risk for late complications of radiation treatment, which can frequently involve the heart. Most of the data pertaining to the cardiovascular toxicities of radiation therapy are derived primarily from survivors of breast cancer and Hodgkin lymphoma, since these are diseases in which radiation is a frequent component of initial management and for which survival is often prolonged to a significant degree.

Radiation, if administered in sufficiently high doses or large volumes, can potentially damage any and all aspects of the heart, including the pericardium, myocardium, heart valves, coronary blood vessels, and conduction system. Pericarditis is a common manifestation of acute radiation injury, while chronic pericardial disease, coronary artery disease, restrictive cardiomyopathy, valvular disease, and conduction abnormalities can present years or decades after the original treatment. All of these conditions can potentially result in significant morbidity and mortality. The increasing recognition of radiation-induced cardiac toxicities has led to the development of improved radiotherapy techniques that aim to minimize the dose and volume of exposure to the heart. These contemporary measures appear to have drastically reduced the incidence of radiation-related cardiac complications, although there is still some residual risk.

## Risk Factors

Several factors increase the risk for developing radiation-induced cardiac toxicities. These include the total radiation dose administered, the dose per fraction, the volume of heart irradiated, and the concurrent delivery of cardiotoxic systemic therapeutic agents, such as anthracyclines and trastuzumab [41]. In breast cancer, for example, the older generation of radiation techniques used in the management of this disease has almost always involved irradiation to the chest wall and surrounding lymph nodes. This classically resulted in a relatively high dose of radiation being delivered to a substantial volume of the heart. There is abundant evidence that this form of radiation delivery was associated with excess cardiovascular morbidity and mortality. Modern techniques currently deliver much less radiation to the heart and appear to have reduced the number of cases and degree of associated cardiotoxicity. In many of these cases, however, longer follow-up is required to confirm these safety findings.

Patient dependent factors, such as younger age at the time of initial radiation exposure and the presence of other personal risk factors for coronary heart disease, including hypertension, high serum cholesterol, and smoking history, may also increase the risk of radiation-associated cardiac dysfunction [41].

## Clinical Manifestations

The main mechanism for radiation-related cardiac toxicities involves radiation damage to coronary blood vessels. This injury is believed to subsequently lead to the production of reactive oxygen species that disrupts DNA strands, which then results in secondary inflammatory changes and ultimately fibrosis. The classic hallmarks of radiation-induced cardiotoxicity consist of diffuse fibrosis of the myocardium coupled with narrowing of arterial and capillary lumens [42]. The ratio of capillaries to cardiac myocytes decreases by 50%, which contributes to cell death, cardiac ischemia, and further fibrosis. Collagen replaces the normal adipose tissue that usually forms around the outer layer of the heart, leading to pericardial fibrosis, effusion, and possibly tamponade. All of these changes can culminate in various forms of coronary artery diseases, valvular heart diseases, pericardial diseases, diastolic dysfunction, and dysrhythmias.

There are subtle differences between chemotherapy-related cardiac dysfunction and radiation-induced cardiac toxicities. First, irradiation causes fibrosis of the myocardium, which can lead to a restrictive cardiomyopathy. This appears to have a greater impact on diastolic rather than systolic cardiac function. This contrasts with the general effects of anthracyclines, which predomi-

nantly cause systolic dysfunction. Second, radiotherapy (specifically mediastinal irradiation) has been associated with an increased risk of clinically significant valvular abnormalities. Of potential clinical importance, many of the common abnormalities found in mediastinal irradiated patients are slowly progressive and may necessitate lifelong follow-up, some of which may also require antibiotic prophylaxis for endocarditis. Third, radiation can cause fibrosis of the conduction pathways in the heart, potentially leading to life-threatening arrhythmias and conduction defects that develop years after initial radiation therapy. Examples of such dysfunction include bradycardia and sick sinus syndrome, as well as complete and lesser degrees of heart block.

### Additional Aspects

Unlike chemotherapy-induced cardiotoxicity, cardiac dysfunction related to radiation may be more challenging to manage in part because of its diverse manifestations. Improvements in radiotherapeutic techniques have been the primary means of decreasing the cardiac risk by minimizing the amount of radiation received by the heart. It is noteworthy that cardiovascular complications still appear more frequently in patients with left-sided than right-sided tumors, providing some evidence that the risk associated with radiation has not been completely eliminated with the newer generation of methods for radiotherapy.

Awareness of key factors that modify the risk of cardiovascular toxicity is another channel in which complications can be reduced. The size of the radiation field and the dose of exposure, for instance, determine the amount of incidental irradiation to the heart. Studies that compared breast cancer patients who received internal mammary lymph node irradiation were noted to have an increased risk of cardiovascular complications compared to those in whom the internal mammary lymph nodes were not included in the field [43]. Thus, radiation field and radiation dose are parameters that should be minimized, whenever possible. Care must also be taken to modify other risk factors for cardiovascular disease, such as hypertension, hyperlipidemia, and smoking, as well as to adequately manage preexisting coronary artery disease, since all of these variables may increase and potentiate radiation-related cardiotoxicity. Special attention is further warranted when radiation is used in patients who have or will receive known cardiotoxic agents, such as anthracyclines and trastuzumab.

## Nonanthracycline Agents

### Fluoropyrimidines

5-Fluorouracil is widely used in various chemotherapy regimens to fight a diverse array of cancers. Because of its frequent use, it is the second most common cause of chemotherapy-related cardiotoxicity after anthracyclines. The most frequent cardiac side effect from 5-fluorouracil is anginal chest pain. Myocardial infarction, acute pulmonary edema, and pericarditis can also occur, but these events are much rarer. The underlying mechanism for 5-flourouracil cardiotoxicity is thought to be due to coronary artery vasospasm. Its incidence is estimated to be around 8% [44]. The risk may be related to the mode of 5-flourouracil administration where infusional therapy is associated with a higher risk than bolus treatment. A prior history of coronary artery disease and concurrent use of cardiotoxic agents, including chemotherapy and radiation, also increase the risk. Fortunately, cardiac symptoms typically resolve with the cessation of 5-flourouracil treatment and the instigation of standard antianginal medical therapy. Rechallenging patients who have previously experienced 5-fluoruracil-related cardiac toxicities is somewhat controversial and generally not recommended due to high rates of recurrence. If rechallenge is being considered, it should be done under cardiac monitoring and close observation by specialized medical personnel. Alternatively, switching to non-fluoropyrimidine regimens is preferred. Furthermore, symptomatic patients should ideally undergo cardiac testing to rule out occult coronary ischemia.

Capecitabine is an oral fluoropyrimidine that is metabolized to 5-flourouracil, which is the active anticancer form of the drug. Thus, the cardiac toxicity profile of capecitabine is very similar to that observed for 5-flourouracil [45].

## Taxanes

For taxanes such as paclitaxel, mild bradycardia and heart blocks can occur, although these are usually relatively asymptomatic. Overall, the incidence of these events is very low, and thus routine cardiac monitoring is not required for typical patients without risk factors. It is important to note that the nanoparticle albumin-bound paclitaxel (e.g., nab-paclitaxel) bodes the same cardiac toxicity profile as the regular, non-albumin-bound formulation. Similarly, conduction abnormalities and angina have been reported in users of docetaxel. Both paclitaxel and docetaxel also appear to potentiate the cardiotoxic effects of anthracyclines, as described previously [46].

## Anti-angiogenic Agents

The vascular endothelial growth factor (VEGF) signaling pathway plays a critical role in tumor angiogenesis and has been a major target for cancer therapies leading to approval of more than a dozen drugs for a variety of cancers. Inhibition of the VEGF pathway can be achieved by several ways including the use monoclonal antibodies that block VEGF (such as bevacizumab) or its receptor (VEGFR2) such as ramucirumab or the use of VEGF-trap as in the case of aflibercept which acts as a decoy receptor for VEGF. Alternatively, sunitinib and pazopanib are examples of small molecule inhibitors of VEGF receptor tyrosine kinases (TKIs).

VEGF inhibitors have been associated with a variety of cardiovascular complications such as hypertension, thromboembolic events, cardiac arrhythmia, and cardiomyopathy, to name a few. Hypertension, in particular, is very common and ranges from 20% with bevacizumab to upward of 50% with some of the newer agents such as lenvatinib. This association is likely multifactorial. Inhibition of the VEGF pathway may result in an imbalance between vasodilators and vasoconstrictors and loss of capillary circulation [47]. Interestingly, the development of hypertension was associated with improved outcomes in some reports [48]. Active monitoring and management with standard antihypertensive therapy are recommended specially during the first few weeks of therapy.

LV dysfunction has been reported with several of these agents. For instance, in trials of sunitinib, a VEFG TKI commonly used in the treatment of metastatic renal cancer and gastrointestinal stromal tumors was associated with a decrease in LV function and overt heart failure in 10–3%, respectively [49]. Retrospective analyses suggest an even higher incidence of cardiovascular complications. Similar to trastuzumab, functional recovery of myocardial function is frequently (albeit not invariably) seen after their interruption suggesting a type II injury.

Arterial thromboembolic events such as stroke and myocardial infarction have also been linked to some of these agents such as bevacizumab (twofold increase in risk), whereas the association with venous thromboembolism has also been suggested but is less clear.

## Small Molecule Tyrosine Kinase Inhibitors

TKIs block the function of tyrosine kinases which are enzymes responsible for the activation of several proteins integral in the signal transduction pathways responsible for cell growth, proliferation, and differentiation. These drugs have emerged as a major component in the treatment of several cancers, and their use has increased exponentially in the past few years. Unlike traditional chemotherapy, these agents are administered orally and often used for prolonged periods of time ranging from months to even years as in the case of imatinib and other ABL1 kinase inhibitors used in the treatment of chronic myeloid leukemia (CML). These factors further emphasize the potential for being “overlooked”

as a potential cause for cardiac diseases and underscores the importance of familiarity with their side effect profiles not only for oncologists but also for primary care physicians and cardiologists.

The range of cardiac complications seen with these small molecule inhibitors is wide; however, individual drugs have unique side effect profiles. For example, vandetanib, a multi-kinase inhibitor used to treat patients with medullary thyroid cancer, is known to cause prolongation of QTc in 16% of patients [50]. Torsades de pointes and sudden death have also been reported leading the Food and Drug Administration (FDA) to issue a US box warning. It should be avoided in patients using other drugs known to cause QT prolongation and in patients with electrolyte abnormalities.

A detailed discussion of these agents and their cardiac manifestations is beyond the scope of this chapter.

## Cardio-oncology

As more cancer therapies become available, a growing number of cancer survivors face many challenges including the consequences of cancer treatment. The field of cardio-oncology addresses the cardiovascular issues arising from cancer therapy. It has evolved over the last decade in response to a massive expansion of novel therapies in cancer, many of which carry significant cardiac morbidity. In addition, the interplay between cancer and the cardiovascular system extends beyond toxicology as cancer by itself is associated with cardiovascular and metabolic complications [47]. Finally, cancer and the cardiovascular system seem to share common pathways which are not fully understood; therefore, cardio-oncology can serve as a novel platform for clinical and translational research to help cardiovascular drug discovery [51] and provides an excellent opportunity for collaboration between oncologists and cardiologists both in the care of patients and in clinical trial design.

## Summary

In summary, advances in early detection and treatment strategies have prolonged the natural history of many cancers and contributed to an increasing prevalence of cancer survivors. Some of these patients are now faced with the sequelae of early and late treatment-related toxicities, many of which involve the cardiovascular system. Cardiotoxic chemotherapy, molecular targeted therapy, and radiation are increasingly incorporated into current treatment paradigms, but each agent is associated with a spectrum of cardiac side effects. As members of the cancer team, a basic awareness of the mechanisms, risk factors, management, and prognosis of these various treatment-associated cardiac toxicities is important for addressing the specific needs and optimizing care for present and future cancer survivors.

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# Cardiac Manifestations of Cancer and Their Management

12

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## Introduction

### Key Points

1. Cancer exerts its effects on the heart both directly and indirectly.
2. The magnitude of this effect is the function of baseline cardiac reserve, the severity of the cancer-related cardiac pathology, and the functional status of an individual patient.
3. Primary cardiac malignancy is rare and often carries a poor prognosis.
4. Pericardial effusion and SVC obstruction are the most common cardiac manifestations of cancer.

While primary cardiac cancers are rare, representing less than 0.5% of cancers, secondary malignancies are much more common and can exert their effect on the heart directly or indirectly, often with dramatic consequences [1]. Figure 12.1 provides a conceptual outline of different ways that cancer can affect the heart. Direct involvement of the pericardium can lead to pericardial effusion and tamponade and, less commonly, pericarditis; involvement of the endocardium or myocardium with tumors can lead to conduction disturbances and failure of the myocardium. Tumors can also exert impact indirectly as a result of vasoactive substances produced by the cancer, such as carcinoid, deposition of proteinaceous materials in case of cardiac amyloid, or through distant mechanical impact on circulation, as in the case of cor pulmonale or SVC (superior vena caval) thrombosis with a consequent hemodynamic effect on the heart. Often the effects of cancer are complex and the heart is affected in more than one way. For example, carcinoid effect is mediated by vasoactive substances but may also lead to valvular dysfunction. Lastly, cancer treatment itself, specifically chemotherapeutic agents and radiotherapy, can cause an adverse impact on the heart (see Chap. 11 for a specific discussion on the impact of anticancer therapies on the heart).

The effect of cancer and its treatment on the heart are likely to be amplified in the setting of preexisting cardiac conditions. Thus, the impact of cancer on the heart is a function of the baseline cardiac reserve and the magnitude of the direct cancer effect. The interplay between these two factors needs to be carefully considered in the management of these conditions and their long-term outcomes.

This chapter will outline common cardiac manifestations of cancer, their prevalence, impact, diagnostic work-up, and management.

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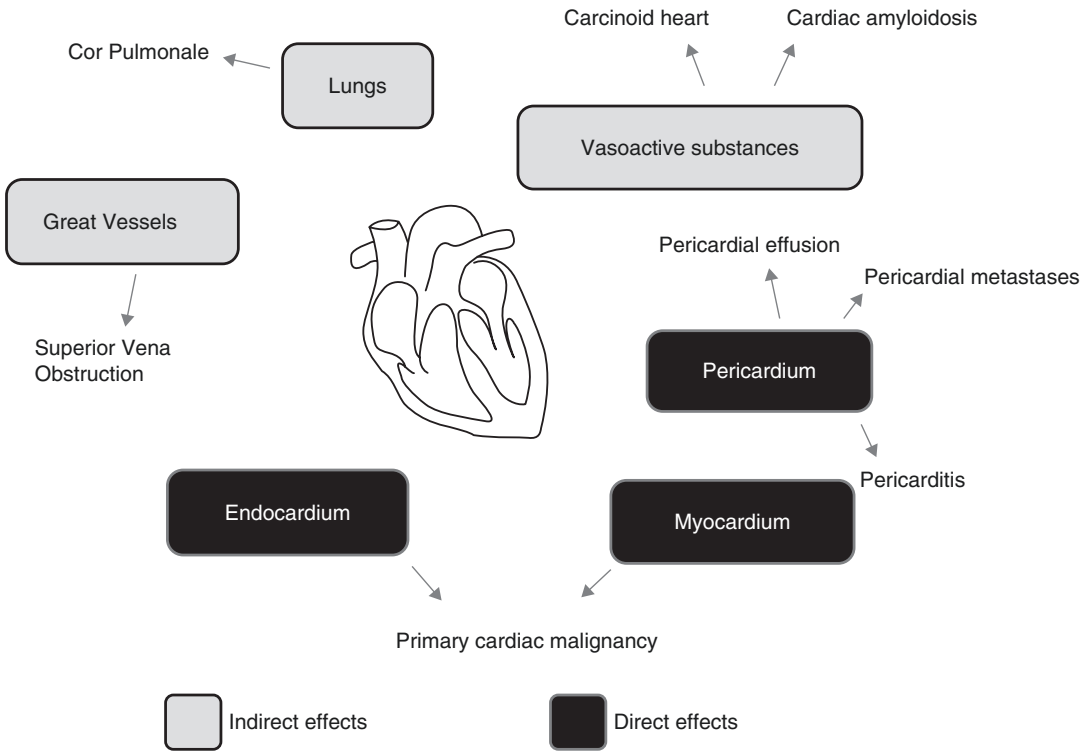


**Fig. 12.1** A conceptual outline of different ways that cancer can affect the heart

## Direct Involvement of the Pericardium and Epicardium: Pericardial Effusion

Pericardial and epicardial involvement are by far the most common manifestations of cardiac involvement with cancer, as compared to involvement of the myocardium and endocardium [2]. While primary cardiac malignancies like malignant mesotheliomas, fibrosarcomas, lymphangiomas, hemangiomas, teratomas, neurofibromas, and lipomas can develop in the pericardium, these are very rare, and the most common pericardial malignant presentation is that of pericardial effusion or tamponade and, less frequently, pericarditis.

### Epidemiology and Pathophysiology

Common malignancies causing pericardial effusions include lung, lymphoma, breast, leukemia, gastric cancer, melanoma, liver, and colon cancer [3]. Malignant pericardial effusion can be caused by direct invasion of the pericardium, lymphatic or hematogenous spread, or lymphatic obstruction due to mediastinal lymphadenopathy [4]. Pericardial tamponade is caused by slow or rapid accumulation of pericardial fluid leading to decreased right-sided filling pressure as well as reduced cardiac output due to pressure exerted by the pericardial fluid on the heart. In a large series, approximately 5% of patients presented with pericardial tamponade or pericarditis associated with neoplasia with no prior diagnosis of malignancy [5].

### Presentation

Signs and symptoms of pericardial effusion are determined by the speed of fluid accumulation. Rapid accumulation of small amounts of fluid in the pericardial space may cause dramatic symp-

toms. Relatively slow accumulation of pericardial fluid causes gradual increase in pericardial pressure and may result in accumulation of large effusions before causing any symptoms [6]. Classic symptoms of pericardial effusion include exertional dyspnea, orthopnea, and chest pain or discomfort. Additional occasional symptoms due to local compression on adjacent structures may include nausea, dysphagia, hoarseness, and hiccups.

Physical examination can be normal in the absence of large pericardial effusions. Signs of tamponade include elevated jugular venous pressure and distended neck veins, pulsus paradoxus, and muffled heart sounds on cardiac auscultation in moderate to large effusions. Pericardial friction rubs suggest associated pericarditis.

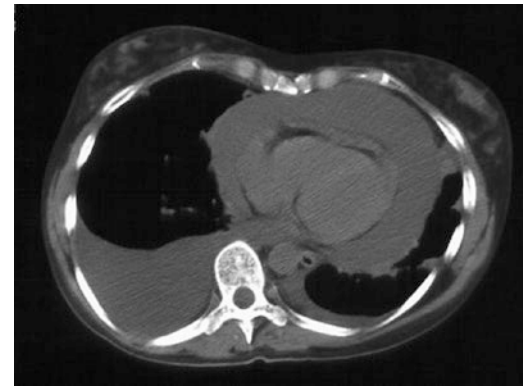

**Fig. 12.2** A CT scan of a patient with pericardial effusion showing large pericardial and pleural effusion

## Investigations

The diagnostic approach to suspected pericardial disease includes electrocardiography (ECG), chest imaging, echocardiography, and pericardial biopsy or pericardiocentesis for histologic/cytological analysis. ECG findings include a low-voltage QRS complex, sinus tachycardia, and electrical alternans (cyclic beat-to-beat shift in the QRS axis) which is commonly seen in large pericardial effusions and tamponade and results from swinging of the heart in the pericardial fluid. On a chest radiograph, an enlarged cardiac silhouette in the presence of clear lung fields suggests a pericardial effusion. CT and cardiac MRI can provide additional useful information regarding loculation and thickness of effusions, better visualization of small or focal effusions, and other associated abnormalities in adjacent structures—see Fig. 12.2 [6].

Echocardiography remains the main diagnostic modality due to its availability, diagnostic accuracy, and low cost. It can detect as little as 15 mL of pericardial fluid with as much as 100% diagnostic accuracy. An important echocardiographic finding of a large pericardial effusion is diastolic collapse of the right atrium and ventricle [3].

Diagnosis of a malignant pericardial effusion is confirmed on the basis of histologic findings seen on pericardial biopsy or on cytology performed on aspirated fluid and has sensitivity of 90% and 56%, respectively [3]. Cytology is positive in 44–87% of malignant pericardial effusions and more frequently in solid tumors than hematologic malignancies [7]. Negative cytology should not be used to exclude the diagnosis of malignancy, particularly if the index of suspicion is high.

## Management

Treatment of neoplastic pericardial effusion and tamponade is directed toward symptom relief, prevention of recurrence, and prolongation of survival. In acute settings symptom control can be achieved with therapeutic drainage of pericardial fluid through percutaneous or surgically inserted drains. Different drugs with sclerosing and antineoplastic properties can be used to prevent the recurrences with varying success. Systemic anticancer therapies in combination with local treatment can also be used to prevent recurrences.

### Percutaneous Procedures

Percutaneous needle pericardiocentesis is used in life-threatening situations requiring immediate evacuation of pericardial fluid. This procedure however is associated with complications like ventricular puncture, cardiac lacerations, damage to coronary vessels, pneumothorax, arrhythmia, cardiac arrest, and death [8]. Procedural accuracy

can be improved with the use of echocardiography. With ultrasound guidance indwelling catheters are inserted in the pericardial space to drain large effusions and instill sclerosing and cytotoxic agents. Complications are rare and include catheter occlusion and infections. Pericardiocentesis with prolonged drainage can prevent recurrence in up to 88% of patients with a malignancy [9].

Balloon pericardiotomy is another percutaneous procedure that involves rapid inflations of a balloon inserted through a subxiphoid approach, ensuring opening of the parietal pericardium permitting pericardial fluid to drain into pleural or peritoneal spaces. Technical success rates in the literature have been reported at 92%, with a complication rate of 20% including fever (12%), pleural effusion (4%), and pneumothorax (4%). The procedure may be unsuccessful because of recurrence of the effusion in 4%, bleeding requiring surgery in 2%, and persistent catheter drainage requiring surgery in 2% of cases [10].

## Local Sclerosing and Chemotherapy Agents

Bleomycin has been used as a sclerosing agent for pericardial effusions and tamponade in different doses and techniques. In a single-institution study, 11 patients with malignant pericardial tamponade received 10–20 mL of intrapericardial bleomycin [11]. Ten patients (82%) had a complete response (resolution of pleural fluid) and one patient suffered recurrence after 253 days. In another study seven patients with lung cancer received 5 mL of intrapericardial bleomycin [12]. Five patients achieved complete response with no significant side effects. In a prospective randomized study, 79 patients with lung cancer-associated pericardial effusion had percutaneous or surgical drainage and then were randomized to observation only or 15 mg intrapericardial bleomycin followed by 10 mg bleomycin every 48 h. Bleomycin was associated with superior median overall survival (119 vs. 79 days) and effusion-free survival at 2 months (46% vs. 29%) [13].

Triethylenethiophosphoramide (thiotepa), an alkylating agent, has both cytotoxic and sclerosing properties. In a retrospective study of 60 patients with malignant pericardial effusion, 35 were managed with instillation of 15 mL thiotepa in the pericardial space, and 25 patients were managed with surgical drainage. Results showed comparable complication rates, post-procedure effusion recurrence, and survival. This study also showed that pericardiocentesis followed by sclerotherapy was more cost-effective in comparison with surgical procedures [14]. In another study thiotepa (15 mg in 20 mL of normal saline) was used in 33 patients (mainly patients with breast and lung cancer) following pericardiocentesis with the aim of preventing recurrence in addition to systemic therapy [15]. There was no recurrence within 30 days of treatment. Breast cancer patients had prolonged survival as compared to patients with lung cancer (median 272 days vs. 85 days).

Tetracyclines, like doxycycline and minocycline, have also been used as sclerosing agents for the control of malignant pericardial effusions. Despite the reported success of up to 73% 30-day effusion control and an overall control rate of 81%, the use of tetracyclines has declined because of complications (fever, arrhythmia, and chest pain) [16].

Other chemotherapies have been used to achieve cytotoxic rather than a sclerosing effect. Intrapericardial cisplatin has been used in multiple doses and single dose for neoplastic pericardial effusion and found to be safe and effective in preventing pericardial effusion recurrence [17, 18]. Moriya et al. treated ten patients with small cell lung cancer with pericardial effusions with 300 mg of carboplatin in 50 mL of saline through intrapericardial catheters [19]. Among ten patients treated, there were eight major responders, one moderate responder, and one non-responder. No significant adverse events were observed.

## Radiotherapy

Clinical improvement has been observed with external beam radiotherapy in patients with cardiac metastasis including pericardial effusions related to lymphomas, leukemias, and breast cancer [20]. Intrapericardial instillation of radioactive agents, such as $^{32}P$ colloid (chromic phosphate), has also been shown to be effective and safe [21].

## Surgery

Surgical approaches are usually reserved for the management of recurrent effusions and most commonly involve creation of a pericardial window. A pericardial window is created surgically by forming an opening or window for drainage of pericardial fluid into the adjacent pleural space. It can be done by using various techniques: open surgery (subxiphoid pericardial window) by thoracoscopy including video-assisted thoracoscopic surgery (VATS) or by percutaneous balloon pericardiotomy. This procedure is effective with a minimal failure rate. It also provides better diagnostic opportunity with availability of fluid for cytology, pericardial tissue for histological examination, and direct visualization of the pericardial space [3].

Subxiphoid pericardiotomy is safe and can also be attempted in critically ill patients with local anesthetic to create the pericardial window. In one series of 127 patients, the overall initial success rate was nearly 99% and the reaccumulation rate was 11% overall [3]. Complications of the procedure include arrhythmias, myocardial laceration, pneumothorax, and wound infection [22]. In a retrospective study, subxiphoid pericardiotomy as compared to open thoracotomy was associated with similar operative mortality; however, open thoracotomy leads to more pulmonary complications including pneumonia, pleural effusion, prolonged ventilation, and reintubation [23].

Other more invasive procedures include thoracotomy and thoracoscopy or VATS to create a pericardial window for drainage of fluid into the plural or peritoneal space. Advantages include diagnostic accuracy and rapid symptomatic improvement. Disadvantages include the need for general anesthesia and the occasional need for prolonged postoperative ventilatory support.

Figure 12.3 outlines a recommended management algorithm for patients with pericardial effusion.

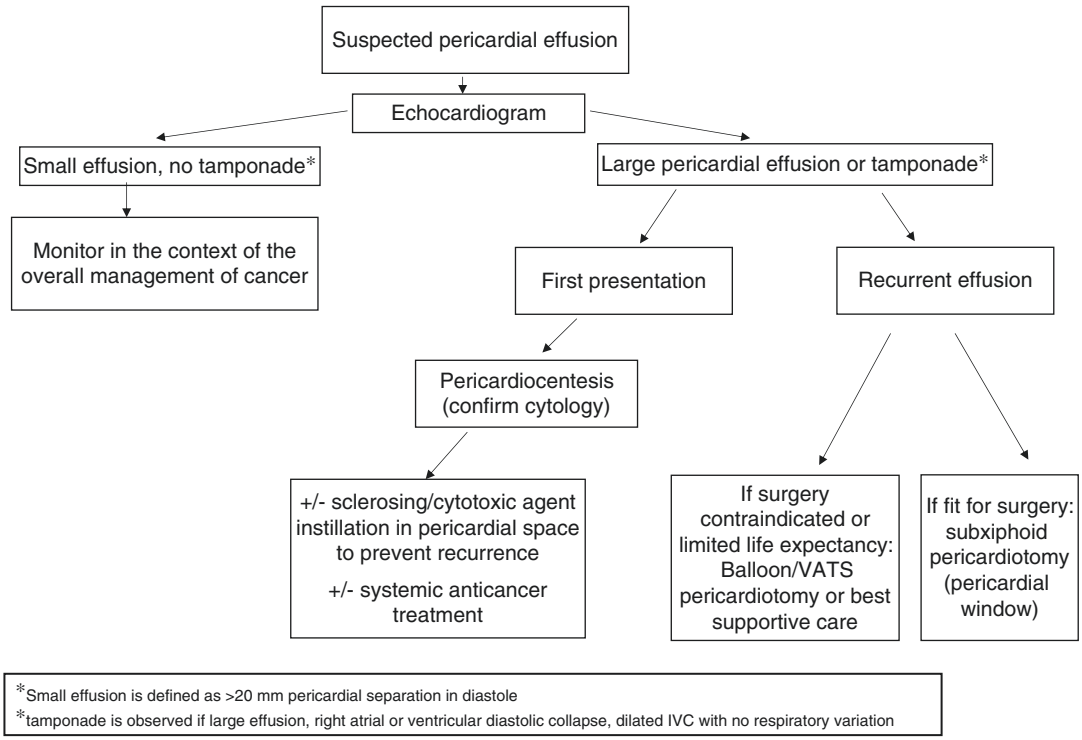


**Fig. 12.3** A management algorithm for pericardial effusion

## Direct Involvement of the Pericardium: Pericarditis

### Epidemiology and Pathophysiology

Acute pericarditis involves inflammation of the pericardial sac that can potentially progress to pericardial effusion, tamponade, and constrictive pericarditis. In a retrospective study, 7% of patients with acute pericarditis were found to have associated malignancy [24]. Constrictive pericarditis can develop due to any pericardial disease and involves scarring and decreased elasticity of the pericardium resulting in the inability of the heart to expand during inspiration. This causes rapid inspiratory filling and ultimately decreased ventricular volumes and stroke volumes and impaired diastolic ventricular filling. The reported incidence of neoplastic constrictive pericarditis is around 3% [25].

### Presentation

Patients with acute pericarditis present with pleuritic chest pain that improves on leaning forward and sitting up. Fever, dyspnea, and other symptoms related to pericardial effusions or tamponade may also develop. Pericardial friction rub if present is quite specific for pericarditis.

Patients with pericardial constriction complain about fatigue, peripheral edema, breathlessness, and abdominal swelling. On examination elevated jugular venous pulse (JVP), Kussmaul's sign (the lack of an inspiratory decline in JVP), pulsus paradoxus (exaggerated drop in systemic blood pressure greater than 10 mmHg during inspiration), cachexia, venous congestion, hepatomegaly, pleural effusions, and ascites may occur.

### Investigations

Typical findings of acute pericarditis on ECG are saddle-shaped ST segment elevation, PR depression, and reciprocal PR segment elevation which can be seen in augmented limb lead (aVR). Echocardiography is usually performed to rule out any development of a pericardial effusion. Echocardiography is also an important diagnostic investigation for constrictive pericarditis and shows impaired diastolic filling and prominent respiratory filling variation of the ventricles and signs of right heart failure. CT, cardiac MR, and cardiac catheterization can be used if echocardiography is nondiagnostic or a more detailed account of the associated abnormalities is required.

### Management

Symptomatic management and management of the primary tumor are used in cases of cancer-related pericarditis. Pericardiectomy is the only definitive treatment option for patients with chronic symptomatic constrictive pericarditis. Diuretics may be used for patients not suitable for surgery for optimizing the symptoms. While the majority of patients have significant symptoms following pericardiectomy, there is a significant perioperative morbidity and mortality. Late mortality rate after pericardiectomy was around 23% in one retrospective study [26].

## Direct Involvement of the Heart: Endocardium and Myocardium

There is considerable overlap between endocardial and myocardial involvement in the discussion of both primary and secondary tumors, and these are thus discussed together.

### Epidemiology and Pathophysiology

Even as a collective entity, primary cardiac tumors of the myocardium or endocardium are uncommon. The published data on incidence relies mainly on autopsy studies and retrospective single-center series. In an aggregation of 22 published series including more than 700,000 autopsies, Reynen estimates this at 0.20% or 200 per 1 million autopsies [27]. The majority of

resected cardiac tumors are benign myxomas, ranging from an incidence of 71–85% in surgical series [28–31]. The majority of primary malignant tumors are sarcomas, the most common subtype being angiosarcomas [29, 32–34]. These often occur in younger patients, progress quickly via myocardial infiltration, and portend a poor prognosis, at 9–12 months without surgical intervention [34]. Primary cardiac lymphoma represents approximately 1–2% of primary cardiac tumors [33].

Secondary malignancies may reach the heart by direct or transvenous extension or via hematogenous or lymphatic spread. The incidence of cardiac metastases at autopsy is higher than might be expected. In one hospital, with an anatomical pathology department with a remarkably high rate of postmortem examinations (>80% of deceased inpatients), 9.1% patients with any malignancy were found to have cardiac metastases [35]. The most common tumors were mesothelioma, melanoma, non-small cell lung cancer, and breast carcinoma, and these findings are in keeping with other series [35, 36]. Unsurprisingly, the likelihood of cardiac metastasis was higher with the overall burden of metastatic disease.

## Presentation

Symptoms caused by cardiac tumors are entirely dependent on location and size; thus, even benign tumors can cause dramatic clinical sequelae. Three quarters of myxomas originate in the left atrium, often hanging from a short pedicle, and can oscillate with blood flow to block the mitral valve. This may manifest as cardiac syncope, paroxysmal pulmonary edema, and even sudden cardiac death [29, 32].

Otherwise, the symptoms of intracardiac malignancy are variable and nonspecific. Chest pain, dyspnea, and presyncope are among the more common complaints. Patients may present with signs of left-sided heart failure, including orthopnea and fatigue, or right-sided heart failure, such as lower limb edema and ascites. A significant number of diagnoses are accompanied by arrhythmia or cardiac conduction defects. Alternatively, they may be detected incidentally on imaging for another indication [33, 36].

## Investigations

Transthoracic echocardiogram is a readily available, noninvasive modality and the most appropriate initial investigation for a suspected cardiac tumor. Large body habitus or comorbid emphysema may affect the study quality. Transesophageal echocardiogram is more invasive but much more sensitive in identifying intracardiac and pericardial disease [37]. MRI is preferred over CT, providing superior images and detailed information which can help differentiate benign versus malignant tumors. Malignant tumors typically have ill-defined borders, a wider base, and a right-sided location, involve more than one chamber, are greater than 5 cm, and may be associated with a pericardial effusion or extension into adjacent structures [38].

## Management

All patients should be treated by a multidisciplinary team involving surgeons, hematology or medical oncology, radiation oncology, and allied health members [29]. Both treatment and outcomes are determined by the histological subtype. Surgical excision is appropriate for benign tumors such as atrial myxoma. Perioperative mortality is acceptable, with rates of 0–2% in more modern series [39–41]. Cardiac sarcoma may be considered for resection if there is no distant disease but will generally recur. Chemotherapy typically involves anthracycline- and ifosfamide-based treatment [34, 42, 43] although due to overall rarity of these tumors, there are no prospective trials to inform the use of chemotherapy, and experience is confined to case reports and series [42, 44]. Cardiac transplant is an option for a very small number of patients [45]. Management of cardiac metastases consists of systemic chemotherapy for the primary malignancy.

## Involvement of Great Vessels: SVC Obstruction

### Epidemiology and Pathophysiology

Malignancy has accounted for the majority of superior vena cava (SVC) obstruction since the decline in infective etiologies such as tuberculosis and syphilis in the 1980s; 30 years ago malignancy had been estimated to cause 90% of all SVC obstruction [46]. Obstruction of the superior vena cava (SVC) can be caused by extrinsic compression or intravascular thrombosis. Extrinsic compression may result from a tumor mass within the lung or compressive mediastinal lymphadenopathy. The increased use of intravascular devices, however, has led to a more recent rise in thrombotic causes, both in a benign and malignant setting. The use of peripherally inserted central catheters (PICC) and central implanted venous ports for the administration of chemotherapy increases the risk of thrombosis and consequent SVC obstruction [46].

### Presentation

SVC obstruction may be asymptomatic or present as an acute emergency depending on the acuity of onset and degree of vena caval narrowing. Typical symptoms include dyspnea, wheeze, facial flushing, or a sensation of "fullness" in the head. Rarer complaints include dysphagia, hoarseness, and chest pain. Symptoms may be precipitated by lying flat or bending over. The most common presenting complaint is dyspnea [47, 48]. Distinct from an asymptomatic or mildly symptomatic obstruction, superior vena cava syndrome can be acute emergency, requiring prompt recognition and treatment. In the most extreme cases, cerebral edema may lead to confusion, headache, and obtundation [46].

Signs are often subtle, unless obstruction is critical. These may include distention of veins across the upper thorax and edema of the face and neck. Facial plethora, cyanosis, or stridor may rarely be seen.

### Investigations

If the diagnosis is suspected, the most appropriate investigation is contrast-enhanced computed tomography (CT) of the chest (see Fig. 12.4). This will confirm the diagnosis, as well as provide information about etiology, extent of obstruction, and the existence of collateral vessels [49]. Magnetic resonance (MR) venography may be used if the patient has an allergy prohibiting the use of iodine-based contrast [50].

SVC obstruction may be the initial presentation of malignancy or develop in a patient with known malignancy. In the case of a new diagnosis, a work-up for a primary site of malignancy, including imaging to assess extent of disease, and biopsy of tissue will be important. The most common primary malignancies in one series of 124 patients were small cell lung cancer (SCLC) (28%), non-small cell lung cancer (NSCLC) (25%), and non-Hodgkin lymphoma (25%) [51].

### Management

There are no randomized trials comparing treatment modalities for SVC obstruction nor are there likely to be. Instead, treatment should be planned

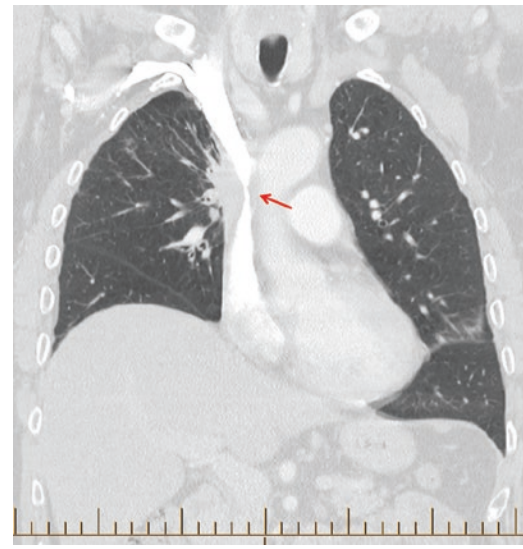

**Fig. 12.4** A CT scan of a patient with SVC obstruction—arrow indicating a level of obstruction

on a case-by-case basis, taking into consideration the patient's physical wellness, comorbidities, contraindications for various interventions, and the urgency of the clinical situation. The most appropriate management needs to take into account the underlying malignancy, patient performance status, and prognosis. General supportive measures, which are frequently advised, are to position the patient's bed with the head elevated to avoid an increase in hydrostatic intravascular pressures; despite a lack of evidence, this seems a logical and low-risk intervention. The use of glucocorticoids is frequently cited but not well evidenced, except in the case of lymphoma or thymoma, where there is reasonable rationale that they may induce a reduction in tumor mass. Despite the absence of supportive data, glucocorticoids when radiotherapy is used seem reasonable to mitigate any tumor swelling caused by radiotherapy. Diuretics have been used with the aim of reducing edema [52, 53].

### Chemotherapy

Chemotherapy can have a role in the management of SVC obstruction, but time to response and sequence of treatment will depend on the severity of symptoms, histological tumor type, and extent of disease elsewhere. Patients with SCLC, lymphoma, or germ cell tumors are likely to be more chemosensitive and further have a greater clinical urgency to achieve systemic disease control. One single-institution case series reports relief of symptoms in 93% of patients treated with chemotherapy (some in combination with concurrent or sequential radiotherapy) and a longer time to recurrence of SVC obstruction symptoms in those who were treated with both modalities [54]. Symptomatic relief could be expected within 1–2 weeks.

Conversely, in less chemosensitive tumor types, time to symptomatic relief is likely to be longer if chemotherapy is used alone and is unlikely to be an appropriate single modality choice for patients with more urgent symptoms. Consideration must also be given to performance status and other contraindications to systemic therapy.

Although many patients will have advanced, incurable disease at diagnosis, consideration should be given to curative treatment in patients with limited or earlier stage malignancies.

### Radiotherapy

Historically, emergency radiotherapy was the treatment of choice for SVC obstruction. Although it has been recognized that other modalities may be equally useful, radiotherapy remains the cornerstone of treatment for many patients. Complete resolution is uncommon; however, partial resolution allows symptomatic improvement in the majority of patients [48, 51]. Radiotherapy can be an attractive choice for patients with a poorer performance status or in whom the risks of endovascular intervention are felt to be prohibitive. Radiotherapy is a reasonably effective and well-tolerated treatment option in this setting. One review reported a 63% resolution of symptoms for patients with NSCLC and 78% for patients with SCLC treated with radiotherapy alone [53]. Dysphagia is the most commonly described adverse effect. Individual case series describe different response times with conventional radiotherapy, varying from 3 to 30 days. It would be reasonable for clinicians to look for an improvement in symptoms within 7–10 days [48]. There are no prospective studies to guide fractionation of radiotherapy. Stereotactic body radiotherapy (SBRT) is a technique of delivering a high radiotherapy dose per fraction with greater precision. Published experience with SBRT in the setting of SVC obstruction is extremely limited; one case report describes encouraging results, with the patient experiencing a resolution of symptoms by the completion of the planned five fractions and experiencing definitive disease control. However, caution is prudent in the setting of limited experience; Stam et al. reported a series of 803 patients treated for NSCLC with SBRT, which noted an association between the dose to right atrium or SVC and non-cancer-related death [55, 56].

### Endovascular Stenting

Interventional radiology techniques have enabled the prompt relief of symptoms via endovascular stenting. First described in 1986, it is a rapid and effective method of symptom relief. Uberoi et al. described a technical and clinical success rate of 99% and 96%, respec-

tively [37]. Recurrence remains however a possibility, with potential dramatic consequences of stent blockage. Stenting also has the greatest potential for procedure-associated morbidity. The same systematic review describes complication rates between 0 and 19% and a mortality of 3–4%. Adverse events include hemorrhage, SVC rupture, cardiac tamponade, and stent migration. Although uncommon, clinicians should be vigilant for early stent thrombosis, which can lead to an acute life-threatening SVC syndrome [57].

### Thrombolysis and Anticoagulation

Endothelial disruption by use of PICCs and central implanted venous ports for chemotherapy delivery increases the risk of central venous thrombosis, including SVC thrombosis. There may also be an element of thrombosis associated with intravascular stasis in the case of extrinsic compression. Rates of central implanted port thrombosis range from 1.3 to 9.3% in available case series [58–60]. The National Comprehensive Cancer Network (NCCN) guidelines recommend anticoagulation for venous thromboembolism broadly but do not make a specific recommendation for SVC thrombosis [61].

Reports have been described of successful thrombolysis where percutaneous options were considered inappropriate, but once again, this is largely observational evidence [53, 62]. Thrombolytic therapy at the time of endovascular stenting increases the risk of complications, particularly hemorrhage, and caution should be used if the two are considered concurrently.

The rationale for anticoagulation post endovascular stenting seems logical, but the need for longer term anticoagulation has not been well delineated, and there is a paucity of evidence to guide practice [53, 63, 64]. One retrospective case series found no difference in recurrence of SVC thrombosis with or without anticoagulation [65]. Some clinicians have described the use of prophylactic low-molecular-weight heparin after stent insertion, instead of therapeutic dosing; however, properly designed prospective trials are required to address this area of uncertainty [66].

## Indirect Effects on the Heart: Pulmonary Hypertension and Cor Pulmonale

Cor pulmonale refers to right-sided heart dysfunction as a consequence of pulmonary hypertension caused by chronic pulmonary disease. Since 2008, the World Health Organization has adopted the Dana Point etiological classification as seen in Table 12.1 [67].

### Epidemiology and Pathophysiology

The causes of cor pulmonale relevant to cancer are mainly associated with parenchymal lung disease or thromboembolic disease, both of which lead to an increase in vascular resistance, causing consequent increased pulmonary vascular pressures. This in turn causes right ventricular remodeling in an attempt to overcome the elevated pulmonary pressures. When the right heart fails to compensate, this manifests as hepatic congestion, ascites, and peripheral edema [68]. Parenchymal lung disease may be preexisting; for example, many patients with a significant smoking history will develop both emphysema and lung cancer. Additionally, systemic therapies used to treat cancer may cause or worsen interstitial lung disease; examples include bleomycin, gemcitabine, and anti-PD1 therapy. Lymphangitis carcinomatosis has been described in association with pulmonary hypertension and is generally a poor prognostic sign [69].

Acute right heart failure in the context of cancer is most commonly caused by pulmonary embolus. Rarely, cases of pulmonary tumor thrombotic microangiopathy causing acute right heart failure have been described [70–72]. It is rapidly progressive and rarely diagnosed antemortem. A clue to diagnosis may be the presence of hemolysis and macroangiopathic changes on blood film [72]. Gastric cancer is the most common primary cancer associated with this condition. It is unclear why this is the case. Tumor microemboli within pulmonary arteriolar vasculature are typically found at

**Table 12.1** Dana Point classification of pulmonary hypertension (PH)

| | |
|---|---|
| Group 1 | Pulmonary arterial hypertension (includes multiple etiologies like heritable, idiopathic, connective tissue disease related, HIV related, and others) |
| Group 2 | PH secondary to left heart dysfunction |
| Group 3 | PH secondary to chronic lung disease or hypoxemia |
| Group 4 | PH secondary to chronic thromboembolic disease |
| Group 5 | Multifactorial/miscellaneous |

autopsy; it is hypothesized that this triggers local activation of the coagulation pathway and intimal proliferation [73]. Patients who had targeted investigations in case reports often have pulmonary hypertension and cor pulmonale, in the absence of visible pulmonary embolus on CT angiography [71, 72]. There is negligible data to guide the management of this rare neoplastic phenomenon.

There is a notably small body of literature on this subject specifically in relation to cancer, and it is likely that this phenomenon is under-recognized in patients with malignancy. The reasons for this include the fact that cor pulmonale often has a gradual, insidious onset, and patients with advanced malignancy often have other, more prominent symptoms; secondly, prognosis may be such that the time taken for the pathophysiological adaptations to occur is longer than the patient's expected lifespan.

### Presentation

The clinical signs of right heart dysfunction are not specific. Patients may report ankle edema or increasing abdominal girth. Clinicians should perform an examination for elevated jugular venous pressure, peripheral edema, and ascites. Precordial examination may reveal a cardiac murmur of tricuspid regurgitation, a loud or palpable second heart sound, and a parasternal lift [74].

### Investigations

Echocardiography is a key diagnostic tool, showing right ventricular hypertrophy or flattening of the interventricular septum. Pulmonary artery systolic pressure can be used as a surrogate measurement but is dependent on accurate interpretation of tricuspid regurgitation and may frequently be over- or underestimated. Right heart catheter measurements remain the gold standard for diagnosing pulmonary hypertension but may not be necessary. A mean pulmonary arterial pressure of 25 mmHg or more at rest is considered diagnostic for pulmonary hypertension [74, 75].

### Management

There are no specific management guidelines for cor pulmonale directly related to malignancy. Treatment for reversible underlying causes should be instituted. There is no strong evidence to suggest that supplemental oxygen changes the natural history but is helpful for symptom palliation. Diuretics have a role in providing relief from right ventricular overload and avoidance of deleteriously high renal perfusion pressures [74, 76].

## Indirect Effects on the Heart from Vasoactive Substances: Carcinoid

### Epidemiology and Pathophysiology

Among patients with carcinoid syndrome, nearly 50% eventually develop carcinoid heart disease. In about 20% of patients, it may be the initial presentation of carcinoid [77, 78]. Carcinoid heart disease (CHD) is caused by formation of fibrous plaques leading to thickening of valvular cusps, endocardium, papillary muscles, and subvalvular apparatus. Vasoactive substances (serotonin, bradykinin, tachykinins, prostaglandins, and histamine) lead to the development of carcinoid heart disease and involve right-sided valves and typically cause retraction and fixation of tricuspid

and pulmonary valves. These changes may cause valve stenosis or regurgitation. Tricuspid regurgitation is most common; however, tricuspid stenosis and pulmonary regurgitation and stenosis are also possible [79–81]. The fibrous deposits may result in a diminished right ventricular function as well. Left-sided heart disease is uncommon. The clinical manifestations of carcinoid heart disease include signs of right-sided heart failure with fatigue dyspnea, edema, ascites, and cardiac cachexia.

## Presentation

Patients with carcinoid syndrome typically present with flushing, secretory diarrhea, abdominal pain, tachycardia, hypotension, and bronchospasm. The diarrhea may range up to 30 stools a day and can lead to electrolyte loss, abdominal cramps, and pain [81]. On physical examination, principal findings are the right-sided murmurs of tricuspid and pulmonary valve regurgitation and/or stenosis, elevated jugular venous pressure, and a palpable right ventricular (RV) impulse. Patients with advanced disease experience development of peripheral edema, ascites, and hepatomegaly owing to right ventricular failure [82].

## Investigations

Elevated urinary 5-hydroxyindole acetic acid (5-HIAA) levels are the hallmark of carcinoid syndrome. In these patients, tryptophan is converted into serotonin which is further metabolized to 5-HIAA and excreted in urine. 5-HIAA can be elevated up to ten times the upper limit of normal in patients with carcinoid heart disease [83]. Therefore, indirect evidence is present to support the role of 5-HIAA in the development of cardiac complications related to carcinoid syndrome. NT-proBNP levels can be used to screen for carcinoid heart disease. In a cross-sectional study, N-terminal pro B-type natriuretic peptide (NT-proBNP) and plasma 5HIAA were found to be both sensitive and specific biomarkers for the presence of carcinoid heart disease and NT-proBNP to some extent correlated with disease severity.

Echocardiography is essential for the diagnosis of carcinoid heart disease. Due to tricuspid valve thickening and retraction, it is usually found to be immobile on echocardiography in moderate to severe valve dysfunction. Tricuspid stenosis, pulmonary valve regurgitation, and stenosis are infrequent. In a series of 74 carcinoid patients with comprehensive echocardiographic data, all patients had tricuspid valve regurgitation, 81% had pulmonary valve regurgitation, 53% had pulmonic stenosis, and 7% had left-sided valve involvement. Four percent of these patients were found to have cardiac metastasis [77]. Metastatic carcinoid tumor to the heart although relatively rare can be detected with echocardiography if tumor size is $\geq$1.0 cm [84]. Cardiac MRI and CT scan can be used to assess valvular pathology, right-sided ventricular function, and size.

## Management

Medical management of carcinoid heart disease is limited in effectiveness. Diuretics can be used for temporary symptom control and reduction of edema; however, risk of decreased cardiac output needs to be considered. Somatostatin analogues, although effective in carcinoid syndrome, have a limited role in preventing and reversing the valvular damage related to carcinoid heart disease. Similarly, everolimus and telotristat (oral tryptophan hydroxylase inhibitor) have no proven role in prevention of carcinoid heart disease at this stage.

Surgical valve replacement is the only effective treatment for valvular dysfunction associated with carcinoid heart disease. Surgery should be offered to patients with symptomatic valve disease (fatigue, dyspnea, edema) and declining right ventricular function. Patients with metastatic disease with controlled systemic disease are candidates for valve replacement [85]. Mechanical valve placement requires lifelong anticoagulation and bioprosthetic valves are prone to degeneration due to vasoactive substances. There is about a

4% yearly risk of thrombosis with tricuspid mechanical valve replacement [86]. Balloon valve valvuloplasty is suitable for patients not candidates for open surgery or patients who had previous bioprosthetic valve replacement.

## Indirect Effects on the Heart from Amyloid Deposition: Cardiac Amyloidosis

### Epidemiology and Pathophysiology

Two forms of amyloidosis may lead to cardiac impairment. Immunoglobulin light chain (AL) amyloidosis can occur as a result of deposition of light chain fragment, which may occur in monoclonal plasma disorders, namely, multiple myeloma, but also non-Hodgkin lymphoma and Waldenström's macroblobulinemia. Lambda light chains are more commonly implicated than kappa light chains. Monoclonal protein is detectable in the blood or urine in more than 95% of these patients [87]. Reactive (AA) amyloidosis occurs in disease processes with chronic ongoing inflammation, including infection, rheumatological disease, inflammatory bowel disease, and malignancy. In this case the insoluble fibrous deposits are acute phase reactant amyloid A, formed by hepatic synthesis in response to interleukins 1 and 6 [88]. The kidneys are the most frequently involved organ, and a diagnosis of cardiac amyloid for this subtype is rare.

### Presentation

The typical presentation of cardiac amyloidosis is that of heart failure with preserved ejection fraction. Deposition of insoluble fibrils in the endocardium causes an infiltrative cardiomyopathy, with decreased compliance and ventricular filling. Cardiac involvement is common in AL amyloid and may be the first presentation of occult malignancy in a small group of patients. Nonspecific symptoms may include fatigue and weight loss. More fulminant heart failure may be evidenced by an elevated jugular venous pressure, pulmonary edema, signs of pulmonary hypertension, and lower limb edema [53]. Postural hypotension due to decreased compliance of the cardiac musculature may be present in 40% of patients [89]. In a prospective observational study of 249 patients, higher New York Heart Association class and brain natriuretic peptide correlate with a worse prognosis [90].

### Investigations

Electrocardiogram may provide a clue to the diagnosis, with low-voltage complexes and a pseudoinfarct pattern [56]. Cardiac conduction defects and atrial fibrillation may also occur. Echocardiogram may reveal a normal appearance of the ventricles but restrictive physiology on Doppler study and a speckled appearance of the myocardium. With more advanced disease biventricular dilatation, ventricular wall thickening and impaired diastolic filling may be seen [87, 88]. Elevated peak longitudinal systolic strain correlates with poorer outcomes. Cardiac magnetic resonance imaging (MRI) is useful, with the characteristic finding of late gadolinium enhancement. The degree of late gadolinium enhancement was strongly associated with New York Heart Association category and brain natriuretic peptide levels, as well as echocardiographic indices [90, 91].

Definitive diagnosis is made by the visualization of positive Congo red staining on endomyocardial biopsy, which gives the characteristic apple-green birefringence on light microscopy [48]. Such an invasive procedure may be inappropriate in many patients with advanced cancer. Conversely, in patients being treated with curative intent, this will be much more pertinent. In other cases, investigation of an infiltrative cardiomyopathy may precede the diagnosis of cancer in a patient with no symptoms of their occult malignancy.

### Management

Medical management includes using heart failure medications, including angiotensin-converting enzyme inhibitors, beta-blockers, and antianginal

agents, but their use may be limited by postural hypotension. The recommendation for these does not come from specific studies in patients with cardiac amyloidosis and, rather, is generalized from the larger body of literature regarding heart failure management. Notably, calcium channel antagonists may be contraindicated [92, 93]. Digoxin is also contraindicated, as the drug binds to amyloid fibrils and may precipitate digitalis toxicity [94]. Arrhythmias are managed by standard therapeutic interventions, but atrial fibrillation is tolerated poorly in these patients with diastolic dysfunction, and maintenance of sinus rhythm is important. In patients with a good prognosis otherwise, implantable cardioverter-defibrillators should be considered.

Treatment of the underlying disease process in the case of AL amyloidosis may improve cardiac function. In a very select group of patients where curative treatment with stem cell transplantation is an option, cardiac transplantation may be considered. It is important to remember that without cure of the underlying hematological malignancy, amyloid deposition is likely to recur in the allograft [88].

## General Approach to the Patient with Cardiac Manifestations of Cancer

Much of the treatment in this chapter is based on low levels of evidence. The conditions discussed are rare, present in a heterogenous population, ranging from young patients with a good performance status to a geriatric population with frailty and significant competing risk factors. Within these limitations, key principles of management remain. These include clarity of treatment goals, focus on good symptom control, and a multidisciplinary approach to care. Regardless of the treatment modality chosen in the management to any given condition related to cancer, the optimal treatment pathway will be the one that is tailored to the patient. Performance status, comorbid conditions, prognosis from a cancer perspective, and patient preference are all imperative factors to consider in this. The same pathological process in one patient with good premorbid performance status and a treatable cancer is appropriate to manage aggressively. Conversely, in a patient with advanced malignancy and limited treatment options, a symptomatic approach to good palliative care may be much more appropriate. A combination of multidisciplinary liaisons in a tertiary center with experience in the treatment of these sometimes rare conditions, along with a patient-centered approach, will ensure that the best outcome for each individual patient is achieved.

Much of the evidence that informs our treatment today is 10–20 years old. As imaging, radiotherapy, and surgical techniques are refined, there is a need for reevaluation of our practices, to ensure that our choice of management evolves with our capabilities. As clinical trials for these conditions may be hard to conduct, there is a need for support of prospective clinical registries that collect clinical data on these rare conditions. International collaborations and evolution of the new field of cardio-oncology may be one avenue for building the body of knowledge to support new practices in this challenging field.

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# Part IV

# Respiratory

# Pulmonary Toxicities of Anticancer Treatment

13

Aaron T. Ciner, Richard J. Gralla, Kostas N. Syrigos, and Sam H. Ahmedzai

## General Introduction: Overview of Pulmonary Complications of Malignancy

Malignancy and its treatments are associated with a host of symptoms and clinical syndromes, of which breathlessness and other pulmonary complications are among the commonest. A study of 923 ambulatory mixed cancer patients found that breathlessness was reported overall by 46% and by over 50% of patients with primary cancers of the breast, genitourinary organs, head and neck, and lung and those with lymphoma [1]. Solid tumors may cause respiratory problems directly by their presence in the lungs or mediastinum as a primary disease, through metastatic spread, or through pleural or pericardial involvement [2, 3]. Lymphomas and leukemia can also affect the lungs and airways directly, or through pleural and mediastinal involvement, such as superior vena cava syndrome [4]. They may also be associated with pulmonary hypertension. Non-cancer conditions which have respiratory consequences include anemia, heart failure, pre-existing chronic lung disease, thrombocytosis, and other prothrombotic mechanisms which lead to pulmonary thromboembolism, as seen in Table 13.1.

It is now recognized that all the modalities of cancer treatment, ranging from antineoplastic drug therapies including the newer biological and immunological therapies to radiation treatment and thoracic surgical procedures to intensive treatment with hematopoietic stem cell transplantation, can cause significant and potentially fatal pulmonary complications. These are summarized in Table 13.1, and the rest of this chapter will explore the mechanisms and manifestations of each of these in detail.

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**Table 13.1** Overview of pulmonary effects of malignancy and anticancer treatments

| Anatomical system | Organ | Malignancy-related changes | Treatment adverse effects[a] | Comorbidity[b] |
|---|---|---|---|---|
| Pulmonary | Airways | Bronchial or tracheal obstruction | Bronchospasm (taxanes, gemcitabine),<br>GVHD | Asthma<br>COPD |
| | Lung parenchyma | Tumor infiltration<br>Atelectasis<br>Infection<br>Lymphangitis | Acute pneumonitis (many drugs, immunotherapy, RT)<br>Cryptogenic organizing pneumonia/ bronchiolitis obliterans (many drugs, immunotherapy, HSCT, GVHD)<br>Chronic pulmonary fibrosis (many drugs, RT)<br>Granulomatous changes (methotrexate, immunotherapy)<br>Interstitial lung disease (TKIs)<br>Hemorrhage (bevacizumab, HSCT)<br>Idiopathic pulmonary syndrome (HSCT)<br>Non-cardiogenic pulmonary edema (mitomycin/vinca, gemcitabine)<br>Pseudo-progression (immunotherapy) | Emphysema<br>Idiopathic pulmonary fibrosis<br>Decreased lung elasticity associated with aging |
| | Pleural/ pericardial | Tumor infiltration<br>Malignant effusion | Pleural effusion (dasatinib)<br>Empyema, pneumothorax (chest drain) | Pericarditis |
| | Chest wall/ diaphragm | Cachexia<br>Mesothelioma<br>Ascites | Thoracotomy | Sarcopenia of aging |
| Cardiovascular | Heart | Pericardial effusion | Drug-related cardiac damage (trastuzumab) | Coronary heart disease<br>Chronic heart failure |
| | Circulatory system | Superior vena cava syndrome | Pulmonary hypertension (lymphoma) | Idiopathic pulmonary hypertension |
| Systemic | Anemia | Anemia of malignancy, bleeding | Myelosuppression | Chronic anemia |
| | VTE | Prothrombotic effects of malignancy | Prothrombotic effect of drugs (thalidomide, lenalidomide), HSCT | VTE following surgery, immobility |

*GVHD* graft versus host disease, *HSCT* hematopoietic stem cell transplantation, *RT* radiation therapy, *TKI* tyrosine kinase inhibitor, *VTE* venous thromboembolism

[a]Examples of treatment-related pulmonary adverse effects described in this chapter

[b]Examples of coexisting comorbidity in cancer patients which can cause similar pulmonary effects

## Pulmonary Toxicity from Antineoplastic Drug Therapies

### Introduction

Pulmonary toxicity is a well-documented complication of several antineoplastic drug therapies. While relatively uncommon, these unintended side effects often alter treatment plans, may impair quality of life, and can be fatal. These detrimental effects can occur despite drug discontinuation, supportive care, and the addition of corticosteroids. The frequency of chemotherapy-induced lung toxicity often ranges from 1% to 10% but can be higher depending on the agent used, pre-existing lung disease, concurrence of radiation therapy, and the patient population. With the increasing use and prominence of targeted therapies, numerous studies demonstrate the capacity of these new drugs to cause

significant pulmonary toxicity as well. The scope of clinical signs and symptoms, radiographic findings, pulmonary function tests (PFTs), and pathology is broad. Alternative causes of lung damage such as infection, cancer progression, and cardiogenic pulmonary edema often coexist and may mimic the clinical abnormalities seen with antineoplastic therapies. These factors make the diagnosis of drug-induced pulmonary toxicity challenging. Clinicians therefore must maintain heightened awareness of this potential problem and focus on its early detection [5, 6].

The presentation of pulmonary toxicity ranges from dry cough and shortness of breath to fulminant respiratory failure. While symptoms and lung damage can appear early, even during the initial cycle of treatment, it is more common for this toxicity to present in a cumulative manner. In some instances, late toxicity can occur, even years after treatment initiation. Chest imaging can reveal diffuse or patchy, unilateral or bilateral, ground-glass opacities or consolidations. Even lung biopsy specimens vary widely from diffuse alveolar damage to bronchiolitis obliterans to pulmonary fibrosis. In light of this, radiographic and pathologic results should be considered diagnostic of drug-induced lung toxicity only if pneumonitis develops shortly after the initiation of treatment, there is lack of an alternative explanation for respiratory symptoms, and the resolution of lesions occurs shortly after corticosteroid treatment and withdrawal of the presumed agent. Appropriate cultures, serology, and bronchoscopy with lavage can be helpful to exclude other causes of pulmonary disease [5–7].

The primary constituents of the alveolus are type I and type II pneumocytes, which serve distinct roles and interact with the surrounding vasculature to facilitate gas exchange. Drug-induced pulmonary toxicity usually results from a breakdown of this functional unit and can stem from several different processes:

(a) Direct damage to the endothelium or pneumocytes
(b) Indirect damage from inflammatory chemokines
(c) Inhibition of important regulators of pulmonary function and normal repair
(d) Disruption of airflow to the alveolus

Often, there are multiple factors at play. Direct and indirect damage to pneumocytes may be mediated by reactive oxygen species, which can lead to apoptotic dysfunction through either the death receptor (FasL) or mitochondrial pathway. Furthermore, many soluble mediators such as epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) play an important role in lung function, angiogenesis, and repair, and their inhibition by chemotherapy or targeted agents may exacerbate parenchymal disease [6–8].

## Conceptual Framework of Drug-Related Pulmonary Toxicity

One approach to classifying drug-induced toxicity is by the mechanism of toxicity. It may be useful to apply such an approach to pulmonary toxicity as well. Table 13.2 illustrates the basic schema and is followed by specific examples.

1. "Off-target"—the toxicity is related to the mechanism of action of the drug but affects a different "target," to that which is the driving pathway of the cancer.

   Examples: Erlotinib and Osimertinib

   Tyrosine kinase inhibitors (TKIs) are a group of anticancer agents which bind to and inhibit the enzyme tyrosine kinase in certain cells. These inhibitory agents can be fairly specific or can affect many different tyrosine kinases. The tyrosine kinase associated with the epidermal growth factor receptor (EGFR) plays an important role in tumorigenesis. With

**Table 13.2** Framework for mechanisms of pulmonary toxicity from antineoplastic drugs

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| 1. Mechanism of action of the agent: "off-target" |
| 2. Antitumor activity of the agent: "on-target" |
| 3. Properties inherent in the agent, including its metabolism or elimination |
| 4. Idiosyncratic reaction of the patient |

first-generation EGFR TKIs, such as erlotinib, the target is the abnormal EGFR receptor, which results from single nucleotide mutations in the EGFR gene (especially in exons 19 and 21). The off-target in this case is the non-mutated wild-type EGFR, as EGFRs are present in many normal cells. Common side effects include rash and diarrhea, and these events may be related to inhibition of the normal receptor, an off-target effect. It appears that the less common pulmonary toxicity of these first-generation TKIs is also an off-target effect. Osimertinib is a new third-generation small-molecule TKI, which appears to be more specific for the standard EGFR target. This drug also targets the product of an additional EGFR genetic mutation (T790 M, in exon 20) often found in patients with resistance to older-generation TKIs. The greater specificity for the desired targets, when compared with the older TKIs (such as erlotinib, gefitinib, and afatinib), appears to lead to less off-target toxicity. Studies to date with osimertinib in patients with advanced non-small cell lung cancer show decreased incidences of rash and diarrhea. It is not yet clear whether this will also lead to less pulmonary toxicity [9].

2. "On-target"—the toxicity is intrinsically linked with the mechanism of action of the drug, and there is no clear way to separate the toxicity from the beneficial effects.

   Example: Bevacizumab

   Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). An influential early phase two trial evaluated its efficacy and toxicity when combined with platinum-based regimens in patients with advanced or recurrent non-small cell lung cancer. Pulmonary hemorrhage occurred in 9% of patients and was seen especially in those with squamous cell histology and with centrally located tumors close to major blood vessels [10]. While alternative explanations exist, it is conceivable that reducing the size of the malignancy led to marked pulmonary hemorrhage. The tumor was "plugging" the wall of the blood vessel, and by successfully attacking the tumor, major hemoptysis resulted.

3. Properties inherent in the agent—the toxicity is related to the pharmacokinetics or pharmacodynamics of a drug, including its mode of absorption, metabolism, or excretion

   Example: Bleomycin

   Interstitial pneumonitis is a well-described complication of bleomycin, a chemotherapeutic agent used to treat lymphomas and germ-cell tumors. This toxicity is dose-related and has increased frequency in patients with renal insufficiency. Furthermore, bleomycin's predilection for causing damage in the lungs is linked to the relative lack of its breakdown enzyme, bleomycin hydrolase, in this organ. Its adverse effects on the lungs appear to be related to its metabolism and elimination [11].

4. Idiosyncratic reaction—the toxicity is an unpredictable reaction without any relation to the mechanism of action or the pharmacodynamic profile of the drug.

   Example: Methotrexate

   The pulmonary toxicity of methotrexate is not dependent on a dose-toxicity relationship. Bronchoalveolar lavage often shows relative lymphocytosis, and noncaseating granulomas are occasionally seen on lung biopsy. These details raise the possibility that the mechanism of toxicity may be a hypersensitivity reaction, unrelated to its antimetabolite activity or metabolism. However, there is no direct evidence proving an immunologic etiology for this toxicity [12, 13].

In the pursuit of a mechanistic understanding of toxicity, two lines of evidence have been employed: experimental and circumstantial. The experimental model involves nonhumans, either mice or cell lines, treated with the drug of interest and subsequently examined either pathologically or through detection of biochemical markers for major mechanistic players. The strength of this approach lies in its ability to specifically and directly assess those cells and chemokines, which play a role in the process of toxicity. The second approach uses circumstantial evidence such as the dose-toxicity relationship, epidemiological data, clinical presentation, and results of lavage and biopsy to conceptualize how the drug might lead to a specific adverse effect.

The practical construct outlined above can be used to assess and potentially minimize toxicity. If the pharmacokinetics play a role, the dose can be reduced, avoided in certain populations with renal or hepatic dysfunction or given via a different route. If the toxicity is an "off-target" effect, the "off-target" mechanism should be elucidated and the pathway avoided by creating a more specific drug. "On-target" side effects are by definition impossible to eliminate without compromising the drug's efficacy, and therefore the pros and cons must be carefully weighed. Considerations of drug dosage and schedule may be important as well.

Many anticancer agents cause pulmonary toxicity, and the number continues to grow especially with the increasing use of multimodality approaches to treat cancer. Table 13.3 below lists many of these chemotherapies and targeted drugs and reflects the scope of this problem [7]. Some of the major agents involved in pulmonary toxicity will be discussed incorporating the approach outlined above.

## Chemotherapeutic Agents

1. Bleomycin

   The incidence of toxicity ranges from 2% to 45%, depending on the diagnostic criteria used. Risk factors include older age, high cumulative dose, renal insufficiency, prior thoracic irradiation, and high fraction of inspired oxygen (especially during surgery). The most common toxicity is interstitial pneumonitis, which presents subacutely with dyspnea and nonproductive cough, usually within 1–6 months of treatment initiation. This can progress to pulmonary fibrosis, an irreversible condition seen with other chemotherapeutic agents as well including carmustine (incidence is dose-dependent and occurs in up to 30% of patients) and cyclophosphamide (incidence is dose-independent, occurs in less than 1% of patients, and is associated with concurrent oxygen therapy). Symptoms, signs, laboratory, and radiographic findings as well as pathology are often non-specific with bleomycin-induced pneumonitis. PFTs are frequently obtained prior to bleomycin treatment, but there is great variability in practice. Treatment includes permanently stopping the drug and consideration of steroids. The mortality of bleomycin-induced pneumonitis is 3% [5, 6, 11, 14, 15].

   The risk factors listed earlier are based on epidemiologic studies and highlight the role of pharmacokinetics in bleomycin-induced pneumonitis. Experimental evidence points to oxygen radicals as key players in both its antitumor activity and toxicity [11, 14]. This may indicate an "on-target" effect, although it remains possible that the pathway leading to interstitial pneumonitis is an off-target effect. While much is still unknown, these advances have led to important interventions including minimizing the dose, avoiding the drug in those with chronic kidney disease, and reducing supplemental oxygen as much as possible.

2. Mitomycin

   Mitomycin is known to cause interstitial pneumonitis in 1–10% of patients. It has a similar presentation to bleomycin described earlier and includes the insidious onset of shortness of breath and dry cough. Radiologic imaging ranges from a normal chest x-ray to extensive bilateral interstitial infiltrates. It is

**Table 13.3** Classes and specific antineoplastic agents causing pulmonary toxicity

| Older and classical chemotherapy agents | Newer chemotherapy agents | "Targeted" therapies | Immune checkpoint inhibitors |
|---|---|---|---|
| Bleomycin | Gemcitabine | Gefitinib | Nivolumab |
| Mitomycin | Etoposide | Erlotinib | Pembrolizumab |
| Busulfan | Thalidomide | Temsirolimus | Atezolizumab |
| Carmustine | Oxaliplatin | Bevacizumab | |
| Methotrexate | Docetaxel | Rituximab | |
| Cyclophosphamide | Paclitaxel | Trastuzumab | |

important to maintain a high index of suspicion for mitomycin-induced pneumonitis and exclude other etiologies of pulmonary toxicity. Treatment consists of drug discontinuation and steroids [16–18].

There is also a different pulmonary toxicity syndrome, which is described only with the combination of mitomycin and a vinca alkaloid. This distinct syndrome is characterized by the onset of acute dyspnea, generally within an hour or two of the administration of either agent. This usually occurs after three cycles of mitomycin and always on the day of vinca alkaloid administration. Radiographs show bilateral opacities in over 50% of cases, but most patients have significant improvement within 24 hours. One series of over 300 patients revealed an incidence of 4%. Additional risk factors are unknown, and treatment is supportive [19, 20].

Evidence for an underlying mechanism of this distinct syndrome is circumstantial. Its acute presentation with exclusive dyspnea and rapid improvement may indicate a transient bronchospasm. However, the abnormal radiographs seen in the majority of cases point in a different direction, possibly non-cardiogenic pulmonary edema. At this point in time, more data is needed to determine whether this pathologic process is in fact "on-target," "off-target," or idiosyncratic or whether the pharmacokinetic and pharmacodynamic features of the two drugs play a role.

3. Busulfan

This alkylating agent is now typically prescribed as part of a preparative regimen prior to hematopoietic stem cell transplantation. The incidence of pneumonitis ranges from 1% to 10% and usually occurs within the first year post-transplant. Clinical symptoms include cough and progressive limitation in exercise tolerance. Its implication in lung disease is complicated by use of additional chemotherapeutic agents or total body irradiation pre-transplant, graft-versus-host disease, and cytomegalovirus pneumonitis. PFTs generally show restrictive defects and decreased diffusion capacity. Busulfan can also precipitate an obstructive pattern of lung injury termed bronchiolitis obliterans [23]. Treatment for busulfan-induced pneumonitis is supportive and may include steroids depending upon severity and histopathology.

Lung pathology often reveals degeneration of type I pneumocytes and atypical hyperplastic type II pneumocytes. While this may point to direct epithelial toxicity from this drug, there is no experimental evidence to point toward a specific mechanism. Radiation and use of other alkylating agents may enhance the pulmonary side effects. Further studies evaluating risk factors and key pathophysiologic players are needed [6, 7, 21, 22, 24].

4. Methotrexate

The risk of parenchymal lung disease with this drug is 2–8%. Symptoms usually occur days or weeks after therapy initiation but onset is variable. The clinical presentation consists of progressive shortness of breath, dry cough, pleuritic chest pain, and often fever. Additional investigations can help rule out alternative causes of respiratory decompensation. Most patients recover completely after drug cessation and supportive measures including steroids [6, 7, 12].

As noted earlier, there is circumstantial evidence for a hypersensitivity pneumonitis. If the lung toxicity is truly an idiosyncratic reaction, creating a more specific drug or reducing the dose will have no impact on reducing this adverse event.

5. Taxanes

Docetaxel and paclitaxel are known to cause a type I hypersensitivity reaction, which includes post-infusion onset of bronchospasm, rash, fever, and hypotension. This effect may largely be due to the agents in which the taxanes are mixed to make an intravenous preparation. Paclitaxel is dissolved in polyoxyl castor oil along with anhydrous citric acid and dehydrated alcohol, while the solvent for docetaxel is anhydrous citric acid with polysorbate and dehydrated alcohol. The toxicity can be fatal, especially with paclitaxel. This hypersensitivity reaction appears to be reduced by the prophylactic use of antihista-

mines and corticosteroids. Parenchymal lung damage with these agents is rare [6, 7, 25, 26].

6. Gemcitabine

   Transient dyspnea, most likely due to acute bronchospasm, is reported in 8–10% of patients within hours of administration. The more serious toxicity, consisting of bilateral interstitial infiltrates from non-cardiogenic pulmonary edema, is seen in 1–5% of those treated with this drug. Management consists of supplemental oxygen, steroids, and potentially diuretics [2, 3, 27–29].

   Gemcitabine is thought to cause pulmonary edema by damaging endothelial cells in the pulmonary vasculature. Multiple lines of circumstantial evidence support this approach:

   (a) Alveolar edema is often detected on biopsy.
   (b) The drug commonly causes lower extremity edema leading to the conclusion that it creates a leaky endothelium in multiple areas of the body.
   (c) It is structurally similar to Ara-C, which is widely believed to be able to cause non-cardiogenic pulmonary edema [27–29].

   Again more research is needed to better understand risk factors for this particular toxicity and its mechanistic underpinnings.

7. Thalidomide

   This drug is given as monotherapy and as part of combination regimens in multiple myeloma. When prescribed with dexamethasone or chemotherapeutic agents such as anthracyclines, there is an increased risk of venous thromboembolism (VTE). This usually occurs within 2 months of therapy initiation with an incidence of 5–43%. Factors such as immobility, surgery, and other known precipitants of VTE increase the risk of this toxicity.

   Thalidomide modulates the expression of several pro-inflammatory and proliferative cytokines. The exact mechanism of action is likely multifactorial, and its relationship to the mechanism of toxicity is unclear. Given its efficacy and known risks, antiplatelet or anticoagulation agents are often prescribed alongside thalidomide. Studies are conflicting about the best method of thromboprophylaxis for those with an increased risk of VTE [7, 30, 31].

## Targeted Therapies

1. Trastuzumab

   This monoclonal antibody, which targets the HER-2 receptor, can lead to pneumonitis in less than 1% of patients. Onset is variable but may occur after only one dose and clinically presents as acute respiratory failure with progressive pulmonary infiltrates. Steroids may be useful in severe cases [5, 32].

   The mechanism may be related to inhibition of EGFR signaling or may reflect an alternative mechanism, but more circumstantial and experimental evidence is needed. Of course the well-known cardiotoxicity of this agent can lead in some patients to progressive breathlessness and fatigue owing to heart failure.

2. Dasatinib

   Dasatinib is a TKI, which inhibits the product of the BCR-ABL1 fusion gene. It has efficacy as first- or second-line treatment in chronic myelogenous leukemia, and the main pulmonary side effect is pleural effusion. Risk factors include higher dose and patient age as well as pre-existing cardiac and pulmonary disease. The incidence of any grade pleural effusion is between 10% and 40%, while the incidence of grade three or four pleural effusion is 1–20% (with symptoms including shortness of breath, cough, and chest tightness). Treatment may include dose reduction, drug discontinuation, diuretics, steroids, or invasive procedures such as therapeutic thoracentesis depending on severity.

   One suggested mechanism of toxicity is an off-target effect due to secondary inhibition of platelet-derived growth factor receptor (PDGF-R). Experimental evidence suggests this pathway is involved in angiogenesis and vascular stability, and therefore blocking this receptor may lead to extravasation of fluid into the pleural space. Relative differences in

PDGF-R inhibition might explain the lower incidence of pleural effusion with imatinib [33–35].

3. Rituximab

   This anti-CD20 monoclonal antibody is associated with pneumonitis in less than 1% of patients. Presentation may include progressive dyspnea with ground-glass opacities on chest imaging and decreased diffusion capacity and restrictive defects on PFTs. Treatment generally includes drug discontinuation and steroids. The mechanism of toxicity is unknown but may involve an off-target release of inflammatory cytokines such as TNF-alpha [36–38].

4. Temsirolimus

   While there is a lack of a large pool of data, this mechanistic target of rapamycin (mTOR) inhibitor is implicated in pneumonitis. Most phase two studies reveal an incidence of 1–5%. In one series of 22 patients, 36% developed pulmonary abnormalities. Symptoms, radiographic findings, and PFTs are non-specific. Based on circumstantial evidence with sirolimus, its parent drug, a delayed-type hypersensitivity reaction may be responsible for this temsirolimus-induced pneumonitis [7, 39].

5. Erlotinib and Gefitinib

   Interstitial lung disease (ILD) with EGFR TKIs was first emphasized in Japanese trials with an incidence of 1–5%. Subsequent studies have identified certain risk factors including male sex, smoking history, pre-existing lung disease, and possibly Asian ethnicity. ILD usually develops within 3–7 weeks of treatment initiation. Symptoms include dyspnea and cough, and diffuse ground-glass opacities are often seen on imaging. There have been no studies on the dose-toxicity relationship. Treatment is supportive and includes supplemental oxygen and steroids. The ILD is a very serious toxicity, with a fatal outcome in approximately one third of cases [40–42].

   Experimental studies indicate the potential role of inflammatory mediators including IL-6 in the pathogenesis of EGFR TKI-induced pulmonary toxicity. One study revealed increased mRNA and protein expression of IL-6, when lung cancer cells were treated with EGFR TKI or an EGFR monoclonal antibody. If these results are precise and valid in vivo, they may point to an "on-target" effect of TKIs and ILD. Another experiment using a mouse model suggests this toxicity may be an off-target effect by inhibiting wild-type EGFR on type II pneumocytes, thereby impairing normal repair mechanisms. This may explain the increased risk for patients with pre-existing lung disease [43, 44].

6. Anti-CTLA-4, Anti-PD-1, and Anti-PD-L1

   Immune checkpoint inhibitors are increasingly affecting therapeutic approaches in a variety of malignancies, including advanced melanoma, non-small cell lung cancer (NSCLC), and Hodgkin's lymphoma. However, through their mechanism of action, these agents can also activate the immune system against healthy tissues and have caused a new class of toxicities termed "immune-related adverse events" (irAEs). One of the most concerning irAEs is pneumonitis, a potentially life-threatening complication, which often requires drug discontinuation and treatment with steroids.

   The programmed-death-1 (PD-1) antibodies pembrolizumab and nivolumab are among the most frequently used checkpoint inhibitors. Several prospective studies including phase two and three trials show a 3–5% risk of pneumonitis, with a 1–3% risk of grade three or higher pulmonary toxicity. The risk appears greater for patients with NSCLC (according to one meta-analysis) than in melanoma and for those receiving treatment with two immune-modulating agents (anti-PD-1 and ipilimumab) than with a PD-1 antibody alone. Like the chemotherapeutic drugs and TKIs associated with lung toxicity, the clinical and radiographic presentation of immune-related pneumonitis varies considerably. Onset is seen from less than 2 weeks to greater than 6 months after treatment initiation. Longer-term follow-up with these anti-PD-1 agents is needed to better clarify the time of greatest risk. In one retrospective analysis, cryptogenic organizing pneumonia was the most common radiographic abnormality [45–50].

Ipilimumab is also an immune-modulating agent which works through an alternate pathway, targeting CTLA-4 protein on cytotoxic T lymphocytes. When used alone, pulmonary toxicity is rare. The initial clinical presentation may include dyspnea and dry cough. Bronchoalveolar lavage may show lymphocytic alveolitis, and histopathology can demonstrate organizing pneumonia. In multiple case reports, there was rapid improvement with drug discontinuation and steroid treatment [51, 52].

Interestingly, CTLA-4 and PD-1 antibodies can also infrequently lead to the development of sarcoid-like granulomatous reactions in thoracic lymph nodes, lung parenchyma, and skin. This may manifest clinically with dyspnea and cough and new skin nodules. Radiographs can show enlarged mediastinal and hilar lymph nodes and new pulmonary lesions, and biopsy reveals epithelioid and giant cell granulomas. It is important to consider this unusual toxicity in patients on immunomodulatory agents, when new symptoms and lesions develop, which may mimic cancer progression [52–55].

When treating patients with immune checkpoint inhibitors, it is important to be aware of a phenomenon termed "pseudo-progression." This refers to radiographic progression (often manifested by the appearance of new lesions) without actual disease progression. Anecdotally, this may occur more often in patients with melanoma than in those with lung cancer. Some speculate that this phenomenon is due to immunologic anticancer effects, which produce inflammatory reactions in pulmonary tumor sites. It may be that certain metastatic lesions were too small to be detected prior to therapy, but the inflammatory response at these sites leads to new radiographic abnormalities. The challenge for the oncologist is in differentiating between pseudo-progression and true progression [56].

The pneumonitis seen with checkpoint inhibitors may be due to an autoimmune mechanism stemming from over-activated T cells targeting healthy pneumocytes. This seems even more likely given the additional toxicity of sarcoid-like granulomatous reactions with these drugs. Interestingly, early studies with anti-PD-L1 agents suggest—but do not establish—a lower incidence of overall and grade three or higher pneumonitis compared to anti-PD-1 drugs. This potential discrepancy may be partly due to PD-1 antibodies affecting both PD-L1 and PD-L2 as targets. This is in contrast to anti-PD-L1, which may not affect PD-L2. Preliminary research indicates that PDL-2 is present in healthy lung tissue and plays a role in immune tolerance. This raises the question of whether this toxicity could be an off-target effect [57–60].

## Principles of Diagnosis and Management

Clinicians should be aware of the spectrum of drug-induced pulmonary toxicity. Maintaining a high index of suspicion is necessary in order to combat this complex problem. Although the clinical presentation of pulmonary toxicity is nonspecific, there often are typical time patterns, symptoms, and radiographic abnormalities. Certain anticancer agents pose an increased risk, and specific patient populations are more susceptible to toxicity than others. Increased awareness is warranted in these circumstances, as well as dose reduction, avoidance of supplemental oxygen, or pretreatment with steroids depending on the particular scenario. It is important to note that changes in imaging studies may be the initial signs of toxicity. However, if the only findings are radiographic, the phenomenon described above of pseudo-progression must be considered especially in patients receiving immune checkpoint inhibitors.

Drug-induced pulmonary toxicity is usually a diagnosis of exclusion. Infection, cancer progression, cardiac disease, anemia, pulmonary emboli, and obstructive airway disease, among other etiologies, must be ruled out. Clearly, the therapeutic approach will differ greatly for these varied causes of respiratory distress. It is also true that multiple problems may coexist and exacerbate

each other, such as COPD and EGFR TKI-induced ILD. Smaller degrees of pulmonary toxicity from anticancer agents may become symptomatic more rapidly if the patient has poor pulmonary reserve from pre-existing lung disease or has had prior thoracic surgery or radiation therapy.

Treatment of drug-induced pulmonary toxicity or radiation toxicity relies on rigorous supportive pulmonary care, drug discontinuation, and often steroids. While discontinuation of antineoplastic therapy is always recommended in severe cases of toxicity, in circumstances of mild toxicity, a careful assessment of the risks and benefits involved in this step is necessary. A multidisciplinary approach involving pulmonary consultation can be instrumental in providing optimal care. Neither the dose, type, route, nor duration of therapeutic steroids is clearly established. Typically, high doses of steroids (1 mg/kg per day) are initially used with a slow and cautious taper. If reintroducing the anticancer agent, which caused the pulmonary toxicity, is attempted, it must be done with extreme care [6].

## Conclusion

Several general principles for the management of antineoplastic pulmonary toxicities emerge from this review and are outlined in Table 13.4 below.

With the expanding repertoire of antineoplastic therapies and the increasing use of multimodality approaches to treat cancer, the list of drugs associated with pulmonary toxicity will continue to grow. These adverse effects often require treatment discontinuation and can lead to significant morbidity and mortality. A framework is presented here to conceptualize toxicity with a focus on the underlying mechanism. Subsequently, the epidemiology, clinical presentation, and management of several pulmonary toxicities associated with chemotherapies and targeted agents are described, with a focus on the above framework. With a better mechanistic understanding of toxicity and its relation to the mechanism of action of a particular drug, it may be easier to predict, avoid, and treat the iatrogenic damage, which arises from our best efforts to care for patients with cancer.

**Table 13.4** General principles of managing pulmonary toxicity associated with anticancer treatment

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| Symptoms and signs of pulmonary toxicity are often non-specific |
| Maintain high index of suspicion for drug-induced toxicity |
| Identify patients at greatest risk (i.e., pre-existing lung disease, renal insufficiency) |
| More targeted therapy can reduce toxicity as well as improve efficacy (i.e., osimertinib) |
| Use caution with supplemental oxygen, especially with certain anticancer agents |
| Treatment must be individualized but generally includes drug discontinuation and steroids (depending on the clinical status) |

## Pulmonary Toxicity from Radiation Treatment

It has long been recognized that radiation therapy (RT) can be associated with both early and late pulmonary toxicities, whose pathological and molecular mechanisms have recently become elucidated. Radiation-induced lung injury (RILI) is a major dose-limiting complication that arises in 7–37% of patients having radiation treatment for lung cancer [61, 62].

Radiation causes lung damage through multiple pathways. The acute phase which occurs 1–3 months after RT is associated with the production of reactive oxygen species and activates inflammatory cascades, which damage primarily type II pneumocytes and endothelial cells, leading to the radiological and clinical picture of acute pneumonitis [62, 63]. Recent studies have shown that this stage consists of separate phases: an immediate, clinically silent phase (lasting hours to days) with a leukocytic inflammatory response, resulting in intra-alveolar edema and vascular congestion; a latent phase (days to weeks) characterized by the accumulation of thick secretions because of an increase in goblet cells and ciliary malfunction; and an acute exudative phase (weeks to months) consisting of hyaline membrane formation, type II pneumo-

cyte proliferation, epithelial and endothelial sloughing, and the clinical features of pneumonitis (breathlessness and cough). Several molecular markers of these changes, involving pro-fibrotic cytokines, have been observed of which TGF-β is the best predictor of RT damage [63, 64].

Subsequently, the initial pathologic processes can ultimately lead, over 6–24 months, to abnormal repair and progressive fibrosis mediated by fibroblasts depositing collagen, which occupies alveolar spaces and reduces effective lung volume. The end result is pulmonary radiation fibrosis.

The volume of irradiated lung and the total dose of radiation are important risk factors in the development of pulmonary toxicity. The earliest clinical signs of this disease usually occur 2–3 months after the completion of therapy and include shortness of breath and cough. This early stage, termed radiation pneumonitis, may progress to symptomatic pulmonary fibrosis. One of the radiographic hallmarks of radiation-induced pulmonary toxicity is that the abnormal changes are limited to the borders of the radiation field. Treatment of early radiation pneumonitis includes steroids with a slow taper. Rapid steroid tapering can exacerbate symptoms or lead to new bouts of radiation pneumonitis. Steroids have no role in the treatment of radiation-induced pulmonary fibrosis [7, 64].

## Pulmonary Complications After Thoracic Surgery

The best curative treatment for primary intrathoracic solid tumors such as non-small cell lung cancer and esophageal cancer is complete surgical excision, which has traditionally been conducted by open thoracotomy. This procedure is highly invasive and leads to many pulmonary and cardiac complications that can cause delayed recovery, admission to intensive care, and a small but significant rate of mortality. It is beyond the scope of this chapter to review all the pulmonary complications that may arise with surgery. It will focus instead on recent advances to reduce pulmonary complications in the surgical management of esophageal cancer.

Curative esophagectomy normally involves both thoracic and abdominal incisions. Open thoracic surgery is associated with postoperative respiratory infections, but the use of thoracoscopic techniques can reduce these infectious complications. An international multicenter trial comparing open esophagectomy with minimally invasive esophagectomy (MIE) showed that postoperative infections were significantly reduced in the MIE arm (37% versus 13%, $p = 0.004$) [64]. Moreover, MIE patients experienced less pain and had a shorter hospital stay. An additional benefit was reduction in the development of recurrent laryngeal nerve palsy. The incidence of ICU admission was not different. Overall, a higher risk of postoperative infection was seen in patients who had open esophagectomy and in those with a higher BMI.

A Japanese trial has gone further and examined the role of replacing the abdominal incision with laparoscopic gastric mobilization [65]. Again the use of thoracoscope compared to open thoracotomy resulted in fewer postoperative pulmonary complications (15.8% versus 30.3%, $p = 0.015$); however the gastroscopic intervention in place of abdominal incision gave only minimal additional protection.

Another thoracic surgical intervention employed in patients with lung cancer or mesothelioma is drainage of a malignant pleural effusion (MPE) with pleurodesis. MPE is a late complication and carries a median survival of 4 months [65]. In order to reduce the invasiveness and associated complications of surgically inserted drains and pleurodesis, the use of tunneled indwelling pleural catheters (TIPC) has grown. This procedure allows the patient to return home for drainage without returning to the hospital. A review of 19 studies (all but one case series) including 1370 patients showed that the use of TIPC was without pulmonary complications in 87.5% of cases, with 95.6% reporting symptomatic improvement. The complications that did occur were empyema (2.8%), pneumothorax (9.8%), cellulitis (3.4%), and blockage (3.7%) [65].

## Pulmonary Complications of Hematopoietic Stem Cell Transplantation

An aspect of cancer that has advanced significantly in recent years is hematopoietic stem cell transplantation (HSCT). This has significantly extended the survival of patients with hematologic malignancies including multiple myeloma (MM) and lymphoma. Many patients with MM now also benefit from a second transplant. However, HSCT is accompanied by many acute toxicities, affecting the mucosae, gastrointestinal tract, and lungs. Lower respiratory tract infections from bacterial, viral, and fungal causes are largely kept in check with prophylactic antimicrobials and frequent blood cultures to look for new and resistant organisms.

Noninfectious pulmonary toxicities include idiopathic pulmonary syndrome (IPS) which can occur in 5.7% of pediatric and adult patients after autologous HSCT or in 8% after allogeneic HSCT [66]. It is characterized by widespread alveolar damage in the absence of lower respiratory tract infection and after exclusion of other pulmonary, cardiac, and renal problems or iatrogenic fluid overload. From experimental models, it is thought the mechanisms involve cytokine/chemokine signal transduction cascades, including tumor necrosis factor (TNF-alpha), interferon (IFN-gamma), and lipopolysaccharide (LPS). Even with high-dose systemic corticosteroids and maximal supportive care, mortality can be extremely high (reported series show rates of 15–87%). Agents such as etanercept have been tried but the evidence for benefit is inconclusive.

Phenotypic variants of IPS during and after the transplant procedure include peri-engraftment respiratory distress syndrome (capillary leak syndrome), diffuse alveolar hemorrhage, delayed pulmonary toxicity syndrome (only seen after autologous HSCT), and cryptogenic organizing pneumonia (previously called bronchiolitis obliterans organizing pneumonia or BOOP). Other causes for acute and chronic respiratory problems include toxicities from the drugs used for conditioning (such as carmustine). Venous thromboembolism is recognized as a late event, occurring from 60 days post-transplant onwards and has an overall incidence of 4.6% in the first 180 days [66, 67]. Graft-versus-host disease (GVHD) is a well-recognized complication occurring after allogeneic transplants in up to 66% of patients, and affecting many organ systems including the lungs [68, 69]. The mechanisms of pulmonary GVHD include cryptogenic organizing pneumonia and a range of interstitial lung diseases, often in the context of widespread extrathoracic manifestations [69].

As a consequence of these multiple toxicities arising in HSCT, it is not surprising that a cohort study of MM survivors (median time from diagnosis of 6 years and median of 5 years since first HSCT) revealed a heavy load of multi-system morbidities. In spite of "normal" respiratory histories and physical examinations, 45% had abnormal spirometry results with a range of obstructive, restrictive, and mixed pictures [70]. Maximum inspiratory pressure was subnormal in 33% and maximum expiratory pressure was subnormal in 26%.

### Conclusions

This review shows that although in general patients are living longer with a diagnosis of malignancy, and morbidity rates for most treatments have continued to improve, there is still a significant burden of pulmonary toxicities for all types of anticancer treatment. Whether it is antineoplastic drug treatment, radiation therapy, surgery and other interventional procedures or the highly intensive scenario of HSCT, the oncologist needs to be constantly looking out for acute and more insidious forms of respiratory compromise. To date, the options for active management are limited in most cases to corticosteroid therapy and full supportive care including escalation to an intensive care unit. A significant proportion of patients still die from pulmonary toxicities. As these patients are highly symptomatic from breathlessness, cough, and sometimes hemoptysis, it is essential for supportive and palliative care specialists to work alongside oncologists to give patients the best combination of survival and quality of life.

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# 14 Management of Respiratory Symptoms in People with Cancer

David Currow and Magnus Ekström

## Breathlessness

### Definitions

Breathlessness, the subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity (severity) [1], is mediated by complex somato-psychic interactions at several levels of the peripheral and central nervous system [2]. Like many symptoms, chronic breathlessness [3] is a constant reminder of the underlying pathology, and its effects on the person, intensity and the affective component of degree of unpleasantness may vary independently. The underlying pathological causes of the sensation of breathlessness are usually multifactorial with superimposed psychological aspects to the subjective sensation. The ever-present sense of impending doom heightens anxiety as a person struggles to breathe [4].

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At its most primal level, severe breathlessness is perceived as a direct and constant threat to a person's very existence. Fears about breathlessness are at the forefront of people's minds as cancer is diagnosed and as the disease progresses, especially when primary or secondary lung lesions are identified. Such fears are well founded, not because people suffocate in this setting but because increasing breathlessness has been identified as an independent risk factor for mortality in people with advanced cancer [5, 6].

In one study, the relative risk of death was more than double that of the rest of the population (hazard ratio 2.04; 95% confidence interval [CI], 1.26–3.31; $p < 0.01$) [5]; another study links poorer performance status and higher physical symptom scores with poorer survival [6]. Breathlessness is also associated with increased risk of sudden death in patients undergoing palliative care [7].

The correlation is poor between breathlessness with the level of hypoxemia ($P_aO_2$) and common measures of respiratory function such as the forced expired volume in 1 second ($FEV_1$). Breathlessness reflects an ongoing dynamic imbalance between the need to breathe and the ventilatory capacity and is closely related to the level of ventilatory drive ("need to breathe") during exertion [1]. The association between the ventilatory capacity, level of ventilatory drive and exertional breathlessness seems to be similar both in healthy people and patients with airway



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obstruction and restrictive lung disease (such as interstitial lung disease or space-occupying lesions) [8]. Breathlessness in the daily life of cancer patients is also influenced by psychological factors such as anxiety, depression and the presence of concurrent pain and other troublesome symptoms [7, 9].

## Incidence, Prevalence and Trajectory of Breathlessness

In a sample of the general population ($n = 8396$), 9% of people are troubled by substantial breathlessness on a daily basis [10]. Superimpose cancer on this baseline community prevalence of breathlessness, together with worsening control of comorbid illnesses, and both the incidence and intensity of breathlessness increase markedly. The National Hospice Study in the USA estimated that more than 50% of people with advanced cancer have substantial breathlessness [11], which is in keeping with large studies of people with cancer [7, 12, 13]. In a consecutive cohort of more than 5000 people referred to a regional palliative care service with routinely collected data at every clinical encounter, the number of people with some report of breathlessness increased from 35% 3 months before death to 50% at the last clinical encounter before death [14], closely reflecting other longitudinal data [12, 15, 16]. During the same time period, there was an increase in severe breathlessness (≥7 on a 0–10 numerical rating scale) from 10 to 26% of the people in the cohort despite continued access to a specialised palliative care service and symptom control measures.

In people with cancer, the estimates of the number of people troubled by the symptom vary widely. These varying estimates are likely to reflect the different points in the trajectory of functional decline when breathlessness is measured, and differing underlying cancers and comorbidities. Not surprisingly, primary lung cancer and lung metastases are the cancer manifestations most frequently associated with breathlessness [7, 17].

Even in the setting where it is expected that a person can be cured of their cancer, breathlessness can still be a substantial problem. Breathlessness is likely to pre-exist for many people given the associations between tobacco smoke, chronic obstructive pulmonary disease (COPD), ischaemic heart disease and lung cancer. The treatment of primary lung cancer with surgery or radiotherapy will diminish vital capacity and often translate to long-term breathlessness on exertion, or even at rest, as a result.

In a person with progressive cancer, unlike most other symptoms (with the exception of fatigue), breathlessness often worsens as functional status declines and death approaches despite efforts to optimise symptom control [12, 18]. For the majority of people in this situation, reversible causes of breathlessness will not be found, although they should be sought in the overall clinical context of the person. In addition to fatigue, worsening cachexia may be associated with worsening breathlessness. Other neuromuscular factors that may contribute to the sensation of breathlessness include phrenic or recurrent laryngeal nerve (RLN) palsies. Physical restriction of breathing effort can occur with lung entrapment (as seen with mesothelioma or following an empyema) or malignant infiltration of the chest wall (carcinoma *en cuirasse*).

Factors contributing to breathlessness that require complex investigations and burdensome interventions or have a marked lag time between starting definitive therapy and gaining symptomatic benefit will become less relevant the closer a person is to death. Not only will reversible causes not be found for many people near the end of life, but also a cardiorespiratory pathology will not be evident either [19].

## Defining the Goals of Care

There is a need to generate a careful balance between disease-modifying therapy for primary or metastatic cancers and the need to palliate symptoms. Whether the aim of therapy is to cure, prolong life or palliate, breathlessness needs to be treated symptomatically in parallel with inves-

tigating and commencing other therapies. Symptom reduction and optimising function (physical, social and emotional) are key goals of supportive care. Patients will be the only judge of whether their breathlessness is being adequately managed, while their clinicians have the role to evaluate carefully the likely benefits and harms of any interventions, the time until the onset of any net benefit and the likely duration of any symptomatic benefit. Clinicians must have a level of honesty in having these discussions so that people can make an informed decision.

## Assessment

### Reversible Causes

As with any symptom, the best treatment is to reverse the underlying cause(s) whenever possible. Although direct causes of worsening breathlessness can be identified, this is in the minority of patients. Causes directly linked with the cancer itself include pleural effusion, large and intermediate airway obstruction and lung volume loss due to surgery, radiotherapy or permanent occlusion of proximal airways or worsening tumour burden especially in the setting of multiple pulmonary metastases including *lymphangitis carcinomatosis*. Anaemia, whether as a result of systemic therapy, chronic disease or other causes, should always be explored as a potentially reversible cause. Mild anaemia is unlikely to account for significant breathlessness, and any treatment of anaemia should be followed by careful monitoring to establish whether a transfusion actually improved the patient's breathlessness [20].

Intermittent exacerbations of COPD, asthma, ischaemic heart disease, chronic and intermittent arrhythmias and thromboembolic diseases should be sought as reversible causes of suddenly worsening breathlessness. COPD is present in around 50% of people with lung cancer [21]. Optimising the clinical management of any contributing underlying conditions or concurrent symptoms such as pain [7, 9] may help decrease the sensation of breathlessness, although reversal of clinical signs or abnormal laboratory findings will not always translate into improved symptom control.

### Dimensions of Breathlessness

Breathlessness is multidimensional. As such, the comprehensive assessment of breathlessness requires each clinician to assess the dimensions that have been identified as being important [22]—the physical sensation (both intensity and the affective component of how unpleasant the sensation is) [2], anxiety and other emotional consequences [13, 16], the existential questions generated by chronic breathlessness [23] and the symptom's social and functional impacts [1, 24]. Each dimension needs to be assessed in order to have an adequate picture of breathlessness for each a person. Such an assessment will vary between people and, importantly, over time in each person, requiring continuous reassessment.

An important question for clinicians to ask is what has the person themselves encountered by way of breathlessness during life—in themselves or in people they have seen. Linked intimately with this question is the exploration of what they expect to experience and specifically what fears they have about future breathlessness or the fear of suffocation. Giving voice to these questions allows clinicians to reassure a person that symptoms will be addressed actively and that every effort will continue to be made to reduce suffering and avoid the sensation of suffocation.

Another important question to consider asking is "what they have given up due to the symptom in order to avoid breathlessness?" This is because people will often not identify breathlessness as a problem despite more and more limited function because of the physical limitations of the symptom. If clinicians only ask about breathlessness, it is likely that there will be a significant underestimate of the true impact of breathlessness on people's lives.

The other crucial aspect of assessment is to consider the effect that breathlessness has on caregivers. Again, caregivers have specific needs in providing care for people where breathlessness

is a troublesome symptom [24, 25]. The role of caring for someone with chronic breathlessness and advanced cancer is, in itself, very confronting to caregivers, and the ability to be able to take on and continue the role needs careful assessment by clinicians, given the identified burdens perceived by caregivers when this symptom is present [26].

## Measuring Breathlessness

A distinction needs to be made between measures of breathlessness for research and day-to-day clinical evaluation. Objective measures of the function required to induce breathlessness include tests such as the 6-min walk test [27]. For many people, especially in the face of advancing disease or significant multi-morbidity, even a 6-min walk test will be beyond their ability, and this is in itself a telling clinical finding. In the clinical setting, it is important to distinguish between breathlessness and leg fatigue as the rate-limiting factor in functional assessments [28]. Although there are functional tests for people unable to tolerate a 6-min walk test, the clinical application of these is still limited.

Given the subjective nature of breathlessness, the cornerstone of measurement remains self-report by the patient. When the patient is unable to self-report, measurement by proxy (caregiver or staff) is useful for detecting the presence of breathlessness [29]. Measures should include the intensity or how unpleasant the sensation is [1, 30]. Unidimensional categorical scales, such as Likert scales or the Borg scale, and numerical rating or visual analogue scales all have relevance for measuring breathlessness (intensity and unpleasantness) and its impact on the person's life. The modified Medical Research Council (mMRC) breathlessness scale (Table 14.1) is useful for measuring the impact on physical function [31]. The Cancer Dyspnoea Scale and the recently developed Multidimensional Dyspnoea Profile can be used to measure several dimensions of breathlessness [32, 33]. A combination of categorical and continuous measures is likely to be able to be used for rating by most people. Numerical or analogue rating scales are abstract, and for some people categorical scales may be much easier to use [34]. Most importantly, clinicians should consistently use at least one measure of subjective intensity and of physical impairment and/or health status routinely in clinical practice and use the same scales for follow-up to understand the net effect of interventions designed to help manage breathlessness and monitor change over time for each patient.

**Table 14.1** Modified Medical Research Council (MRC) breathlessness scale (Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581–6)

| Grade | Description of symptom |
|---|---|
| 0 | "I only get breathless with strenuous exercise" |
| 1 | "I get short of breath when hurrying on the level or walking up a slight hill" |
| 2 | "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level" |
| 3 | "I stop for breath after walking about 100 yards or after a few minutes on the level" |
| 4 | "I am too breathless to leave the house" or "I am breathless when dressing" |

*Note*: This modified MRC scale uses the same descriptors as the original MRC scale in which the descriptors are numbered 1–5

## Symptomatic Treatment of Chronic Breathlessness

Exploring any reversible causes for breathlessness should occur *at the same time* as initiating therapy for the symptom itself in people with advanced cancer as illustrated in Fig. 14.1. Continuing review of the net effects of management plans will help to ensure the best possible symptom control for patients.

With reversible causes optimally addressed (and this could include diuretics for cardiac failure or bronchodilators for reversible bronchoconstriction), all efforts should focus on the symptomatic relief of the sensation of breathless-

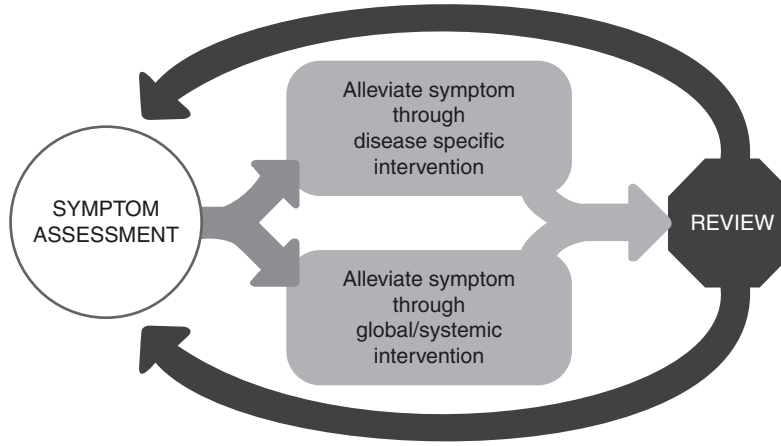


**Fig. 14.1** Exploring any reversible causes for breathlessness should occur at the same time as initiating therapy for the symptom itself in people with advanced cancer

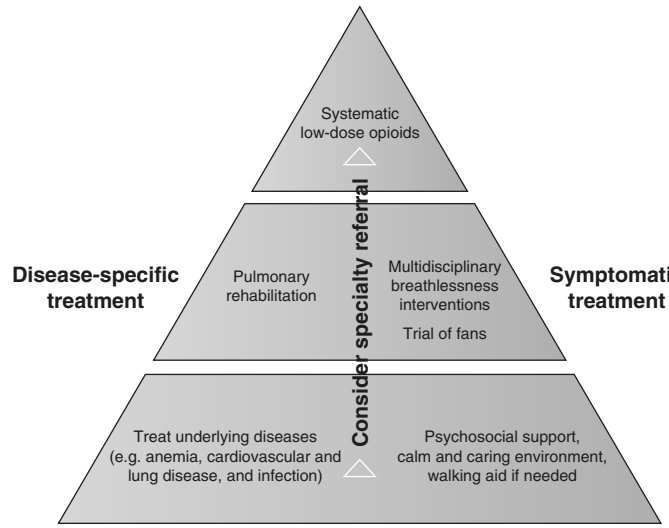


**Fig. 14.2** An overview of the management of breathlessness

ness. An overview of the management of breathlessness is shown in Fig. 14.2. Options include non-pharmacological and pharmacological interventions. Recent evidence-based reviews have been done in each of these areas [34–39].

## Systemic Opioids

The mechanisms of action through which opioids relieve breathlessness include a central modulation of the respiratory drive and symptom perception [1, 40]. Endogenous opioids (endorphins) have a physiological role in modulating the perception of exertional breathlessness, as blockage of endogenous opioids with naloxone increased exertional breathlessness when compared to placebo, without affecting exercise tolerance or respiratory function [41].

Extended release (ER) morphine is the first-line pharmacological intervention for the symptomatic treatment of breathlessness with the most robust data behind the recommendation [42]. When carefully titrated and administered regularly in low doses, there are no data to suggest that respiratory depression is a significant clinical issue [43]. Data from the acute care setting where relatively larger doses of opioids are given parenterally to people who are opioid naïve for pain cannot be extrapolated to the use of low-dose,

oral-extended release morphine in the setting of chronic breathlessness [44].

A systematic review by Jennings et al. [35] showed that, in the palliative care setting, opioids demonstrated efficacy in reducing breathlessness. The direction and magnitude of the findings in this study were confirmed by an adequately powered, crossover, randomised, placebo-controlled trial of 20 mg sustained release oral morphine daily in people with chronic breathlessness, mostly with COPD [45]. More recently, two systematic reviews of controlled trials confirmed that systemic opioids reduced the subjective sensation of breathlessness in people with cancer [36, 37]. The Jennings study makes a clearer distinction between single-dose studies and steady-state studies. Importantly, these systematic reviews all conclude that, to date, there are no consistent data to support a role for nebulised opioids for chronic breathlessness [35–37, 39].

The magnitude of symptomatic benefit experienced by patients from the pooled data was of the order of 8 mm on a 100-mm visual analogue scale (overall pooled effect size, −0.31; 95% CI, −0.50 to −0.13; $p = 0.0008$), which is both statistically and clinically significant [46] given the progressive nature of this breathlessness and the fact that baseline scores were of the order of 50 mm [35]. This does include single-dose studies that may move the estimate away from a net clinical benefit (in a similar way to early single-dose trials of opioids for pain). A recent meta-analysis reported a less consistent effect but had a number of important methodological limitations [39]. In the safety measures reported, there was no evidence of respiratory depression or obtundation.

Optimal dosing and titration studies are still awaited for both people who are opioid naïve and for people already on opioids for other indications such as pain. To date, a starting dose of between 10 and 20 mg of ER morphine in 24 h in divided doses is reasonable. Further work also needs to ensure the safety of these medications in everyday practice, but, to date, evidence of toxicity in steady-state is minimal. Constipation remains the most constantly reported effect of taking regular opioids and should be treated expectantly. In people already on opioids for pain who develop breathlessness, an increase of 25% of the dose of current opioids has some evidence to support it [47].

## Non-opioid Medications

A wide range of psychotropic medications (anxiolytics [benzodiazepines, buspirone], phenothiazines [promethazine], selective serotonin reuptake inhibitors) have been used to try and relieve chronic breathlessness. Oral promethazine interestingly also deserves further study in people with cancer and breathlessness given the evidence base to date [36]. Again, optimal dosing has not been defined. Other agents did not have supporting phase III trials, although phase II data suggest the need for further studies of selective serotonin uptake inhibitors.

There is no evidence that benzodiazepines relieve chronic breathlessness [48] in a series of small studies brought together in a meta-analysis. If there is a clear component of anxiety, benzodiazepines may have a role in acutely breaking the cycle of anxiety, while other treatments are introduced. A recent phase III study reported the outcomes of a randomised, double-blind, placebo-controlled trial of the anxiolytic buspirone in people with cancer who had breathlessness [49]. It was no more effective than placebo in reducing chronic breathlessness.

Apart from its diuretic effects, several small studies have explored the role of nebulised frusemide. Although it has been demonstrated to protect against bronchoconstriction, it also appears to affect the perception of breathlessness in people who do not have bronchoconstriction. This intervention has not been studied in people with cancer; however, in people with chronic obstructive pulmonary disease, it appears to significantly lessen breathlessness after exercise when compared with placebo in a blinded trial [50] and change the perception of breathlessness in healthy volunteers when challenged with breath holding or loaded breathing [51]. A systematic review has not provided con-

clusive evidence for inclusion in practice at this time [52].

## Oxygen

Oxygen is often prescribed with the palliative aim to relieve breathlessness but evidence for benefit is limited [38, 53]. While levels of oxygenation are being established, it is reasonable for ambulance and emergency staff to do this. Having introduced oxygen in the acute setting, what is its role in the ongoing care of people with chronic breathlessness? There is evidence that patients are very discerning about the net benefit offered by domiciliary oxygen balancing the symptomatic benefit with the burden of administration and concerns about being dependent on a machine [54].

In an adequately powered, parallel arm, randomised, double-blind study of oxygen compared to medical air for 1 week, there was no difference across the population ($n$ = 241) in relief of breathlessness or quality of life. Both arms showed benefit over baseline of a similar magnitude, suggesting that flow of gas may be a key to reducing the sensation of breathlessness. People with the most severe breathlessness appeared to derive more benefit, and more so from oxygen than medical air, but the study was not powered for sub-group analyses [45]. A recent Cochrane meta-analysis (32 studies; 865 participants) in COPD showed that oxygen might relieve breathlessness during an exercise test but that there is no evidence for benefit of domiciliary therapy in daily life in people who are not hypoxaemic [38]. This finding is consistent with the largest randomised trial of long-term oxygen therapy to date which included 738 patients with COPD and moderate hypoxemia at rest ($S_aO_2$ 89–93%) or during a walk test [55]. Compared with no treatment, long-term oxygen therapy at rest or during exertion did not affect any endpoint including exercise capacity, symptoms or health-related quality of life over a median 18.4 months of follow-up. In a crossover study in patients at the end of life, participants were randomised to oxygen, air or no treatment, with no between-group difference in breathlessness [56].

There is thus little evidence to support the use of oxygen in people who are not hypoxaemic. A trial of oxygen might still be appropriate in selected patients with moderate exertional hypoxemia and intractable breathlessness despite best evidence-based management. The treatment should be evaluated through blinded exercise tests on air/oxygen and discontinued if the patient perceives no benefit during the test or within a day or two [53, 57].

## Nonpharmacological Management of Breathlessness

Given the multidimensional construct of breathlessness, it is to be expected that a range of interventions may be required to optimally treat the symptom (Fig. 14.2). An increasing number of clinical trials identify nonpharmacological interventions that benefit people with chronic breathlessness, including psychosocial support and optimising breathing techniques [58].

### Handheld, Battery-Operated Fans

In keeping with the observations made in controlled clinical studies of oxygen, flow of air across the face may in itself help to relieve the sensation of breathlessness. Controlled trials have confirmed benefit, and, given the negligible costs, absence of harms and potential benefits, it is reasonable to suggest that patients trial fans when they are short of breath during or after exertion [59, 60].

### Breathlessness Clinics

Breathlessness clinics that focus on breathing techniques, relaxation, coping strategies including activity pacing and counselling have shown benefits for people with cancer [58]. Weekly sessions for 3–8 weeks have been shown to provide benefit well after the sessions have con-

cluded [61]. A recent randomised trial ($n$ = 105) found that an interdisciplinary breathlessness support service improved the patient's mastery of their respiratory symptoms at 6 weeks [58]. However, availability of this nurse-led resource remains limited and predominantly focused in the UK.

### Breathing Techniques

A forward leaning position in which the person's weight is supported by their arms appears to help relieve breathlessness by more effectively using the respiratory muscles. This includes better use of the diaphragm and less reliance on accessory and abdominal muscles. Pursed lip breathing is expiration that lasts at least 4 s and reduces dynamic airway collapse in COPD by providing gentle back pressure to small airways. These approaches require a motivated and cognitively capable patient who is well enough to learn and practise these techniques.

## Cough

Cough is frequently encountered in people with cancer involving the lung, especially when larger airways are affected by malignancy. Upper or lower airways irritated chronically by a number of substances can produce a chronic cough. Like most other symptoms, there may be a protective component to a cough, but for many people, chronic cough interrupts their social interactions and essential functions such as sleep.

Work is currently underway to understand better the underlying mechanisms of cough. Functional MRI demonstrates the involvement of both the cortex and the brainstem in cough. Although asthma and gastro-oesophageal reflux disease are associated with some people having a chronic cough, the role of upper airway sensitization (especially involving the transient receptor potential vanilloid-1 receptor) may better explain the reason that some people experience this troublesome symptom and others do not [62, 63].

### Assessment

Reversible or modifiable causes for cough need to be sought. The three most commonly encountered causes that are potentially modifiable include asthma or chronic bronchitis, swallowing disorders (particularly in this cohort of people where age remains a risk factor for dysphagia to liquids) or gastro-oesophageal reflux disease. There are data to support the use of inhaled corticosteroids or ipratropium in reducing cough in people with airway disease. There are limited data to support the use of proton-pump inhibitors in reducing cough in people with gastro-oesophageal reflux disease [64].

It is also important to determine whether the cough remains a protective mechanism (excess secretions) or is ultimately serving no physiological benefit.

### Symptomatic Treatment

There is no gold standard symptomatic therapy for chronic cough [65]. In the palliative setting, nebulised saline may help reduce the viscosity of mucous. Encouraging more effective use of coughing is the aim for many therapies, where excess mucous secretion is the major cause for coughing [66]. Smokers are likely to benefit from smoking cessation.

Cough suppressants often employ opioid-based compounds, but blinded trials have not shown benefit over placebo or the characteristics of a subpopulation who may benefit from the intervention. Codeine or its derivatives are used in modest doses, but there is a very high placebo response rate in the blinded studies that have been conducted and a significant period effect given that the natural history of cough is that it resolves for most people [66].

Over the recent decade, some promising evidence has emerged for centrally acting neuromodulators on chronic cough, including gabapentin [65]. In a recent randomised trial of 62 non-smokers with chronic cough, gabapentin in doses up to 1800 mg per day decreased cough frequency and severity and improved

cough-specific quality of life compared with placebo [67]. Onset of action was within 4 weeks, and the effect was maintained during the study of 10 weeks but not after drug discontinuation. Due to frequent side effects, the usefulness of gabapentin for palliation is unclear [65]. Similarly, there are some promising efficacy data for amitriptyline and baclofen, but their clinical usefulness is yet to be established [65].

## Pleural Effusions

Pleural effusions are frequently encountered in the setting of cancer. This discussion will be limited to people who have previously been diagnosed with cancer and now have a pleural effusion.

The symptom burden of the effusion needs to be weighted carefully against the burden of intervention. For example, in someone with widespread cancer and a small unilateral effusion, one could argue that further investigation or intervention is unlikely to improve comfort or function. Conversely, in someone who has been offered definitive treatment for their cancer and is now presenting with an effusion for the first time, it will be imperative to establish the nature and likely cause(s) of the effusion. Importantly, up to 50% of people who have an effusion drained will not have an improvement in their breathlessness or exercise tolerance after drainage [68].

The nature of pleural fluid is important as likely causes are explored. The distinction proposed four decades ago for categorising effusions into transudates and exudates using Light's criteria [69] still has clinical application—one or more of three criteria will make the diagnosis of an exudate: pleural/serum protein >0.5, pleural/serum lactate dehydrogenase (LDH) >0.6 and/or pleural fluid LDH >0.66 of the upper limit of normal. The major caveat in using these is when someone is on diuretics as there is a risk of underdiagnosing transudates in favour of exudates [70]. Raised pleural fluid cholesterol levels are associated with exudates independently of diuretic use [71]. The differential diagnosis for frequently encountered causes of transudates includes cardiac failure, hepatic failure or other low-albumin states such as nephrotic syndrome. The most frequently encountered causes of exudates include malignancy, pneumonia, pulmonary embolism or, in some parts of the world, tuberculosis. Gram stain and culture of pleural fluid should occur in suspected para-pneumonic causes and adenosine deaminase and gamma interferon estimates in people with suspected tuberculosis.

The treatment of pleural effusions needs to distinguish between diagnostic drainage and the relief of symptoms. Symptomatic relief needs to take account of the person's overall functional status. Someone with a poor level of function where nothing else can change the course of the illness may require a far more circumspect approach than someone for whom this was the only site of symptomatic disease who is otherwise functioning without compromise. The size of the effusion should be carefully evaluated before intervention—only effusions that are causing symptoms should be considered for intervention. Small effusions are unlikely to cause a significant symptom burden in all but people with the most severe respiratory compromise creating a difficult benefit/burden equation to balance before intervening in this extremely unwell cohort.

In people well enough to tolerate it, a pleurodesis should be performed. Although there is continuing debate in the literature as to the optimal sclerosant, talc has been most studied and appears to offer higher success rates and longer periods of benefit for symptomatic pleural effusions [72]. Whether the sclerosant should be introduced thoracopically or with the insertion of an intercostal chest drain is open to debate and will often be dictated by local resources and experience [72]. Thoracopically performed pleuradeses appear to have lower rates of effusion recurrence and have the advantage of being able to physically breakdown septa that cause loculation in many effusions, but with the disadvantage of requiring general anaesthetic with selective lung intubation on the contralateral side. In people with excellent performance status, this is the intervention of choice for pleurodesis [72].

Pleuroscopy is less invasive (a single entry point) and can be done under conscious sedation rather than general anaesthetic. At the time of pleuroscopy, a sclerosant can be introduced if necessary.

The other therapy gaining popularity is small bore tunnelled intercostal catheters that can be implanted in people on an outpatient basis and can be emptied by community nurses or family members using a vacuum-sealed attachment (PleurX™) in the long term. This appears to have a similar rate of "auto-pleurodesis" at 1 month as intercostal drainage, without the need for inpatient care at the time that a formal pleurodesis was done. Daily drainage increase the rate of auto-pleurodesis compared with drainage every other day [73, 74].

In people with poor performance status and limited life expectancy, a trial of recurrent thoracentesis or the insertion of small bore tunnelled intercostal catheters are treatments of choice. This needs to be judged within the context of a person's overall systemic function. Preliminary data support that chemotherapy can be given safely also to patients with an indwelling pleural catheter [75].

Although fibrinolytics have been used to reduce loculation in para-pneumonic exudates and systematically analysed [76, 77], their role in malignant pleural effusions has been defined by a small number of case series with no comparative effectiveness data available [78]. The administration of methylprednisolone into the pleural cavity did not change the time to reaccumulation nor breathlessness scores [79].

## Haemoptysis

Like breathlessness, the fear of bleeding from the respiratory tract is a constant concern for many people with cancer involving their lungs. Up to 20% of all people with cancer involving the lung will have haemoptysis at some stage during their illness—either as a presenting complaint or subsequently [80]. Differential causes that need to be considered include thromboembolism to the lungs and pro-bleeding states such as coagulopathies or thrombocytopenia. Anticoagulants, non-steroidal anti-inflammatories and antiplatelet agents should be reviewed carefully. The rate of bleeding should be considered in three categories—mild, moderate or severe (immediately life-threatening).

Episodes of mild bleeding warrant investigation for any reversible causes of a pro-bleeding state. They also are an opportunity to have a conversation about the small but real risk of an increased volume of bleeding at some point in the future. Exhaustive investigations in this setting are not warranted. Most low-level bleeding stops spontaneously.

Moderate bleeding is an area where the threshold for aggressive investigations may well be met, even if the functional status is very poor. Beyond coagulation and platelet studies, it may be worth seeking to visualise the large airways and coagulate any bleeding points seen with photocoagulation or local instillation of adrenaline [80]. If a lesion cannot be visualised, then a select group of patients with persistent bleeding should be considered for selective angiography to identify and potentially treat the bleeding point. In reality, few of people with haemoptysis will qualify for angiography.

Other potential therapies for moderate haemoptysis include external beam radiotherapy to a known tumour deposit. It appears that high-dose endobronchial radiotherapy may offer little benefit over external beam radiotherapy and may have higher rates of catastrophic bleeding [81]. Systemically, the use of tranexamic acid regularly for up to 5 days while clot organises over the bleeding source is also an option. This medication is contraindicated in people who have a history of thromboembolism or a recent history of bleeding in the urinary tract or other sites.

In severe, large volume bleeding, although many textbooks and authorities talk of emergency orders, the reality is that these happen very rarely, and when they do occur, there is rarely sufficient time to respond with sedating medication before the person dies. Such events are distressing for all involved—the patient, their family and friends and the staff providing care. Important nursing considerations continue to include the

availability of linen that is not white—green or red towels will help mask the extent of blood loss.

## Hoarse Voice

The diagnosis of exclusion is damage to the recurrent laryngeal nerve (RLN), itself a branch of the vagus. Given the descent of both laryngeal nerves into the thorax, damage can occur from the tumour or local therapies such as radiotherapy. The left RLN wraps under the arch of the thoracic aorta and the right side around the right subclavian artery. Mediastinal, thoracic or head and neck malignancies can cause damage to the nerve.

Patients are most likely to present with a change in the character or volume of their voice. The major clinical concerns are about the ability to protect the airway when the vocal cords cannot appose adequately. Aspiration and poor cough is a dangerous combination. Bilateral damage, which is unlikely in this clinical setting, will cause aphonia and often difficulty in breathing.

Treatment for unilateral damage most frequently now includes injection of collagen into the paralysed cord to improve adduction of the cord. Patient reassurance is a key since hoarse voice can be very noticeable.

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# Part V

# Endocrine and Metabolic

# 15 Endocrine and Metabolic Symptoms of Cancer and Its Treatment

Rony Dev

## Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), a potentially life-threatening complication for patients with cancer, has been subclassified into either laboratory TLS or clinical TLS. Laboratory TLS is characterized by the rapid development of two or more of the following abnormalities—hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcaemia, and azotemia—which occur in cancer patients most often 28–72 h after the initiation of chemotherapy or radiation; however, spontaneous cases have been reported [1]. Clinical manifestations of TLS include renal failure (glomerular filtration rate ≤60 mL/min) and organ damage leading to cardiac arrhythmias or seizures. Predisposing factors for TLS include neoplasms with high growth rates, patients with a large tumor size or burden, high white blood cell count (>50,000/mm$^3$), cancers highly sensitive to chemotherapy or radiation, and patients with extensive bone marrow involvement [2].

Comorbidities that increase the risk for developing TLS include elevated uric acid level prior to treatment, preexisting renal insufficiency, obstructive uropathy, dehydration or inadequate hydration during treatment, and advanced age [2]. Patients with hematological malignancies including high-grade lymphomas (i.e., Burkitt's lymphoma) and acute or chronic leukemias are more likely to have complications of TLS. In adults with solid tumors, TLS is a rare complication in chemosensitive tumors including bulky small cell lung cancer and metastatic germ cell carcinoma. In children, TLS is more frequently associated with malignancies that have an increased proliferative fraction, large tumor burden, widely metastatic disease, or increased sensitivity to chemotherapy.

The pathogenesis of TLS involves the acute release of intracellular products into the systemic circulation secondary to the destruction of cancer cells after chemoradiotherapy. Uric acid, calcium phosphate, or hypoxanthine may precipitate in the renal tubules resulting in acute renal failure. Other hemodynamic changes resulting in decreased glomerular flow have also been postulated to contribute to renal failure. Clinical symptoms associated with TLS include nausea, vomiting, fatigue, hematuria, cardiac dysrhythmias, seizures, muscles cramps, and sudden death reflect consequence of metabolic derangements including hyperkalemia, hyperphosphatemia, and hypocalcaemia [3].

Early recognition of TLS and identification of patients at high risk are essential to prevent complications. A panel of international experts recommended therapy based on risk stratification of

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TLS [4]; however, the recommendations were based on expert opinion and have not been validated (Table 15.1).

Prophylactic measures should be ideally initiated 48 h prior to tumor-specific therapy. The first approach for the prevention of TLS involves vigorous intravenous volume expansion to improve renal perfusion, which promotes urinary excretion of uric acid and phosphate [5]. In addition, administration of sodium bicarbonate in order to alkalinize the urine above a pH of 7 to prevent uric acid nephropathy has been historically recommended [6] but is controversial and only recommended in patients with metabolic acidosis [3]. Alkalinization may prevent hyperuricemia; however, it can exacerbate hyperphosphatemia that may result in calcium phosphate precipitation in renal tubules. Prophylactic drug therapy includes allopurinol (300–800 mg daily) that blocks the activity of xanthine oxidase in the liver, preventing the conversion of hypoxanthine and xanthine to uric acid, which decreases the risk of uric acid crystallization in the kidneys [7]. Alternative prophylactic drug therapy includes rasburicase, a

**Table 15.1** TLS prophylaxis recommendations based on TLS risk

| Low-risk disease (LRD) | Intermediate risk disease (IRD) | High-risk disease (HRD) |
|---|---|---|
| ST[c] | N/A | N/A |
| MM | N/A | N/A |
| CML | N/A | N/A |
| Indolent NHL | N/A | N/A |
| HL | N/A | N/A |
| CLL[a] | N/A | N/A |
| AML and WBC <25 × $10^9$/1 and LDH <2 × ULN | AML with WBC 25–100 × $10^9$/1 | AML and WBC ≥100 × $10^9$/1 |
| Adult intermediate grade NHL and LDH <2 × ULN | AML and WBC <25 × $10^9$/1 and LDH ≥2 × ULN | N/A |
| Adult ALCL | Childhood ALCL stage III/IV | N/A |
| N/A | Childhood intermediate grade NHL stage III/IV with LDH <2 × ULN | N/A |
| N/A | ALL and WBC <100 × $10^9$/1 and LDH <2 × ULN | ALL and WBC ≥100 × $10^9$/1 and/or LDH ≥2 × ULN |
| N/A | BL and LDH <2 × ULN | BL stage III/IV and/or LDH ≥2 × ULN |
| N/A | LL stage I/III and LDH <2 × ULN | LL stage III/IV and/or LDH ≥2 × ULN |
| N/A | N/A | IRD with renal dysfunction and/or renal involvement<br>IRD with uric acid, potassium, and/or phosphate >ULN |
| *Prophylaxis recommendations* | | |
| Monitoring | Monitoring | Monitoring |
| Hydration | Hydration | Hydration |
| ±Allopurinol | Allopurinol | Rasburicase[b] |

*ST* solid tumors, *MM* multiple myeloma, *CML* chronic myeloid leukemia, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *CLL* chronic lymphoid leukemia, *AML* acute myeloid leukemia, *WBC* white blood cell count, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *ALCL* anaplastic large cell lymphoma, *N/A* not applicable, *ALL* acute lymphoblastic leukemia, *BL* Burkitt's lymphoma/leukemia, *LL* lymphoblastic lymphoma

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[a]CLL treated with fludarabine and rituximab and/or those with high WBC (≥50 × $10^9$/1) should be classified as IRD

[b]Contraindicated in patients with a history consistent with glucose-6-phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol

[c]Rare solid tumors, such as neuroblastoma, germ cell tumors, and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD

recombinant urate oxidase enzyme, which converts uric acid to a compound more urine soluble, allantoin [8]. Rasburicase is contraindicated in patients with B6PDH deficiency, methemoglobinemia, patients at risk for hemolytic anemia, and pregnant or lactating females. The choice of prophylactic treatment is generally selected based upon the estimated risk of TLS [4].

Clinical TLS is an emergency with the potential to result in the death of a patient. Aggressive hydration and diuresis and treatment of electrolyte abnormalities, plus allopurinol or rasburicase for hyperuricemia, are recommended for the treatment of established TLS [3]. In pediatric patients with TLS and hyperuricemia, rasburicase has shown better results [9]. Early consultation with a nephrologist is advisable.

## Tumor Fever

Normal human body temperature displays a circadian rhythm, which is lower in the early morning, at 36.1 °C or less and rises to 37.4 °C or higher in the afternoon. Elevation of a patient's body temperature results from either hyperthermia or pyrexia (fever). Hyperthermia represents a failure of the thermal regulatory control system that normally balances heat loss with heat production. In pyrexia, thermoregulation mechanisms are intact, but the hypothalamic set point for body temperature is increased by either exogenous or endogenous pyrogens. A person's response to fever varies with age. Older patients, secondary to inadequate thermoregulatory mechanisms, may develop hyperthermia, which makes them susceptible to complications of arrhythmias, heart failure, or changes in mental status, while children may develop febrile convulsions.

In patients with cancer, the major causes of fever include infections, drugs, transfusion of blood products, graft-versus-host disease, or secondary to the tumor itself (also known as paraneoplastic fever) [10]. Paraneoplastic fever has previously been considered to be a more frequent complication of patients with primary malignancies such as renal cell carcinomas, Hodgkin's and non-Hodgkin's lymphomas, and acute leukemias; however, data suggest that it may occur in cancers from various primary sites [11]. Currently, the exact etiology of tumor fever is unknown, but potential causes include hypersensitivity reactions, pyrogen or cytokine production, or secondary to tumor necrosis. In cancer patients, other etiologies of fever that must be excluded include infections, drug withdrawal (i.e., opioids or benzodiazepines), bowel or bladder obstruction, neuroleptic malignant syndrome, or tumor embolization. Other comorbidities associated with fever include venous thrombosis, connective tissue disorders, and bleeding in the central nervous system [10].

Establishing a diagnosis underlying the febrile response is critical since it may impact on the management of symptoms and response to therapy. Obtaining a thorough history, medication review, and completion of a whole body examination is important when assessing a patient with fever. Blood, urine, and sputum cultures as well as radiographic imaging may be indicated to complete the initial evaluation.

In debilitated cancer patients, a fever may lead to increased metabolic demands and dehydration. Symptoms commonly associated with a fever include fatigue, myalgias, diaphoresis, and chills. Interventions for the management of fever include treatment of the underlying cause, hydration with parenteral fluids or hypodermoclysis, and nonspecific palliative measures to alleviate symptoms. Antibiotics are effective in the palliation of symptoms associated with fever secondary to infection. Site-specific symptoms such as cough secondary to pneumonia or localized pain due to an underlying abscess may be ameliorated by appropriate antibiotic therapy. Neutropenic (granulocyte count <500) fever requires prompt initiation of broad-spectrum antibiotic therapy. For patients with neutropenia, a single temperature elevation above 38.5 °C or three measurements above 38 °C in 24 h would be defined as fever [10]. Without rapid treatment within 48 h, the mortality rate is as high as 70% of patients with neutropenic fever. Recommendations [12] for the treatment of neutropenic fever are rapidly changing, and clinicians are advised to obtain appropriate consultation.

The ideal management of paraneoplastic fever is treatment of the underlying neoplasm. If antineoplastic therapy is not available or ineffective, nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice for the palliation of symptoms. Some clinicians to treat tumor fever have favored naproxen. A structurally different NSAID may be substituted to treat paraneoplastic fever if initial treatment loses its effectiveness. In patients who have suspected paraneoplastic fever after undergoing thorough clinical, laboratory, radiological testing, and appropriate antibiotic treatment, a trial of naproxen, which results in fever lysis within 24 h, can be diagnostic [13].

Aspirin and acetaminophen may also be used to control tumor fever but are often less effective than NSAIDs. Aspirin should be used with caution in cancer patients with thrombocytopenia and patients with Hodgkin lymphoma; also, aspirin is not recommended in pediatric patients because of the risk of Reye syndrome. Corticosteroids have also been reported to control paraneoplastic fever in some patients [14].

Nonspecific palliative treatments for fever include increasing fluid intake, removing excess clothing or linens, and bathing/sponging with tepid water [15].

## Sweats and Hot Flashes

Sweating by promoting transdermal heat loss is an integral mechanism to managing core body temperature. Fever secondary to underlying disease and other nondisease states including warm environmental temperature, menopause, or exercise can also result in sweating.

Hot flashes and sweats are common symptoms in cancer survivors as well as cancer patients with advanced disease. Research suggests that moderate-to-severe sweating occurs in roughly 14–16% of advanced cancer patients receiving palliative care [16]. The underlying physiological mechanism of sweating is complex, and treatment options include hormonal agents, nonhormonal drug treatments, and various integrative therapies [17].

Hot flashes characterized by the vasomotor instability of menopause are complicated by sweating and occur in two-thirds of postmenopausal women with a history of breast cancer and three-quarters of men with locally advanced or metastatic prostate cancer treated with medical or surgical orchiectomy.

Tumor, cancer treatment, or comorbidities can also result in sweating in cancer patients. Hodgkin lymphoma, pheochromocytoma, and neuroendocrine tumors including carcinoid cancers are often associated with sweating. Medical comorbidities including fever, menopause, male castration, drugs, and abnormalities of the hypothalamus can also contribute. Drugs associated with sweats include tamoxifen, aromatase inhibitors, opioid therapy, tricyclic antidepressants, steroids, hormonal therapies, as well as a number of cytotoxic agents.

Treatment of the underlying cause of sweats and hot flashes is appropriate when effective therapy is available. Antineoplastic therapy, if effective, can control sweating in patients with tumor recurrence or progression of disease. If curative treatment is not available, a number of palliative interventions may be attempted to improve quality of life.

If not contraindicated, estrogen replacement may control hot flashes in postmenopausal women. However, evidence suggesting an increased risk of breast cancer associated with the use of hormonal replacement therapy has arisen. The Women's Health Initiative study, a large, randomized, placebo-controlled trial evaluating estrogen plus progestin in healthy postmenopausal women, was stopped prematurely secondary to detection of a 1.26-fold increased risk for breast cancer in women receiving hormonal replacement [18]. No clear increased risk was evident with unopposed estrogen therapy [19]. In breast cancer survivors, it is widely recommended to avoid hormonal replacement therapy [20].Other interventions including megestrol acetate (i.e., 20 mg twice daily) and intramuscular depot medroxyprogesterone acetate have undergone testing and are promising treatment options for hot flashes in women with a history of breast cancer [21]; however, concerns stimulat-

ing breast cancer with long-term use limit enthusiasm [22].

Other nonhormonal pharmacologic interventions for the treatment of hot flashes that have been shown to be effective include selective serotonin reuptake inhibitors (SSRIs), gabapentin and pregabalin, and the alpha-adrenergic agonist (clonidine). For breast cancer patients being treated with tamoxifen, venlafaxine, citalopram, gabapentin and pregabalin, and clonidine have been shown to be effective for hot flashes [23]. For breast cancer patients receiving tamoxifen, paroxetine, fluoxetine, and sertraline should be avoided secondarily reducing the efficacy of tamoxifen via inhibiting CYP2D6 [23].

Nonpharmacological, commonsense interventions that improve the management of hot flashes include the use of loose-fitting clothing, fans to circulate cool air, stress management techniques (i.e., relaxation and slow, deep breathing exercises), and self-hypnosis, using cooling suggestions. All have been shown to be effective for controlling hot flashes in approximately 50% of cases in pilot studies and may be considered.

Herbs and dietary supplements including soy phytoestrogen, vitamin E, and black cohosh have been proposed interventions to control sweating and hot flashes. Vitamin E (400 IU twice daily) has shown modest benefit. In a recent systematic review, soy phytoestrogen supplements reduced hot flashes to a greater extent than placebo [24]; however, potential risk of hormone-related adverse events limits the enthusiasm for this treatment. Black cohosh, historically used as a remedy for menstrual problems, has shown mixed results for the treatment of hot flashes, and more research is needed. Other alternative therapies used to control hot flashes but not well studied include acupuncture, flaxseed, dong quai, milk thistle, red clover, licorice, and chaste tree berry, which need further research to determine efficacy.

As with women, men with prostate cancer undergoing androgen deprivation therapy may have complications of sweats and hot flashes that can diminish their ability to sleep, cognitive function, and overall quality of life. Treatment is similar and includes treating the underlying cause and, if ineffective, palliation with the following: estrogens, progesterone, SSRIs, gabapentin (300 mg three times daily), cyproterone acetate, and antiandrogens. Treatment, which is effective for women, may be less effective in men with hot flashes, and more research is needed.

## Hypercalcemia

Approximately 20–30% of patients with cancer have complications of hypercalcemia at some time during the course of their illness. Hypercalcemia is responsible for a significant number of hospitalizations and results in distressing symptoms in patients with cancer. Hypercalcemia is an indicator of poor prognosis with the exception of patients with breast cancer or multiple myeloma. In a study in 1990, 50% of cancer patients with hypercalcemia died within 30 days [25]. Treatment with bisphosphonates may be decreasing the incidence and improving the outcome for cancer patients.

Hypercalcemia results in nonspecific clinical symptoms—"bones, stones, abdominal groans, and psychic moans." Symptoms include anorexia, nausea, abdominal pain, muscle weakness, fatigue, and boney tenderness. Severe complications of hypercalcemia include dehydration, nephrolithiasis, acute pancreatitis, acute renal failure, and altered mental status including coma. The calcium level itself correlates poorly with symptoms, while the rapidity with which calcium rises is closely associated with the development of symptoms.

Hypercalcemia associated with cancer can be classified into four types based on the underlying pathophysiology (Table 15.2) [26]. Elevated calcium (Table 15.3) is a frequent electrolyte abnormality in patients with lung, breast, and head and neck tumors as well as leukemia and multiple myeloma. Bone metastasis is not a prerequisite for the development of hypercalcemia.

Total calcium ranges from 9 to 10.5 mg/dL (2.2–2.6 mmol/L) can be found in the either a free ionized state or bound to other molecules including albumin. Mathematical formulas to correct total calcium concentrations are often

**Table 15.2** Types of hypercalcemia associated with cancer

| Type | Frequency (%) | Bone metastasis | Causal agent | Typical tumors |
|---|---|---|---|---|
| Local osteolytic hypercalcemia | 20 | Common, extensive | Cytokines, chemokines, PTHrP | Breast cancer, multiple myeloma, lymphoma |
| Humoral hypercalcemia of malignancy | 80 | Minimal or absent | PTHrP | Squamous cell cancer (e.g., of the head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer |
| 1,25(OH)2D-secreting lymphomas | <1 | Variable | 1,25(OH)2D | Lymphoma (all types) |
| Ectopic hyperparathyroidism | <1 | Variable | PTH | Variable |

*PTH* parathyroid hormone, *PTHrP* PTH-related protein, *1,25(OH)2D* 1,25-dihydroxyvitamin D, *HTLV* human T-cell lymphotropic virus

*Source*: From Stewart [26] 

**Table 15.3** Severity of hypercalcemia

| Hypercalcemia | Serum calcium level (mg/dL) | Serum calcium level (mmol/L) |
|---|---|---|
| Mild | (10.5–11.9) | (2.6–2.9) |
| Moderate | (12.0–13.9) | (3.0–3.4) |
| Severe | (≥14.0) | (≥3.5) |

used to correct for hypoalbuminemia but have been found to be unreliable [27]. Serum ionized calcium concentrations should be measured in cancer patients and are more accurate. Laboratory evaluation should include intact PTH, which is elevated in primary hyperparathyroidism and suppressed in hypercalcemia of malignancy. In lymphoma patients, 1,25-dihydroxyvitamin D levels should be measured to confirm 1,25-dihydroxyvitamin D syndrome [26]:

$$\text{Corrected calcium formula}\left(\text{mg/dL}\right) = \left(\left(4.0 - \text{albumin}\left(\text{g/dL}\right)\right) \times 0.8\right) + \text{serum total calcium}\left(\text{mg/dL}\right)$$

In the overall management of cancer patients with hypercalcemia, clinicians need to consider the clinical condition of the patient as well as their goals of care and quality of life. Hydration with intravenous saline is essential to reverse the decreased glomerular filtration rate and impaired renal calcium excretion. Furosemide can also promote calcium excretion by inhibiting the Na/K/Cl transporter in the loop of Henle; however, diuretics are not recommended in cancer patients who are volume depleted. Basic supportive care measures include removal of calcium in vitamin supplements and from parenteral feeding solutions and discontinuation of medications that may lead to hypercalcemia (e.g., calcitriol, vitamin D, lithium, and thiazides).

Bisphosphonates, including pamidronate and zoledronate, are first-line medical therapy and work by blocking osteoclastic bone resorption. Bisphosphonates should be given intravenously since they are poorly absorbed when given orally. Common adverse effects include fever, nausea, vomiting, ophthalmologic complications (i.e., anterior uveitis, scleritis, and conjunctivitis), renal toxicity in 6–10% of patients, [28], and osteonecrosis of the jaw—up to 10% of patients with breast cancer or multiple myeloma [29]. Second-line medications include glucocorticoids (useful in lymphoma patients with elevated 1,25(OH)2 vitamin D) and calcitonin, which results in rapid but transient reduction in calcium levels. In cancer patients with hypercalcemia refractory to IV bisphosphonates, denosumab has been recently reported to lower calcium levels [30].

Also, close monitoring of electrolytes is warranted with replacement of phosphorus orally if serum phosphorus is less than 3 mg/dL (0.96 mmol/L). Intravenous phosphorous replacement should be avoided unless phosphorus is critically low <1.5 mg/dL (0.48 mmol/L)

since it can cause seizures, hypocalcemia, renal failure, and arrhythmias. Certain hypercalcemic patients with malignancies that are refractory to standard therapy or have contraindications may be considered for dialysis including patients with glomerular filtration rates less than 10–20 mL/min or congestive heart failure preventing IV rehydration.

## Hypernatremia

Hypernatremia results from impaired water intake resulting in a deficit of water relative to sodium. Diminished intake of water results from dysfunction of the thirst center or osmoreceptors and may occur in tumor infiltration of the lateral hypothalamus, craniopharyngiomas, and primary or metastatic breast and lung cancers. Central or nephrogenic diabetes insipidus may also lead to hypernatremia. Tumor invasion of the hypothalamic-pituitary axis or the osmocenter may impair antidiuretic hormone (ADH) secretion resulting in central diabetes insipidus. A lack of response to ADH in the kidneys results in nephrogenic diabetes insipidus, such as may occur with ifosfamide, resulting in hypernatremia [31]. In cancer patients, other nephrotoxic medications including amphotericin, platinum compounds, methotrexate, cidofovir, and foscarnet may result in hypernatremia. In addition, liberal use of diuretics in the setting of fluid restriction, vomiting and diarrhea, tumor fever resulting in insensible water loss, tumor-related obstructive uropathy, and light chain kidney disease in patients with multiple myeloma may contribute to the development of hypernatremia in cancer patients. In a recent study in a tertiary cancer center, hypernatremia was far less frequent than hyponatremia, often acquired during hospitalization, and associated with a higher morbidity and mortality [32].

## SIADH and Hyponatremia

Hyponatremia is a common electrolyte abnormality that can occur in patients with cancer by various mechanisms. Hyponatremia can result from volume depletion secondary to hemorrhage, diarrhea, intractable vomiting, drainage of ascites or pleural effusion, or a salt-wasting nephropathy. In addition, increase in total body salt and water content can result in hyponatremia, which is clinically manifested as peripheral edema or ascites. In this setting, other common clinical scenarios resulting in hyponatremia include drug-induced congestive heart failure, liver disease, severe hypoalbuminemia, nephritic syndrome, and veno-occlusive disease. Also, hyponatremia is associated with chemotherapeutic agents, particularly cisplatin and carboplatin [33], cyclophosphamide, vincristine, and vinblastine [34].

The SIADH secretion is also a common cause of hyponatremia in cancer patients and has been reported to complicate various types of malignancies including lung cancer (roughly 25% overall incidence in small cell lung cancer) [35], primary and metastatic malignancies of the brain, hematological malignancies, skin tumors, gastrointestinal cancer, gynecological cancer, breast cancer, and prostate cancer. Cancer patients with complications of SIADH clinically appear euvolemic and do not have significant edema. Essential features of SIADH include decreased effective osmolality (<275 mOsm/kg of water), urinary osmolality >100 mOsm/kg of water, and urinary sodium >40 mmol/L [36]. Supplemental features of SIADH include plasma uric acid <4 mg/dL, blood urea nitrogen <10 mg/dL, and fractional sodium excretion >1% [36]. Ectopic secretion of arginine vasopressin (AVP) by tumor cells results in hyponatremia secondary to the retention of free water despite relative serum hypotonicity [37]. Inappropriate release of AVP by tumor cells does not respond to serum tonicity resulting in the absorption of free water at the collecting duct level resulting in worsening hypotonicity and concentrated urine [38].

Hyponatremia has been associated with chemotherapy including both cisplatin and carboplatin [33]. Chemotherapeutic agents are believed to cause damage to the renal tubules, resulting in an inability to retain sodium and increased urinary sodium loss, or renal salt-wasting syndrome (RSWS) [39]. Clinically, patients with RSWS appear hyponatremic with euvolemia, and an elevated spot urine sodium

level suggests RSWS. The treatment of RSWS, rather than water restriction, is sodium supplementation. Vincristine and vinblastine have potentially neurotoxic effects directly on the hypothalamic-pituitary axis resulting in hyponatremia, and cyclophosphamide by augmenting the effect of AVP on the kidney promotes SIADH.

Clinical manifestations of hyponatremia are related to how quickly sodium has declined rather than the actual measured sodium. Hyponatremia may be asymptomatic or be life-threatening. Most symptomatic patients will have a serum sodium less than 120 mEq/L, but symptoms may also occur when sodium is <129 mEq/L [38]. In acute hyponatremia, the clinical presentation is secondary to cerebral edema and includes nausea, vomiting, headaches, seizures, coma, respiratory arrest, and death secondary to herniation if hyponatremia is not treated. In hyponatremia that developed slowly, symptoms may be less severe or more subtle.

Rapidly correcting chronic hyponatremia in patients with minimal symptoms may result in the disastrous complication of osmotic demyelination syndrome (ODS), so clinicians must carefully assess the risks and benefits of therapy prior to aggressive treatment. Symptomatic patients with altered mental status, seizures, respiratory depression, or coma require emergent correction of hyponatremia with 3% saline infusion. A number of approaches and formulas have been developed to determine free water excess and sodium deficit; however, these formulas may be too complicated and not entirely reliable. One simple approach to correcting hyponatremia is to infuse 1 $cm^3$/kg body weight of 3% NS per hour, which will lead to a rise of 1 mEq/L serum sodium per hour [37]. Treatment should be stopped when the following endpoints have been reached: symptoms have been resolved, serum sodium level is 120 mEq/L or above, or an increase of 8 mEq/L per day has been reached [37]. During treatment, hourly monitoring is critical to prevent overcorrection. Relowering of serum sodium with an infusion of D5W has been recommended for the treatment of overcorrection to reduce the risk of ODS [40].

The clinical manifestation of ODS as a consequence of overcorrection of hyponatremia includes quadriparesis or quadriplegia, pseudobulbar palsy, and altered mental status. In severe cases, locked-in syndrome, coma, and death may occur after correction of hyponatremia [41]. The risk of ODS is related to the chronicity of hyponatremia as well as the severity. Most cases of ODS occur in patients with chronically severe hyponatremia, <120 mEq/L; however, in the setting of malnourished patients, ODS has occurred with higher serum sodium levels which may be relevant to patients with cancer cachexia [42]. Rates of correction as low as 8 mEq/L/24 h have been associated with ODS, and most guidelines recommend limiting the correction of sodium to 8 mEq/L/24 h to minimize the risk of developing ODS [37].

Therapy for hyponatremia includes the AVP receptor antagonists, conivaptan, lixivaptan, mozavaptan, satavaptan, and tolvaptan. Conivaptan blocks both $V_{1a}$ and $V_2$ receptors, while the others are selective for the $V_2$ receptor. Studies examining AVP receptor antagonists reveal that they stimulate free water excretion without affecting sodium and potassium excretion and improve plasma sodium concentration in patients with hyponatremia secondary to SIADH [43]. Older drugs used to treat hyponatremia include demeclocycline, urea, and lithium.

## Hypomagnesemia

Hypomagnesemia is a frequent complication in hospitalized patients and may be more prevalent in patients with cancer. In addition to gastrointestinal or urinary magnesium losses, malnutrition and decreased dietary magnesium intake may facilitate the development of hypomagnesemia. Magnesium plays a pivotal role as a cofactor for about 300 cellular enzymes, participates in cellular energy metabolism, and is critical to the stabilization of membrane structures, mRNA translation and transcription, and DNA replication.

In addition, hypomagnesemia may increase or protect against the development of cancer.

Magnesium supplementation for patients with hypomagnesemia, such as chronic alcoholic patients, may reduce the incidence of some malignancies [44].

Approximately 60% of magnesium in the body is stored in the bone, 38% in soft tissues, and <2% in the extracellular fluid compartment. Serum levels typically range from 1.8 to 2.5 mEq/L; unfortunately, they do not reflect the total body stores of magnesium. Serum magnesium below 1.2 mg/dL may cause nonspecific symptoms including neurologic and cardiovascular abnormalities, which may often be overlooked. Neurologic symptoms include muscle weakness, tremors, hyperreflexia, dizziness, apathy, seizures, or coma. Chovstek's or Trousseau's signs may be noted on physical examination. Patients with hypomagnesemia are at risk for arrhythmias including atrial fibrillation, multifocal atrial tachycardia, supraventricular tachycardia, or ventricular tachycardia, and ventricular fibrillation.

Causes of hypomagnesemia can be categorized as gastrointestinal or renal loss, extracellular to intracellular fluid shifts, or transdermal losses. Gastrointestinal losses could be due to diarrhea, dietary deficiency, familial magnesium malabsorption, gastrointestinal fistulas, inflammatory bowel disease, laxative abuse, surgical resection, or excessive vomiting. Renal causes of low magnesium include alcoholism, diabetes, diuretics, hypoparathyroidism, hyperthyroidism, hyperaldosteronism, SIADH, excessive vitamin D, ketoacidosis, hypercalcemia/hypophosphatemia, and other tubular defects. Fluid shifts that result in hypomagnesemia include acidosis, frequent blood transfusions, hungry bone syndrome, refeeding syndrome, and in cases of acute pancreatitis. Transdermal losses include excessive sweating or massive burns.

In cancer patients, drugs that can lead to hypomagnesemia include cisplatin, interleukin-2, cyclosporine, enzastaurin, tacrolimus, pegylated liposomal doxorubicin, carboplatin, gallium nitrate, deoxyspergualin, and drugs targeting the epidermal growth factor receptor (EGFR) including cetuximab and panitumumab [45]. Other drugs often used in cancer patients that may precipitate hypomagnesemia include aminoglycoside antibiotics, amphotericin B, pentamidine, gentamicin, and diuretics [46].

Magnesium can be replaced either orally as magnesium oxide or as a gluconate or parenterally as magnesium sulfate. If hypomagnesemia is mild (level > 1.2 mEq/L) and the patient is asymptomatic, oral replacement is feasible; however, oral supplementation with magnesium may be ineffective due to malabsorption or diarrhea. Symptomatic hypomagnesemia should be treated with intravenous magnesium supplementation; standard dosage is 2–4 g of 50% magnesium sulfate diluted in saline or dextrose over 1 h. Administration faster than 1 h may result in bradycardia, heart block, or hypotension. Hypomagnesemia may worsen despite ongoing replacement in which case stopping chemotherapy for a few weeks may be helpful [45]. Levels of magnesium typically return to normal 6 weeks after termination of chemotherapy.

## Cushing's Syndrome

Patients with Cushing's syndrome develop elevated serum cortisol levels secondary to either a corticotropin (ACTH)-producing pituitary tumor, excessive cortisol secretion by either an adrenal adenoma or carcinoma, or ectopic secretion of ACTH by a nonpituitary tumor. Rarely, tumors ectopically secreting corticotropin-releasing hormone and excess cortisol secretion by ACTH-independent nodular hyperplasia of the adrenal cortex result in Cushing's syndrome.

Chronic exposure to excess glucocorticoids in Cushing's syndrome results in a large spectrum of symptoms, none of which are pathognomonic, including progressive central obesity involving the face, neck, trunk, and abdomen with sparing of the extremities; glucose intolerance with symptoms of polydipsia and polyuria; proximal muscle weakness; hypertension; psychological disturbances; hyperpigmentation (increased ACTH only), easy bruisability, skin atrophy, and striae; bone pain or osteoporosis; and oligomenorrhea or amenorrhea. The presence of androgen excess in women with adrenal cancer or ACTH-

stimulated hyperandrogenism can cause virilization, hirsutism, altered libido, menstrual irregularities, and acne. The simultaneous development and increasing severity of symptoms should raise suspicion for Cushing's syndrome. Increased risk for infectious complications, cardiovascular disease including myocardial infarction, stroke and pulmonary embolism [47], as well as osteoporosis is noted in patients with endogenous Cushing's syndrome. Neurocognitive changes which include insomnia, depression, and memory loss may occur.

Since symptoms are nondiagnostic, Cushing's syndrome must be confirmed by laboratory work-up. Initially, a history excluding exogenous glucocorticoid intake must be sought, including a careful review of medications (all glucocorticoids, megestrol acetate, inhaled or topical steroids). Pseudo-Cushing's syndrome with elevations in cortisol levels can occur in patients with bacterial infections, severe obesity, psychological distress, or rarely chronic alcoholism. Initial laboratory work-up as suggested by the 2008 Endocrine Society Guideline [48] consists of at least two first-line tests—two measurements of urine free cortisol, two measurements of late-night salivary cortisol, 1-mg overnight dexamethasone suppression test, or the longer low-dose (2 mg/day over 48 h) dexamethasone suppression test. For patients with normal results, follow-up testing in 6 months is recommended; however, if patients have normal results but exhibit clinical symptoms highly suggestive of Cushing's syndrome or one abnormal test, an evaluation by an endocrinologist is advised [48].

After the confirmation of hypercortisolism, the next step is to measure serum ACTH levels to differentiate between ACTH-dependent (pituitary or nonpituitary ACTH-secreting tumors) and ACTH-independent (adrenal source). Patients with ACTH-independent Cushing's syndrome are identified by a low plasma ACTH concentration [<5 pg/mL (1.1 pmol/L)] and subsequently will need a thin-section CT to evaluate for an adrenal mass. Adrenal carcinomas are typically larger than adenomas and distinguished by evidence of necrosis, hemorrhage, and calcification on the CT scan [49]. MRI may provide additional information regarding malignant nature of the adrenal tumor and positron-emission tomography (PET) scanning with fluorodeoxyglucose in identifying unilateral adrenal tumors.

The majority of patients with ACTH-dependent hypercortisolism have pituitary corticotroph adenoma (Cushing's disease). Intermediate ACTH concentrations between 5 and 20 pg/mL require corticotrophin-releasing hormone (CRH) testing. Patients with Cushing's disease respond by secreting ACTH and cortisol within 45 min after CRH administration. The remainder of ACTH-dependent patients (ACTH levels >20 pg/mL) should have a high-dose dexamethasone suppression test and a CRH stimulation test to distinguish between Cushing's disease and ectopic ACTH-secreting tumors. If testing is consistent with Cushing's disease, a pituitary MRI should be obtained. If a lesion >6 mm is detected, no further testing is warranted; however, if the imaging on MRI is unclear (<6 mm), petrosal sinus sampling is recommended [50].

Transsphenoidal microadenectomy is the treatment of choice for patients with Cushing's disease. For a patient not cured by transsphenoidal resection of the pituitary tumor or in whom fertility is a prominent concern, pituitary irradiation is the next treatment option. Bilateral adrenalectomy followed by lifelong glucocorticoid and mineralocorticoid supplementation is often needed in some patients who don't want to receive radiation treatment. Cytotoxic chemotherapy for locally invasive pituitary tumors or other aggressive carcinomas, which have metastasized to the central nervous system, is an alternative treatment option. When surgery is delayed, unsuccessful, or contraindicated, medical therapy with steroidogenesis inhibitors or glucocorticoid antagonist is considered [51].

Surgical excision is the optimal treatment for ectopic ACTH syndrome. With tumors that are nonresectable, treatment to control symptoms of hypercortisolism with adrenal enzyme inhibitors including ketoconazole, metyrapone, and etomidate is considered. For patients with primary adrenal disease, treatment is directed at removal of the adrenal gland(s). Mitotane can also be used as medical adrenalectomy in patients with indo-

lent tumors, and in patients with inoperable, residual, or recurrent disease, mitotane may provide palliation [52].

## Hypoglycemia of Malignancy

Hypoglycemia associated with malignancy is relatively rare. The three main etiologies include the most common cause which is nonislet cell tumor hypoglycemia (NICTH) [53], the most well known which is hypoglycemia due to insulin secretion by islet cell pancreatic tumors [54], and any advanced metastatic carcinoma that has infiltrated the liver or adrenal glands resulting in hypoglycemia [55]. The initial evaluation for hypoglycemia involves careful evaluation for other possible causes of hypoglycemia. After a thorough work-up excluding other causes, curative or palliative treatment of hypoglycemia of malignancy can be initiated.

Clinical findings in cancer patients with hypoglycemia include altered consciousness, obtundation, or bizarre behavior and are not different from hypoglycemia secondary to nonmalignant causes. Whipple's triad includes the presence of hypoglycemic symptoms after fasting or heavy exercise, low plasma glucose levels at the time patient is experiencing symptoms, and relief of symptoms with glucose supplementation to normalize the value that indicates hypoglycemia of malignancy. Since hypoglycemia secondary to malignancy is quite rare, a thorough evaluation for other causes should be initiated. In diabetic patients, medications and oral intake should be reviewed. An evaluation for infection or organ dysfunction should be initiated. Surreptitious use of insulin or other hypoglycemic agents should be considered in patients without a history of diabetes. In patients with cancer, the diagnosis of tumor-associated hypoglycemia may be difficult, and evaluation of glucose, insulin, C-peptide, insulin-like growth factor I and II levels, sulfonylurea, and meglitinide screen may be useful [53].

Insulinomas, well-known but relatively rare tumors, almost exclusively occur in the pancreas. Approximately 90% of insulinomas are benign, and the production of insulin by beta-cell tumors leads to hypoglycemia. Surgical treatment is often curative [56]. Hypoglycemia associated with NICTH involves a variety of tumors including mesenchymal, epithelial, and hematopoietic in origin, the most common being fibrosarcoma, mesotheliomas, leiomyosarcomas, hepatomas, lung cancers, gastric malignancies, and pancreatic exocrine tumors [56]. The secretion of insulin-like growth factor II, which is capable of activating insulin receptors, results in hypoglycemia in NICTH [57]. Metastatic cancer infiltrating the liver or adrenal glands may result in hypoglycemia secondary to tissue destruction or another yet undefined mechanism.

An initial treatment includes the administration of glucose via standard regimens in order to normalize mental status and improve consciousness. After a patient has been stabilized, treatment is directed at the underlying malignancy, either curative or palliative. For insulinomas and tumors associated with NICTH, surgical excision may be curative. Palliative treatment in concert with an endocrinologist may provide symptomatic relief and, depending on the tumor, include treatment with prednisone with or without somatostatin analogs [53].

## Hypothyroidism

The clinical presentation of hypothyroidism, the most common hormone deficiency, is highly variable and may include symptoms of fatigue, cold intolerance, weight gain, constipation, myalgias, and dry skin which may go undiagnosed in cancer patients. Hypothyroidism may result in metabolic abnormalities including hypercholesterolemia, macrocytic anemia, hyponatremia, and elevated creative kinase [58] and result in heart failure, psychosis, and coma if left untreated. Since symptoms are variable and difficult to recognize in cancer patients, laboratory testing with thyroid-stimulating hormone (TSH) concentration and free thyroxine (T4) concentration is required. Primary hypothyroidism, dysfunction of the thyroid gland, is characterized by high TSH and low T4 concentrations. Secondary

hypothyroidism, in the setting of pituitary disease, is characterized by low TSH and T4 levels. In the majority of hypothyroid patients, treatment consists of thyroid hormone replacement.

Patients at risk for hypothyroidism include individuals with a family history of autoimmune thyroid disorders, patients treated with head and neck irradiation or surgery, and patients treated with irradiation or certain chemotherapy drugs for cranial and spinal, thyroid, and gastrointestinal malignancies [59]. Risk of primary hypothyroidism is dose dependent and associated with radiation to the neck, mantle, C2–T2 spine, brain stem, supraclavicular, and nasopharyngeal regions and total body irradiation [60]. Incidence is roughly 50% of patients who received radiation for a head and neck malignancy [61] indicating a need for monitoring thyroid function. In addition, new chemotherapy such as tyrosine kinase inhibitors may cause transient and profound hypothyroidism in 25–70% of patients [62]. Also, vascular endothelial growth factor receptor blockers, interleukin-2, and bexarotene, a selective retinoid X receptor agonist, have been associated with thyroid dysfunction.

Secondary hypothyroidism occurs when diseases interfere with hypothalamic TSH-releasing hormone (TRH) production and delivery to anterior pituitary gland or with TSH production. Pituitary adenomas, radiotherapy, and surgery resulting in secondary hypothyroidism are the most common causes [63]. The emergence of targeted immunotherapy, cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1, has been associated with both primary and secondary hypothyroidism and hypophysitis [64].

## Hypogonadism in Men

Male hypogonadism, characterized by low concentrations of testosterone as a result of disruption in hypothalamic-pituitary-gonadal axis, is not uncommon in cancer patients. Primary hypogonadism results in high amounts of gonadotropins, particularly luteinizing hormone, and testicular failure. Secondary hypogonadism results from dysfunction of the hypothalamus or pituitary gland resulting in secondary testicular failure and diagnosed by low levels of luteinizing hormones. Symptoms of hypogonadism include fatigue and diminished energy, difficulty with concentration, depression, sleep disturbances, reduced muscle mass, and decreased libido [65]. Low testosterone is also associated with osteoporosis, metabolic syndrome, and cardiovascular disease. Primary hypogonadism can result from testicular disease, gonadal surgery or radiation therapy, as well as systemic chemotherapy. Secondary hypogonadism can be the consequence of radiation or surgery of tumors in the central nervous system. In addition to chemotherapy, chronic opioid therapy, corticosteroids, and megestrol acetate may result in hypogonadism. In a healthy, non-cancer patient population, the threshold for testosterone levels which result in symptoms ranges from 250 to 400 ng/dL, and more research is needed in patients with cancer.

The benefits of testosterone supplementation are unclear. Standard guidelines [66] exist to help guide clinicians regarding replacement of testosterone; however, the risks and benefits of testosterone replacement for patients with cancer or cancer survivors are unclear. In male patients, a history of prostate or breast cancer is a contraindication for replacement.

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# Part VI

# Reproductive

# Sexual Problems in Patients with Cancer

16

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## Introduction

Advances in the diagnostic and treatment modalities applied in the field of oncology during the last decades have led to the prolongation of overall and cancer-specific survival in patients with many different types of tumors [1]. Consequently, quality of life (QoL) preservation has emerged as an important additional issue in oncologic patients. There is no doubt that sexuality is considered a factor of capital importance, closely related to QoL, which can only be fully and satisfactorily developed and maintained if the body and soul of a human being are in harmony. Therefore, it is crucial to consider both the somatic and the psychosocial oncologic effects [2]. For the second edition of this book, we completely reviewed the literature. Despite a number of new publications, there are not many new insights or changes. We carefully adapted the chapter to keep it up to date always having in mind that it should function as a practical approach to this for most people complex field.

- Sexual function is an important factor for quality of life in patients with cancer.
- Consider both the somatic and the psychosocial oncologic effects on the sexuality of a patient with cancer.

Both medically and socially speaking, the diagnosis "cancer" catapults the affected person abruptly from a previously healthy to a severely ill human being and leads to profound consequences in all aspects, including the relationship with a partner and sexual life. Sexuality may be affected by both the disease and the necessitated treatment. Concretely, the degree of harm is defined by the type of cancer and the treatment

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implemented. Nevertheless, another important factor is the individual's psychological resources defined by his/her ability to develop specific coping mechanisms, which in turn is highly associated to the type and degree of the environmental support, the level of education, and the situation before the disease. The following can determine the extent of sexual dysfunction:

- Type and extent of cancer
- Its mandatory treatment
- Sexual function before
- Available coping mechanisms
- Support by the social network of a patient with cancer

## Common Mechanisms Leading to Sexual Problems in Patients with Cancer

Sexual problems in patients with cancer can be caused by the anatomical or functional organ impairment due to the presence of the tumor or may result from the treatment applied (surgical procedure, chemotherapy, irradiation), which may be very aggressive, harming not only the tumor cells but also healthy adjacent or remote tissues and body structures such as nerves and blood vessels. Furthermore, the problems can also be psychological in nature through different body feeling, changing in neurotransmitters and central nervous system deregulation. In addition, psychosocial problems may arise with numerous consequences for the patient and the partner. This specific type of problem has received a central scientific interest since the late 1980s. There is much variety in reactions ranging from tension within the couple and misunderstanding to strengthening of their relationship to fight as a union against the illness. Therefore, the partner should always be observed and included in all discussions and decisions on patients' treatments concerning sexuality. To get one step further, it could be claimed that sexuality impairment in terms of cancer should always be considered as a problem of the couple rather than a unique problem of the patient [3].

- Address relationship between patient and partner.
- Consider sexual problems firstly as a problem of the couple.

A definition of sexuality is generally hard to give. Simply speaking, human sexuality is a kind of attitude (experience and expression) driven by the common intuitive tendency for reproduction, which is highly individualized through control by superior psychocognitive centers developed variably among people on the basis of their different built-in characteristics and experiences. For practical reasons, the integrated function of sexuality may be schematically subdivided into the following series of consecutive interrelated events following the human sexual response cycle [4]:

- Sexual desire
- Arousal with erection in males and lubrication in females
- Orgasm with ejaculation in males and culmination in females
- Resolution

Sexual problems in oncologic patients may stem from the impairment of each one of these events in separate or in any combination, and some examples are given below. Fertility impairment is beyond our scope and will be discussed elsewhere in this book.

- Each phase of the sexual response cycle can be affected.

Sexual desire or arousal may be compromised via different mechanisms such as general somatic pain and fatigue due to cancer itself or therapy, deregulation of the hypothalamic-pituitary-gonadal axis via hormonal manipulations (e.g., in metastasized prostate or breast cancer) including surgical castration (e.g., in metastasized prostate cancer, bilateral testicular, and ovarian cancer), and pain during or after intercourse (dyspareu-

nia) following vaginal reconstruction after radical uterus extirpation (e.g., in cervical or muscle-invasive bladder cancer). Postoperative pain may eliminate sexual feelings, while sensitivity may be lost after surgery, irradiation, or chemotherapy, compromising nerves. Furthermore, symptomatic treatment, for example, against vomiting, depression [5], epileptic seizures, or pain, can have an additional direct or indirect effect on sexual function. For example, pain medication such as morphine can lower testosterone production significantly [6], and sleep medication can disturb nocturnal erections.

Erectile dysfunction (ED) may be caused by hormonal manipulations (e.g., in metastasized prostate cancer) or by surgical procedures or irradiation in the small pelvis potentially damaging penile innervation and blood supply (e.g., radical prostatectomy, external beam irradiation for localized prostate cancer). Disorders of ejaculation may appear (anejaculation after radical prostatectomy or retrograde ejaculation after retroperitoneal lymph node dissection). On the other hand, female patients are often unable to achieve orgasm and experience dyspareunia due to insufficient lubrication after irradiation or vaginismus (painful contraction of the pelvic floor muscles and vagina).

Apart from the somatic mechanisms briefly mentioned above, psychological mechanisms are also crucial. The patient experiences difficulties accepting and coping with a potentially life-threatening problem. This psychological burden has also consequences on the patient's social role, which often gets limited since the patient is or feels unable to run a normal life overwhelmed by the so-called experiential problems (rapid mood changes, anxiety for the future, etc.), even with financial consequences in the extreme cases. Under this psychological pressure, sexuality may be set aside. This fact is often complicated further by the changed body image [7]. Breast amputation, orchiectomy, and abdominal radical operations for rectal-, bowel-, or muscle-invasive bladder cancer, with stoma formation, can lead, for example, to a completely different body shape (Fig. 16.1), while chemotherapy can diminish hair growth. Changed body image in turn results in self-confidence deprivation and lowering of self-esteem driven by thoughts of the loss of sexual attractiveness. On the other hand, the partner's sympathy may result in good intended avoidance of seeking physical contact, which may be, though, often misinterpreted by the patient as rejection or neglect, erroneously attributed to the loss of attractiveness.

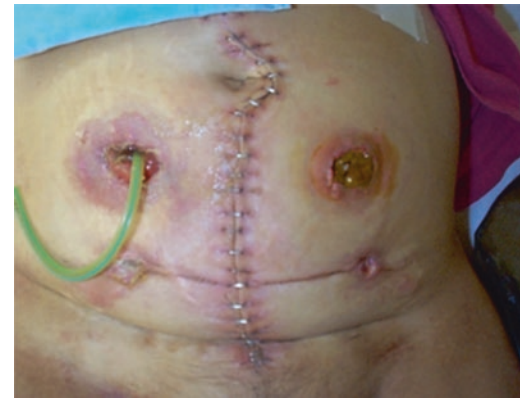

**Fig. 16.1** Changed body shape due to exenteration

In conclusion, sexuality impairment in terms of cancer has an underlying multidimensional and multifactorial pathophysiology. It stems from a combination of distinct but interrelated problems (physical, psychological, relational, social, existential [8], and experiential), secondary to the disease, that may ruin the relationship of the couple. Therefore, cancer should be considered an abrupt psychological trauma rather than a purely somatic, life-threatening disease. The psychotraumatic consequences are revealed repeatedly and unexpectedly in time, provoked by numerous situations or events, which the patient tries desperately to avoid and finally lead to a true post-traumatic stress disorder. This also holds true for the partner [9, 10]. Therefore, it is crucial to overcome the barriers of avoidance and provide support to the affected couple as early as possible by starting talking about the potential sexual problems that may accompany the underlying disease.

- Start talking about sex as early as possible.

## In Which Cancers Should Hidden Sexual Problems Be Suspected?

In general, sexual problems are most likely present in cases where the external or internal genitals are involved (prostate, testicular, penile, breast, uterine, ovarian, and cervical cancer) because sexual function is directly compromised [11, 12]. Sexuality may either be harmed immediately or eventually and insidiously over time during the disease course such as, for example, ED after irradiation of the small pelvis or indirectly due to psychological imbalance. It has been shown that QoL is still relatively good during the period of chemotherapy but worsens after 3 and 6 months compared to baseline, mainly in the sexual and physical domains [13].

Nevertheless, there may be an extensive variability among different patients regarding the degree of physical/psychological impairment and the consequent sexual dysfunction, so that no clear correlation can be detected. On the other hand, sexual dysfunction cannot be predicted well by somatic or treatment aspects, and therefore the psychological component should be taken into account [14] as well as the degree of sexual functioning prior to the diagnosis and treatment initiation.

> Take somatic and psychological factors into consideration as well as the sexual function before the onset of the disease.

It is of utmost importance not only to prescribe medication or apply sex therapy but also to unmask the main problem of the couple, familiarize them with it, and give solutions, which most of the time are individualized and multimodal.

## Trying to Unmask Sexual Problems: Talking About Sex and the Role of the Sexologist/Sexual Therapist

It is of importance that the therapist initiates and frees talking about sex. In order to prevent surprising the patient with this subject, a patient metaphor can be used: "I am currently treating a female/male patient with cancer who told me …, do you recognize these complaints?" It is also an option to generalize: "Many female/male patients with cancer have difficulties in sexual contact, how is this for you?"

When the subject is successfully brought up, it is important to obtain more detailed information about the following topics by asking proper questions:

- Which of the phases of the sexual response cycle is affected?
- Is it a primary or secondary problem?
- Is it a generalized or situated problem?
- What about masturbation and morning erections?
- When did the problem start and what is its course over the time?
- What about strengthening, are there maintaining factors?
- In which context does it occur? How is it influenced by stimuli?
- How was the sexual functioning in previous relationships/before onset of the illness?
- Any psychological traumatic events in the past?
- Any other comorbidity?
- Is the use of any medication negatively influencing sexual function?
- How was the sexual development of patient and partner?
- Is there a partner and how is the relationship with him/her? Is there communication between the partners and of which quality is it?
- What is the sexual wish of the patient and the partner (request for help)?

Afterward, it is important to regard the sexual problem from a biopsychosocial point of view to see what the physical (hormonal), psychological (changed self-image, fear), and relational (change of role) consequences of the cancer are that influence sexual functioning.

Be aware that the patient's partner is involved in these sessions, since sexual functioning concerns both.

Lastly, there should be a possibility to refer the patient and their partner to a sexologist.

Ideally the sexologist should be part of the treatment team in case of sexual problems [15].

> Start the initial talk about sex and find your own manner taking the biopsychosocial model into account. Refer the patient to a specialist if needed.

## What Can Specialized Nurses Do for People Suffering from Cancer and Disturbed Sexuality?

As the first and most important step is to start talking about sex (feelings, changes due to cancer, and emerging problems), it should ideally be done very early during the disease course by the responsible physician or surgeon if an operation likely to compromise sexual organs has been planned [16]. Specialized nurses play an important role, too [17], because they are often in a more intensive and regular contact from the beginning with the patients and their partners, but also during postoperative, chemotherapy, and irradiation periods. At our institution, for example, specialized "stoma nurses" are involved acting as well as andrological consultants (Table 16.1).

Many nurses find it difficult to discuss sexuality with a patient and his/her partner. This may be related to a lack of knowledge and experience to make sexuality discussable. The personal background of the nurse and the work setting make it more or less important for the nurse to be

**Table 16.1** Possible functions of a specialized (andrological) consultant

| |
|---|
| An initial interview to draw conclusions by clarifying: |
| • The problem and how it is experienced |
| • The related emotions |
| • The major concerns that may be confounded by less important issues |
| • The level of communication between patient and partner |
| • The level of knowledge on proper sexual function |
| A more intensive talk after drawing conclusions in order to: |
| • Ensure presence of couple's motivation to follow treatment |
| • Try to find an individual solution |
| Collection of an adapted anamnesis consisting of: |
| • A medical part on the |
| – General health state |
| – Surgery/irradiation of the small pelvis |
| – Use of medication influencing sexual function |
| • Since when and in which qualities of their sexual function the patient and his/her partner are |
| – Satisfied with |
| – Dissatisfied with |
| • How big is the problem growing from this? |
| • What are the personal sexual wishes of patient and partner and to let them talk about frankly? |
| • What could be a desirable and acceptable solution for them? |
| • How far are they ready to go for a solution? |
| • What kind of therapy has been done up to now? |
| Treatment initiation: |
| • Support the patient and his partner with audiovisual information about the use of intracavernous autoinjection therapy and penis vacuum pump in order to achieve sufficient erection, and see if this is a possible option for them |
| • Determine the dosage and teach how to inject intracavernously |
| • Educate the handling with the pump |
| • Instruct small exercises as house work to activate perfusion of the penis |
| • Initiate a conversation between the partners at home on how they personally see their sexual life together and how they can/want to proceed and work on it |
| Teamwork: |
| • Close cooperation with andrologist and sexologist in a multidisciplinary network with interdisciplinary case discussions on a regular base in order to accompany the patient from different angles at the same time |

able to talk about sex with a patient and his/her partner.

But it should never depend on the setting or role in which a nurse is actually working. When seeing a patient either as an outpatient or in an inpatient setting, a nurse should be able to realize that having cancer and its treatment usually affects sexuality and intimacy. Ideally, not the nurse but the patient determines the time when it should be discussed. However, the nurse paves the way heretofore. In order to know when the patient finds it desirable to talk about his/her sexuality, first it must be asked if it is okay and at which time.

Specialized nurses, such as oncology, mammacare, ostomy nurses, etc., see and talk to the patient and his/her partner already at the time the cancer diagnosis has been established.

Nurses working on the wards with inpatients only have contact with the patient later in the treatment process, irrespectively if it is curative or palliative.

It is obvious that deeper knowledge and profound skills may be expected from specialized nurses to discuss sexuality. This does not permit the "basic" nurse on the ward to behave in a passive manner but, in contrast, to be proactive and ensure that all questions about sexuality for patients and partners are truly answered. Furthermore, new questions for the patient and his/her partner can arise during treatment.

What can patients expect from the (specialized) nurses?

- Open attitude
- Talking about sexuality in a professional manner
- Knowledge about what effects cancer and its treatment can have on male/female sexual function
- Open to receive the signals of sexual and intimacy problems
- Adequate referral on individual needs

A dedicated nurse needs therefore the following skills:

- Knowledge of various types of cancer and their treatment
- Knowledge of the physical and mental effects of cancer and its treatment on sexuality and intimacy
- Skills to empathically talk about sexuality and intimacy with patients and partners

The form of the interview should be free and open with enough space for questions and emotional expression. Positive feelings may develop if the couple realizes that the disease prognosis might not be that ominous and QoL is still important. Joint partners' efforts against the disease may strengthen their relationship. Therefore, encouraging revealing the sexual problems and seeking help can further motivate patients toward life, which in turn influences positively their sexuality and vice versa.

## The Terminally Ill Patient

On the other hand, even terminally ill patients still have both the right and the wish for QoL and therefore sexual contacts. As people realize that their life approaches the end, they often experience a stronger need for more intensive relationships especially with their partners getting positive feelings out of it. The differentiation between intimacy and sex is here important to be stressed and clarified during the talk because the meaning of these terms is often confused and misunderstood. The patients' partners often suffer more by lack of intimacy than absence of sex. Therefore, it is important to legitimate intimacy not followed necessarily by sex. However, the limitations should be understood and accepted by both partners. This precludes conflicts and the potential for becoming distant in the future.

> In terminally ill patients, emphasize the importance of intimacy and make clear that it does not have to be followed by sex in order to maximally achieve QoL.

All these issues should be addressed but not necessarily during the initial interview. It is

important to unmask the couples' fears and try to motivate them toward QoL in order to facilitate treatment success. Unfortunately, however, this target cannot be reached in every case.

## Limitations in Treatment Application

For therapeutic success, it is crucial to take into account the patient's actual activity potential as well as the priority that sexual desire has been assigned by the couple especially prior to the onset of the disease. The malignant disease and treatment may lead to such a somatic impairment that daily activities can be very much limited and therefore sexual activity is also physically impossible. The psychological distress may also be so intense that it definitely prevents patients from even thinking of being sexually active. The situation is even worse in cases where sexual life has been already impaired for unrelated reasons before the disease onset or in cases that sex has been assigned a low priority in the couple's list of activities. Nevertheless, in the ideal case, sexual surrender can be increased.

## Giving Professional Help and Treatment

In an ideal setting, the couple has access to an interdisciplinary network consisting of a specialized gynecologist for the female patient and of an andrologist backed up by an andrological consultant for the male patient, together with a sexologist, a psychologist or psychiatrist, and a specialized physiotherapist, working closely with the oncologic surgeons, medical oncologists, radio-oncologists, and general practitioners. In such a multidisciplinary network, multimodal therapy can be guaranteed.

When patients with cancer are transferred for sexual problems, it is mostly due to physical rather than psychological complaints, which are easier described by the patient and conceived by the doctor. It depends on the examiner's skills to find out the degree to which the psychological component has to be handled.

Sexual problems may already have preexisted long before the diagnosis of cancer [18]. Such problems should be detected for the treatment to have chance of being successful. Preinterventional ED, for example, is unlikely to improve afterward, but it is important to start as early as possible with supportive treatment in order to preserve the existing erection status. Open talk is strongly recommended. However, at least in the beginning, it may be very hard for the patient to speak freely about his/her sexual feelings and prior expectation fulfillment. Especially in the case of a newly diagnosed cancer and treatment initiation, variable feelings may appear such as shame or fear, diminishing sexual interactions, and desire and longing for aid or comfort by the partner.

Therefore, it is important to support the couple, showing that the problems are seriously taken into account, and try to convince them that their situation and reactions could be expected under such extreme circumstances. Due to the cause-effect variability and the interindividual variation of complaints, the solution sought should be most of the times individualized based on the various sexological, psychological, and medical approaches available in the current treatment armamentarium.

## Practical (Technical) Solutions

Somatic problems should be at least initially treated with conventional somatic medicine. If the patient's problem turns out to consist of more levels, the treatment should be adapted accordingly. The issue becomes complicated if the somatic problem is irreversible such as an abrupt loss of menstruation due to cancer therapy or permanent such as in stoma patients, aggravated by fecal or urinary incontinence. In such cases, coping strategies have to be developed so that the situation is acceptable for the patient and his/her partner, which is often very hard to achieve and takes time and effort by everybody involved.

## Males

In cases of symptomatic lack of testosterone, which is not intended as a hormonal ablation in prostate cancer treatment, hormonal substitution of testosterone could be used to improve desire, erections, and well-being. According to the actual EAU Guideline Male Hypogonadism [19] and the ISA, ISSAM, EAU, EAA, and ASA recommendations [20], this is a safe and valid treatment.

There are several phosphodiesterase type 5 inhibitors (PDE5i) on the market for the treatment of ED, e.g., sildenafil, tadalafil, vardenafil, and avanafil. Since they only work as amplifiers, their action requires a degree of remaining nerve function and uncompromised blood supply to the penis, after radical prostatectomy, for example. In the case of postoperative ED, which is difficult to measure [21], it is important to instruct the patient how to use the medications and start treatment early [22]. If postoperative treatment initiation is delayed, there is a risk of penile cavernous bodies' fibrotic degeneration. Before switching from one member of the group to another or to other options, the medications should be taken long enough to rule out failure or that side effects do not fade out with time. Administering a daily dosage prevents pressure for sexual action on a certain time slot. However, prophylactic penile rehabilitation has been shown not to be as efficient as originally believed based on basic research and multicenter studies [22–25].

If PDE5i are not considered a therapeutic option due to failure, side effects, or contraindications, vacuum pump devices are available as an alternative. An erection is achieved passively through negative pressure applied to the penis, which is maintained by means of an elastic band at the penile base for a maximum of 30 min. Daily use of the device is possible. The success rate can be up to 70–94%. If it works, the technique represents a good and noninvasive option, given that the patient together with his partner accepts such an artificial way of producing erections. Potential side effects include pain during the application and the penis feeling cold.

As a second-line therapy, intracavernous autoinjection is another but invasive option. To achieve erection, the patient has to inject a certain amount of alprostadil (prostaglandin E1) leading to relaxation of the smooth muscle cells or a combination of papaverin and phentolamine (alpha-blocker) shortly before intercourse. This makes it necessary to include the injection procedure in the sexual foreplay. Potential side effects include pain at the site of injection; priapism (unintended, painful erection for more than 4 h in duration), which represents a urologic emergency due to possible irreversible cavernous damage; and Peyronie's disease, i.e., plaque formation in the corpora cavernosa leading to an abnormal curvature of the penis. A more patient-friendly solution with fewer side effects is the so-called medicated urethral system for erection (MUSE). Using a specially constructed applicator, the patient introduces an alprostadil-containing pellet into the distal part of his urethra. This option is, however, less effective and causes a burning sensation of the penis and urethra; therefore it has to be accepted by the patient as well as the topical application of alprostadil which is only available in selected countries.

As a third-line therapy, the implantation of a penile prosthesis (semirigid or inflatable) can be satisfying for both the patient and his partner. However, it is considered as an end option because it is invasive and irreversible, and the patient together with his partner has to be counseled carefully, and the prosthesis must be a suitable item for them. The use of new, coated prostheses has dropped the incidence of infection.

## Females

For stoma-carrying and breast cancer patients, special lingerie has been developed. Relaxing exercises of the pelvic floor can be initiated in cases of dyspareunia, and a vaginal lubricant can be used in case of a dry vagina, which can make sex easier and more satisfying for both partners. Therapy of the underlying anxiety can also be of help. Unfortunately, for some

women there will be a total loss of vaginal penetration as their vagina has been completely closed due to the radicality of the surgical procedure or is otherwise so constricted due to irritation that no sexual intercourse is possible anymore.

**Conclusion**

Preservation of sexual function in patients with cancer represents an important issue, which can be a driving force to fight against the disease. Sexuality may, however, be compromised. It is very important that the sexual problems of the patient are detected also with the aid of the partner. For the therapy, the different levels of imbalance have to be taken into account and treated by an interdisciplinary specialized group ideally consisting of an andrologist in case of a male or a gynecologist in case of a female patient, a specialized andrological consultant, a sexologist, a psychologist or psychiatrist, and a physiotherapist specialized in pelvic floor exercises.

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# 17 Sterility, Infertility, and Teratogenicity

Hele Everaus

## Introduction

The recent advances and success of cancer therapy, particularly for childhood cancer and patients who had cancer during their reproductive age, significantly increased the demand for selecting the most fertility-friendly approaches for cancer treatment. Cancer itself and different modalities of cancer treatment, including chemotherapy and radiotherapy (RT), are known to have significant deleterious effects on human fertility, both in men and women.

As long as cancer treatments cannot be exclusively targeted to tumor cells, damage to the reproductive system will remain an important aspect of cancer morbidity.

Male and female germ cells vary in their sensitivity to the mutagenic effects of chemotherapy and RT, depending on their stage of maturation and the agent used. No increase in genetic defects or congenital malformations was detected among children conceived to parents who have previously undergone chemotherapy and RT. In female cancer patients, miscarriage and congenital malformations are not increased following chemotherapy.

With improved survival rates among young patients with cancer, recent bench-to-bedside translation of new techniques to preserve fertility, increased awareness of choices for the preservation of fertility, and options for family planning are now being offered to patients who have received a cancer diagnosis. Concerns about fertility are similar for men and women. Several studies conducted over the past years have demonstrated that young women and men are concerned about their endocrine health and the fertility consequences of cancer treatment. Patients who are not informed about later fertility concerns at the time of diagnosis have stress levels in the range of posttraumatic stress disorder during survivorship [1]. Their opportunities for intervention differ considerably. Four main challenges are related to the preservation of fertility in people with cancer: the improvement of patient-specific, life-preserving treatments, the identification and reduction of the harm that cancer treatment poses to fertility, the expansion of safe and effective options for fertility treatment, and the creation of symptom management plans for patients who lose endocrine function from the gonads as a consequence of cancer treatment [2]. The goal is to provide and develop methods of fertility preservation.

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## Direct Effect of Cancer on Human Reproduction

Cancer, in particular, genital cancer, has impact on human reproduction through a direct effect on the gonads as well as through effects on endocrine glands.

The direct effect is clear when the malignant tumor involves the genital system—ovaries and uterus in the female and testicles in the male. Different mechanisms can participate in the induction of adverse effects by cancer itself on human fertility. Cancer evokes a systemic response of the body. This response can be mediated by cytokines. Stress associated with a cancer diagnosis can impair fertility through disturbances at the hormonal levels [3].

Systemic effects, such as fever, have also been implicated adversely affecting semen parameters. An immunological mechanism can be involved as there have been found to be disturbances in the balance between subpopulations of T lymphocytes, which can be the cause of dyspermia in Hodgkin disease patients [4]. There is evidence of a shared etiology for the malignant process and reduced fertility in testicular cancer as part of the testicular dysgenesis syndrome [5].

## The Effect of Cancer Treatment on Female Fertility

### Chemotherapy

Chemotherapeutic drugs are interrupting the vital cell processes and arresting the normal cellular proliferation cycle. The chemotherapy-related risks are connected to the patient's age, the specific chemotherapeutic agents used, and the cumulative dosage administered [6]. Women over 38 years of age have a higher incidence of complete ovarian failure and permanent infertility in comparison with younger women [7]. The ovaries of younger women can tolerate greater doses.

Patients with early-stage breast cancer who do not receive chemotherapy and whose baseline fertility is within the normal range have a relatively small treatment-related threat to fertility. Patients with breast cancer who have tumors larger than 1 cm, cancer that is metastatic to lymph nodes, or hormone-receptor-negative disease often undergo chemotherapy [8]. These patients face a greater threat to fertility [9]. Chemotherapeutic agents used for the treatment of breast cancer include cyclophosphamide, fluorouracil, doxorubicin, paclitaxel, and docetaxel. Alkylating agents (AA), including cyclophosphamide, are toxic to the ovaries [10].

AA have a severe effect on human fertility. Ovarian fibrosis and follicular and oocyte depletion occur [11]. According to Meirow [12], AA are associated with the greatest risk among all chemotherapeutic agents for inducing ovarian failure. The following agents have been shown to be gonadotoxic: busulfan, melphalan, cyclophosphamide, and procarbazine. *Cisplatin* and analogs cause ovarian failure and chromosomal damage. *Vinca alkaloids* induce aneuploidy. Damaged oocytes could produce malformed fetuses. *Antimetabolites*—insufficient data are available on the effects of antimetabolites on female germ cells. *Anthracycline antibiotics*—adriamycin and bleomycin are female-specific mutagens. Etoposide induces pericentric lesions and aneuploidy in oocytes [13]. The addition of adjuvant endocrine therapy in patients older than 40 years was more likely to result in permanent chemotherapy-related amenorrhea [14].

Providers should investigate and discuss the relative gonadotoxicity of any protocol with patients of reproductive age. Fertile Hope provides a risk calculator that may be a useful resource for patients and providers as a starting point for discussion about the reproductive side effects of various treatment protocols [15].

Biologicals are a relatively new class of anticancer drugs that are typically targeted toward specific receptors, growth factors, or other messaging cascades. Due to their relatively recent introduction into clinical practice, there are a limited number of publications concerning the potential gonadotoxicity of these agents [16].

The potential gonadotoxicity of these agents seems to be agent specific. Bevacizumab, a monoclonal antibody that targets vascular

endothelial growth factor, has been demonstrated to induce amenorrhea, a higher incidence of acute ovarian failure, and a lower incidence of subsequent recovery of ovarian function in patients who received bevacizumab [17].

## Premature Ovarian Failure

The risk of premature ovarian failure (POF) must be considered in female patients with cancer.

Regarding the teratogenic effects of chemotherapy, studies that have monitored pregnancies in women exposed to chemotherapy before conception have not registered increased rates of miscarriage or congenital abnormalities in comparison with the general population.

## High-Dose Chemotherapy in Bone Marrow Transplantation

Bone marrow transplantation has come into widespread use in the last 30 years in the treatment of oncohematological malignancies. The conditioning regimens used for BMT include high-dose chemotherapy, with or without whole-body irradiation. It has been reported that there is an extremely high risk of persistent ovarian failure in women who undergo BMT [18]. Growth and sexual development are impaired in children, and sterility is common in adults [19].

## Radiotherapy

From several malignant conditions that affect young women, including melanoma, cervical cancer, leukemia, lymphoma, and ovarian cancer, breast cancer is of the highest incidence [20]. Standard regimens of radiation therapy for breast cancer are not associated with significant ovarian toxicity. Internal scatter radiation can reach the pelvis and ovaries. In vitro fertilization and egg harvesting should not be performed during radiation treatment, and pregnancy should be prevented [21].

Gonadal damage depends on the cumulative dose, the irradiation field, and the patient's age. Older women are at greater risk of damage [19]. Women who are older than 40 years of age when undergoing treatment have a smaller pool of remaining oocytes and require only 5–6 Gy to produce permanent ovarian failure. Exposure of the ovaries to high radiation doses, as is the case for treatment of cervical and rectal cancer, and with craniospinal RT for central nervous system malignancies can cause mutagenic, embryotoxic, embryolethal, and teratogenic effects [22]. The same effects can happen when pelvic lymph nodes are irradiated for lymphomas and with total body irradiation (TBI) before bone marrow transplantation. In these cases, it is recommended that, when possible, the gonads should be shielded, the radiation field restricted, or when possible the ovaries should be surgically relocated away from the radiation field (oophoropexy) [22]. The radiation dosage necessary for loss of ovarian function has been examined in many studies. Chiarelli [23] has demonstrated the percentage of women who suffered from infertility correlated with increasing dosages of abdominal pelvic irradiation: treatment doses of 20–35 Gy caused a 22% rate of infertility, and doses >35 Gy caused a 32% rate of infertility. Survivors who received hypothalamic/pituitary radiation doses of 30 Gy or higher or ovarian/uterine radiation doses higher than 5 Gy and those who were treated with lomustine or cyclophosphamide were less likely to have ever been pregnant [24].

Ovarian failure has been reported in 90% of patients following total body irradiation (TBI) (10−15.75 Gy) and in 97% of females treated with total abdominal irradiation (20–36 Gy)during childhood [25].

Radiation effects on the uterus and subsequent pregnancy outcomes are also known [26]. Irradiation of the uterus is associated with infertility, spontaneous pregnancy loss, and intrauterine growth retardation [27]. Irradiation can cause irreversible changes in the uterine musculature, blood flow, and hormonal-resistant endometrium insufficiency [28].

Radiation doses of >25 Gy directly to the uterus in childhood appear to induce irreversible damage [29].

Physiological sex steroid replacement therapy may improve uterine characteristics in some patients after irradiation at a young age.

Patients who have undergone RT have increased rates of obstetric complications compared to the general population: spontaneous abortions (38% vs. 12%), preterm labor (62% vs. 6%), and low-birth-weight infants (62% vs. 6%) [30]. There is advice to delay pregnancy for a year after the completion of RT.

Teh et al. [31] have suggested that patients receiving >45 Gy in adulthood and >25 Gy in childhood should be counseled to avoid pregnancy. Concerning the dose of radiation to the uterus, above which a pregnancy would not be sustainable, no clarity exists.

Rodriguez-Wallberg et al. reported the first successful delivery after transplantation of cryopreserved ovarian cortical tissue and subsequent in vitro fertilization in a patient with Ewing's sarcoma, who had received sterilizing pelvic radiotherapy (54 GY) and 40 weeks intensive high-dose chemotherapy for the treatment of Ewing's sarcoma 14 years earlier [32].

## Measures to Protect Fertility

At diagnosis, plans for fertility preservation must take into consideration the individual patient's priorities in conjunction with the recommended treatment strategy. Several options are available for women with cancer who wish to preserve their germ line. Patients may elect to delay cancer treatment in order to undergo one cycle of hormone stimulation, followed by cryopreservation of either a mature oocyte or an embryo [33].

*Cryopreservation of mature oocytes* is considered experimental [34]. Around 100 children have been born worldwide from this option [35]. Oocyte cryopreservation should only be performed in centers with the necessary expertise [36].

### Cryopreservation of Mature Oocytes (After Gonadotropin Stimulation)

Oocyte banking is more problematic than cryopreservation of sperm or embryos [26]. The first obstacle is the sensitivity of oocytes to chilling. Cooling and exposure to cryoprotecting agents (CPAs) may aggravate the high incidence of aneuploidy in human oocytes. Exposure to CPAs causes hardening of the zona pellucida, so all oocyte cryopreservation protocols involve intracytoplasmic sperm injection (ICSI) as a precaution. Fertilization has to be carried out about 3–5 h after thawing while the oocyte remains fertile. The disadvantage of the method is that cancer patients may not have more than one opportunity for oocyte harvesting before undergoing potentially sterilizing treatment. The success of the method is depending on the total number of eggs harvested (less than 10 oocytes give very low chances of pregnancy). To date, more than 4300 oocytes have been cryopreserved, and more than 80 children have been born. The overall live birth rate per cryopreserved oocyte is about 2%, which is much lower than that with IVF using fresh oocytes. Pregnancy rates were one-third to one-fourth of the success rates seen with unfrozen oocytes [37].

### Cryopreservation of Immature Oocytes After In Vitro Maturation (Without Gonadotropin Stimulation)

Oocytes are recovered for in vitro maturation (IVM) from fresh tissue or follicular aspirates before the dominant follicle emerges during the mid-follicular phase of the menstrual cycle. Cryopreservation difficulties include the different optimal times of equilibration for the oocyte and its smaller cumulus cells. Oocytes can be recovered from unstimulated ovaries as well as from children, and if harvesting is less expensive and risky, it can be repeated frequently. The procedure still needs further advances in cryotechnology.

### Gonadotropin-Releasing Hormone Analog Treatment

Multiple small studies have evaluated the utility of gonadotropin-releasing hormone analog (GnRH-a) treatment for the preservation of

ovarian function during cytotoxic therapy. Rendering the ovarian follicular development quiescent by suppression of gonadotropins has been proposed to protect women from damage by cytotoxic therapy. One controversy is whether the ovary can be protected during the cancer treatment by using GnRH-a to create a temporary menopause [38]. Blumenfeld et al. in small studies have demonstrated that GnRH agonists are well tolerated and might protect long-term ovarian function [39]. He has reported beneficial effects of GnRH therapy on ovarian function in 55 lymphoma patients receiving chemotherapy.

Despite the research efforts, ovarian suppression with luteinizing hormone-releasing hormone analogs (LHRHa) during chemotherapy is still considered an experimental strategy to preserve fertility by some international guidelines regarding the efficacy of this strategy and the absence of data on pregnancies and long-term ovarian function [40].

Two large randomized trials evaluating the efficacy of ovarian suppression with LHRHa during chemotherapy in breast cancer patients have reported long-term outcome results. Both trials reported a statistically significant reduction in the incidence of chemotherapy-induced POF in patients receiving LHRHa 1 year after the end of chemotherapy in the PROMISE-GIM6 study [41] and 2 years after the end of chemotherapy in the POEMS-SWOG S0230 trial [42, 43].

The 2015 St Gallen National Comprehensive Cancer Network (NCCN) guidelines have been updated to acknowledge the use of LHRHa in preventing chemotherapy-induced ovarian failure of hormone receptor-negative breast cancer [43, 44].

Expert groups were stressing that ovarian suppression with the use of LHRHa during chemotherapy should be considered a reliable strategy to preserve ovarian function and fertility, at least in breast cancer patients [45, 46].

Hormone stimulation may have unfavorable effects in both patients with hormone receptor-positive disease and hormone receptor-negative disease. There is therefore the need for fertility preservation techniques that do not require hormonal exposure [47].

## Sex Steroids

Small observational studies suggest that oral contraceptives may help preserve ovarian function when given during chemotherapy [7]. However, the results are controversial. One possible explanation for the varying results might be that the oral contraceptives do not suppress the gonads completely.

## Ovarian Tissue Cryopreservation

In some centers, the harvesting of ovarian tissue has been started for autotransplantation [40]. Ovarian tissue cryopreservation is an investigational method of fertility preservation. Ovarian tissue is removed laparoscopically and frozen. At a later date, the ovarian tissue is thawed and reimplanted.

The first ovarian transplant procedure was reported in 2000 [48]. Ovarian tissue can be transplanted orthotopically to the pelvis or heterotopically to subcutaneous areas such as the forearm or lower abdomen [49]. Studies have reported restoration of ovarian endocrine function after both types of transplantation [50].

Ovarian tissue can be obtained without additional hormonal stimulation. Oocytes may be aspirated from the ovary, matured in vitro, and then cryopreserved for later use [36]. Individual follicles or strips of ovarian cortical tissue can be cryopreserved for future use in either in vitro follicle maturation or tissue transplantation. There are five reports of live births in women with cancer who underwent autologous transplantation of cryopreserved ovarian tissue [51]. Transplantation of ovarian tissue is associated with a risk of reintroducing cancer cells from the transplanted tissue. This is why it is considered as a last option for the preservation of fertility in patients with cancer. Patients with leukemia are at increased risk for this adverse event [50]. Ovarian tissue screening to detect malignant cells should be performed to minimize the risk of tumor transfer with the ovary.

Donnez et al. (2015) have been reporting 40 live births in cancer patients after transplantation of frozen/thawed ovarian tissue [52]. The best

candidates for ovarian tissue cryopreservation are prepubertal girls. The technique may also be proposed to patients scheduled for treatments with a high risk of premature ovarian insufficiency who cannot delay anticancer treatments, or who have already received chemotherapy, or with contraindications to COS. Patients with cancer with a high risk of malignant contamination to the ovaries (e.g., aggressive hematologic malignancies) should not be considered eligible for ovarian tissue autotransplantation.

## Embryo Cryopreservation Is the Most Effective Approach

The human embryo is very resistant to damage caused by cryopreservation. The postthaw survival rate of embryos is in the range of 35–90%, while implantation rates are between 8% and 30%. However, this approach requires in vitro fertilization and a participating male partner. This option is not acceptable to prepubertal or adolescent girls [53]. Oocytes are fertilized in vitro and cryopreserved after fertilization. A small percentage of cancer survivors have yet returned to utilize their embryos [54].

Women with very early-stage or low-grade gynecological cancer may be able to preserve fertility by having limited surgery, for example, conservation of the uterus and contralateral ovary for women with ovarian cancer or radical trachelectomy (preservation of the uterus despite removal of most of the cervix) for cervical cancer. It has been estimated that nearly 50% of women diagnosed with cervical carcinoma under the age of 40 are eligible for radical trachelectomy, a procedure in which the cervix is resected but the uterus is spared [55]. Ovarian transposition (oophoropexy—surgically moving ovaries as far as possible from the radiation field) can be offered when pelvic radiation is used for cancer treatment. The procedure can be done laparoscopically if laparotomy is not needed for the primary treatment of the tumor [56]. Lateral transposition of the ovaries to remove them from the field of pelvic irradiation is an option that preserves ovarian function in about half of the women treated for cervical cancer or Hodgkin disease [57].

Natural cycle in vitro fertilization, in which follicles are aspirated without exposure to exogenous hormone stimulation, is also an emerging option. Still the success rate associated with this technique is low [58]. For women becoming infertile because of cancer treatment, an option would be the use of donor oocytes to have a child either through a pregnancy or gestational surrogacy when a patient who has had cancer would like to become pregnant by means of any fertility preservation option, and a clinical investigation should be performed to be sure that the patient is disease-free.

Attempts to preserve or restore fertility in women receiving chemotherapy for cancer have been less successful than analogous effects in men. For patients with partners, cryopreservation of in vitro fertilized mature egg is effective and is available at most cancer centers.

Treatment-induced involuntary infertility is a major concern in cured cancer patients. At present, there is no epidemiological proof that there is an increased percentage of malformations in children born after their parents have had cancer treatment. Chemotherapy during the first trimester of a pregnancy would indicate the necessity of termination; but in most cases, where it does not increase the risk of malformation [22], it may result in preterm deliveries and slightly increases the risk of prenatal complications.

Fertility options for women are unfortunately still problematic. Women who do not require urgent treatment may undergo a cycle of in vitro fertilization before cancer treatment and cryopreservation of embryos, but the chance of a pregnancy with future use is still limited [35]. Women with breast cancer can utilize new protocols that may limit exposure of cancer cells to high estrogen levels by adding [54] aromatase inhibitors or tamoxifen to the ovarian-stimulating drugs.

Fertility preservation options in females depend on the patient's age, type of treatment, diagnosis, whether she has a partner, the time available, and the potential that the cancer has metastasized to her ovaries.

The possibility that fertility preservation interventions and/or subsequent pregnancy may increase the risk of cancer recurrence has been most concerning in breast cancer and the gynecologic malignancies.

In recent studies, it has been demonstrated that there are no conclusive data at present that suggest only deleterious effects, such as an increased risk for relapse, due to subsequent pregnancy in women with a history of breast cancer.

Regarding the miscarriage rate, studies that have monitored pregnancies in women exposed to chemotherapy before conception were unable to detect any increased rates of miscarriage or congenital abnormalities in comparison with the general population. The optimal timing of a subsequent pregnancy after cancer is unclear and depends on the patient's prognosis, age, and personal situation. Meirow and Schiff [59] postulated that patients who recover from ovarian failure after high-dose chemotherapy or RT treatments should not delay childbearing for too many years. These patients should try to conceive after a disease-free interval of a few years but not less than 6–12 months after the treatment, due to the possible toxic effects of the therapy on growing oocytes. The delay of 2–3 years after the cancer therapy is recommended, so that the period associated with the greatest risk of recurrence has passed before a pregnancy. In patients with hormone-positive breast cancer, tamoxifen and GnRH-a do not cause permanent amenorrhea, but this treatment can last up to 5 years, during which time a pregnancy is contraindicated [60].

## The Effect of Cancer Treatment on Male Fertility

Several factors can negatively affect male fertility—disruptions of the hypothalamic–pituitary–gonadal axis, damage to the germinal epithelium, and depression related to the diagnosis of cancer [61]. Recent studies have demonstrated that the integrity of sperm DNA is altered before the initiation of treatment in patients with Hodgkin lymphoma or testicular cancer [62, 63]. Testicular cancer is associated with abnormalities of spermatogenesis [3].

*Testicular cancer* particularly compromises fertility as growth factors produced by the cancer may alter the spermatogenesis. Often, it is necessary to remove the affected testis which may decrease the production of sperm. Prostate cancer surgery can induce erectile dysfunction. Radiation therapy is toxic to developing sperm, even at low doses. High-dose pelvic irradiation used for the therapy of prostate, rectal, and testicular cancers may permanently damage testicular function and contribute to erectile dysfunction [64].

Damage to sperm DNA for up to 2 years after completion of therapy has been reported in patients undergoing radiation therapy and chemotherapy for testicular cancer and systemic therapy for Hodgkin lymphoma [63]. It is important to counsel patients concerning contraceptive use and cryopreservation of sperm before the initiation of therapy [65]. Infertility is a major concern for young men of reproductive age undergoing chemotherapy, RT, or surgery. Malignancy is also associated with an increased catabolic state, malnutrition, an increase in stress hormones, and a decrease in pituitary gonadotropin levels, which can also have an impact on fertility [66].

Medical therapy in the form of sympathomimetics may improve ejaculatory efficiency and allow for the antegrade transit of sperm in some patients with ejaculatory dysfunction following retroperitoneal lymph node dissection. In the unsuccessful cases, electroejaculation (EEJ) can be used to achieve antegrade ejaculation [67]. Unilateral orchiectomy for testicular cancer or tumor infiltration can impair sperm production as bilateral orchiectomy will eliminate it. Prior to orchiectomy, semen cryopreservation remains the best option. If no sperm is produced into the ejaculate, a testicular sperm extraction (TESE) has been introduced [68].

Eisenberg et al. (2013) have suggested that men with azoospermia have a higher risk of developing cancer [69].

## Effects of Oncological Surgery

Bladder neck or prostate resection, bilateral retroperitoneal lymphadenectomy, or extensive pelvic surgery might cause anejaculation as a result of retrograde flow of semen in to the urinary bladder.

Modified nerve-sparing surgical procedures have reduced this adverse outcome. Improved surgical techniques in the treatment of bladder and prostate cancer avoid damaging the nerve fibers. Seventy to 80 percent of men with radical prostatectomy or radical cystoprostatectomy maintain sexual function [70].

## Chemotherapy

Most cytotoxic forms of chemotherapy are not tumor specific and target cell types with a high growth fraction. Spermatogenesis is extremely vulnerable to the damaging effects of systemic therapies.

Oligospermia or azoospermia develops often. As cytotoxic treatment targets tissues with a high growth fraction, the spermatogenesis can be impaired after treatment for cancer.

Following cancer chemotherapy, most men develop low levels of sperm (oligospermia) or no sperm (azoospermia). In addition, the cells in the testes that produce testosterone, called Leydig cells, may also be affected by chemotherapy, resulting in low or lack of testosterone production. These conditions may persist for long periods of time and may be permanent. The effect of chemotherapy on the testes depends on the type of drugs and dose and schedule of treatment. Some chemotherapy drugs are more likely to cause sterility, while there tends to be a much lesser long-term toxicity with the newer forms of chemotherapy. The classes of chemotherapy drugs that are more likely to cause sterility are as follows.

The main classes of agents that have been demonstrated to impact fertility include the alkylating agents and platinum-based agents.

## Alkylating Agents

The AA (nitrogen mustard, cyclophosphamide, chlorambucil, busulfan, procarbazine) are major causes of late-testicular toxicity. AA cause depletion of the germinal epithelium in the testes and aplasia of germinal cells, resulting in severe oligospermia or azoospermia within 90–120 days of treatment [71] with poor long-term recovery [3]. Long-term infertility due to treatment with AA may be expected in more than 50% of the patients at a cumulative dose of cyclophosphamide >6 g/m$^2$ and procarbazine >4 g/m$^2$. AA are mutagenic in all stages of maturation of male human germ cells, however, do not cause transmissible chromosomal translocations or aneuploidy in stem cells [72]. The majority of men receiving procarbazine-containing regimens for the treatment of lymphomas are rendered permanently infertile [73].

## Platinum Compounds

Platinum compounds (cisplatin, carboplatin, and oxaliplatin) are major causes of damage to the testis. Long-term infertility due to therapy may be expected in more than 50% of the patients who receive a cumulative dose of cisplatin >0.6 g/m$^2$. *Vinca alkaloids*—arrest spermatogenesis. *Antimetabolites*—5-fluorouracil and 6-mercaptopurine cause chromosomal aberrations. Topoisomerase interactive agents are cytotoxic to all spermatogonial stages. Combination chemotherapy, the MOPP regimen, used for Hodgkin disease, can cause azoospermia in 90% of men up to 4 years after therapy and an increased frequency of aneuploidy for up to years after treatment. The newer ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) is less toxic to spermatogenesis. One study demonstrates that 90% of men had no change in their sperm count 1 year after treatment [74].

## Radiation Effects

Radiation therapy that is used to treat several malignant conditions is toxic to developing sperm even at low doses [75]. Therapy for prostate, rectal, and testicular cancers can require high-dose pelvic irradiation, which may permanently damage testicular function and also contribute to erectile dysfunction [75]. Ionizing radiation has adverse effects on gonadal function in men of all ages. The severity of the damage is depending on the dose, the treatment field, and the fractionation schedule [76]. Doses of more than 4 Gy can cause permanent damage to spermatogenesis [77]. The lowest sperm counts are demonstrated 4–6 months after treatment is completed. Return to pretreatment levels occurs in 10–24 months [78]. TBI as a conditioning regimen for stem cell transplantation causes permanent gonadal failure in approximately 80% of men [79].

Recovery of spermatogenesis takes place from surviving stem cells (type A spermatogonia) and is dependent on the dose of radiation. Complete recovery takes place within 9–18 months following radiation with 1 Gy or less, 30 months for 2–3 Gy, and 5 years or more for doses of 4 Gy and above [73].

Testicular radiation with doses higher than 20 Gy is associated with Leydig cell dysfunction in prepubertal boys, while Leydig cell function is usually preserved with doses of as much as 30 Gy in sexually mature males [80]. Exposing the testes to ionizing radiation at a dose lower than 6 Gy causes disturbances of spermatogenesis and altered spermatocytes with recovery periods dependent on dose; doses higher than 6 Gy cause permanent infertility by killing off all stem cells [81]. For patients with testicular germ cell cancer, using modern radiation techniques (radiation doses to the para-aortic field <30 Gy) and testis shielding providing testis scatter radiation (<30 Gy), radiation-induced impairment of fertility is very unlikely [82]. Sperm counts are typically lowest at 4–6 months posttreatment; return to pretreatment levels usually occurs in 10–24 months, with longer periods required for recovery after higher doses [83].

It has to be taken into account that men who regain spermatogenesis after cancer treatment have low sperm counts and motility and an increased rate of chromosomal abnormalities [84]. These effects are dose dependent and persist for up to 3 years after RT. Contraception for a period of 1–3 years is recommended after testicular irradiation.

## Long-Term Sterility

Sterility is an inability of a man to fertilize an egg or reproduce. Sterility is caused by poor function or failure of the testes. Damage to the testes from radio- or chemotherapy is a common cause of sterility among cancer patients—some type of surgery to treat prostate, bladder, testicular, and colon cancers can also produce sterility by affecting glands and nerves.

Age is an important factor that contributes to recovery of the reproductive function. Older patients are more likely to experience long-term sterility. Patients who undergo chemotherapy treatment for testicular cancer, Hodgkin disease, and childhood lymphomas are likely to experience long-term sterility. Men treated for acute lymphoblastic leukemia may also experience some damage, but most appear to recover their reproductive function.

Testicular cancer now has a cure rate of more than 80% with combination chemotherapy composed of cisplatin, etoposide, and bleomycin. However, approximately 25% of patients have azoospermia for 2–5 years or more after treatment. Additional research with survivors of testicular cancer reveals conflicting results regarding the impact of treatment or reproductive ability. Although one study demonstrates 68% exhibit testicular dysfunction, another study showed that

the release of hormones from the brain compensates for the loss of testosterone production in the testes. Therefore, the response to treatment seems to vary between individuals.

Many men with Hodgkin disease have testicular deficiencies before treatment. Eight percent of patients had azoospermia, and only 30% had normal sperm counts. Thus, 70% demonstrated semen abnormalities before the onset of treatment. Additionally, patients with Hodgkin lymphoma are treated with procarbazine—containing chemotherapy regimens that cause sterility in the vast majority.

Survivors of HD typically progress through puberty normally. Although some will have long-term testicular dysfunction as measured by LH and FSH levels, many will not experience this side effect of treatment. For men, gonadal toxicity can be evidenced by the following three measurements: testicular biopsy, serum hormone analysis, and semen analysis. When male infertility is the result of abnormal hormone production, the use of hormone manipulation may lead to the return of sperm production [85].

## Fertility Preservation in Male Cancer Patients

Preservation of fertility in male cancer patients has been increasingly successful during the last three decades.

### Sperm Cryopreservation

The best option for the preservation of male fertility is cryopreservation of sperm before treatment. This is possible with no apparent capacity for fertilization [40, 86]. Semen cryobanking before chemotherapy, RT, and surgery affecting the reproductive system is a widely available option that yields good results and provides a reasonable chance of establishing a pregnancy after cancer therapy [87]. Traditionally, the banking of at least three semen samples, with an abstinence period of at least 48 h between the samples, has been recommended. Completion of the process usually requires 5–8 days. Additional samples and longer abstinence periods (72–96 h) to achieve higher total sperm counts might also be considered [88].

According to ESMO recommendations [89], all patients at risk of infertility who have not completed childbearing should discuss germ cell storage options with the medical team. Available interventions for male fertility preservation are unlikely to delay cancer treatment. Semen cryopreservation of at least three samples with 48 h abstinence intervals is recommended for men [89]. For azoospermic men, testicular sperm extraction may be an option for fertility preservation.

The subsequent use of cryopreserved sperm is important to investigate and is reported to be low in most series. In a study from the USA involving 164 men who stored sperm between 1993 and 2003, only 6 (3.7%) used their sperm during the follow-up period [90].

Concerning the fertility preservation in the prepubertal male, it is important to stress that the current methods for fertility preservation are only available for men who have undergone puberty and initiated spermatogenesis. At the present time, cryopreserved testicular tissue from prepubertal boys cannot be used in a clinical setting. Current uses of such tissue are considered experimental [91].

## Children with Cancer

Childhood cancer includes hematological malignancies, sarcomas, central nervous system processes, renal cancer, and bone cancer. Treatment regimens for childhood cancers are toxic, and there is a high risk to the fertility of young patients. The patients have increased risk of secondary malignancies [92]. The majority of childhood cancers are managed with a combination of chemotherapy and radiation therapy. These treatments alter the function of the hypothalamic–pituitary–gonadal axis. Direct damage to the ovaries by affecting folliculogenesis or inducing POF can be produced as well [93].

## Gonadal Dysfunction

The degree of gonadal damage depends on the type and total doses of chemotherapy used and dosage of RT received. AA, such as nitrogen mustard, procarbazine, and cyclophosphamide, are the most damaging to the gonads. Thirty percent of prepubertal boys had evidence for gonadal dysfunction with total cyclophosphamide doses >400 mg/kg (12 g/m$^2$) compared to no effect on prepubertal girls. Midpubertal and sexually mature boys frequently had gonadal dysfunction even with total doses as low as 100 mg/kg (3 g/m$^2$). When girls receive chemotherapy during or after puberty, they are affected more severely but are still less sensitive than boys. Girls having abdominal irradiation for Hodgkin disease or Wilms tumor (i.e., ovaries in the radiation field) have a 50% incidence of ovarian failure if both ovaries are in the field and the dose is >1500 cGy. The rate is higher if AA are also used.

A major concern is early menopause [94]. In a large study, the average age at menopause was 31 years in women treated with abdominal irradiation and AA combined. Radiation to the gonads can also affect fertility [95]; 200–300 cGy to the testes causes 100% aspermia with no recovery after as many as 40 months of follow-up. This is important for boys receiving testicular radiation for testicular germ cell tumors or testicular disease from acute lymphoblastic leukemia, abdominal irradiation for advanced Hodgkin disease, or TBI with bone marrow transplant.

The testes are especially vulnerable as germinal epithelium can be seriously damaged, permanently affecting spermatogenesis. The direct toxic effects of chemotherapy and RT are dose dependent.

## Monitoring of Late Effects Ovary

Girls who receive AA or abdominal or pelvic RT should monitor their menstrual histories yearly after therapy. Elevated LH and FSH and low estradiol may indicate ovarian failure if menses do not occur and if signs of POF are present. Hormone replacement therapy is necessary for girls who do not go through puberty or who have evidence of POF.

## Testes

In boys, who receive AA or testicular or pelvic RT, it would be necessary to check baseline LH, FSH, and testosterone once they reach the age of 12 years and then as needed. Puberty is rarely affected. Large doses of alkylators and RT doses >3500 cGy are likely to affect Leydig cells. Sperm analysis represents the criterion standard regarding fertility, although elevated gonadotropins and small testes are indicators of potential infertility [96].

Options for fertility preservation in pediatric patients generally overlap those that are available for adults. Children under chemotherapy can receive GnRH agonists; however, they have little protective effect. Cryopreservation of sperm before the initiation of therapy remains the best method of preserving fertility in postpubertal boys. In the case a young patient who is not able to provide a semen sample, electroejaculation or surgical sperm extraction can be performed [97]. Adolescent girls are not considered to be candidates for assisted reproductive technology [51]. Oophoropexy to move the ovaries away from direct toxic effects of the radiation target can be performed in girls. Children with cancer and their families have not typically been offered options for fertility preservation. However, such options are available for this patient population.

# Teratogenic Effects of Cancer Treatments

Studies indicate that chemotherapy and RT treatments can be mutagenic to human germ cells [23]. Genetic damage of the human germ cell might influence fertilization, increase the rate of abortions, or cause malformations in children conceived by men or women previously exposed to cancer treatment. The potential teratogenic effect of cancer treatment depends upon the developmental stage of the fetus at the time of

exposure. The developmental stages are divided into the preimplantation and early postimplantation periods, the embryonic period or major organogenesis period (3rd–8th week postconception) during which most of the organs develop [98], and the fetal period (ninth completed gestational week to term). During the predifferential period, the conceptus is most resistant to teratogenic insult [99]. Any embryonic damage occurring at this point would most likely lead to death of the conceptus. During organogenesis, damage of any developing organ would most likely lead to major malformation. During the fetal period, the damage is less extensive. The risk of teratogenesis following cancer treatment appears to be significantly lower than is commonly appreciated [23]. Most drugs reach the fetus in significant concentrations after maternal administration as the placenta is not an effective barrier. Of the chemotherapeutic agents examined, cisplatin [100] and cyclophosphamide [101] cross the placenta easily, while epirubicin has limited transplacental passage [102].

An estimate of 10–20% of fetuses exposed to chemotherapy during the first trimester would have major malformations [103]. The risk of anomalies after administration of chemotherapy in the second and third trimesters is probably not greater than the background rate. However, there can be a greater risk of stillbirth, fetal growth restriction, premature birth, and maternal and fetal myelosuppression [104]. Concerning the teratogenic effects of individual agents, the antimetabolites methotrexate and aminopterin have been associated with birth defects more frequently. AA are less teratogenic than antimetabolites [105]. Vinca alkaloids are potent teratogens in animals, although most cases of human exposure resulted in normal infants [105]. Taxanes and platinum compounds are relatively safe to administer beyond the first trimester. Delayed effects of in utero exposure to chemotherapeutic agents are basically undefined. A major concern is intellectual and neurological functions or long-term development following in utero exposure to maternal cancer and its associated treatment. It is recommended that if treatment cannot be delayed and is given in the first trimester (especially if folate antagonists are used), then termination of the pregnancy is recommended [23].

There are no data on pemetrexed, gemcitabine, and vinorelbine. Few pregnant women have been exposed to targeted agents. Trastuzumab caused oligohydramnios in four and abnormal implantation in one out of seven pregnant women, while rituximab only caused transient neonatal lymphopenia in four reported cases. Imatinib was associated with low birth weight and premature delivery in 29 reported cases. In view of the lack of data and past experience with the antiangiogenic agent thalidomide, administration of targeted agents modulating angiogenesis (bevacizumab, sunitinib, sorafenib) should be avoided in pregnant women [89].

To decrease the risk of anomalies to the fetus, chemotherapy should be delayed (if possible) until the second trimester. However, chemotherapy started in the second and third trimesters may increase the risk of stillbirth, fetal growth restriction, premature birth, and maternal and fetal myelosuppression.

## Mutagenic Effect of RT

Radiation has direct mutagenic effects on germ cells in relation to dose. High dose may lead to dominant lethal effects, point mutations, and chromosomal abnormalities [106]. Radiation is also carcinogenic. Classic effects of radiation on developing mammals are embryonic death, gross congenital malformations, and intrauterine growth retardation. During the first 2 weeks postfertilization, the embryo is highly sensitive to the lethal effects of irradiation and is insensitive to the teratogenic effects of radiation [106]. In 3–10 weeks postfertilization, radiation may be teratogenic and cause growth retardation. Very high doses (at least 1.0 Gy) may be lethal to the embryo.

The central nervous system develops throughout gestation and may therefore be sensitive to radiation at all stages of pregnancy. High doses of ionizing irradiation, mainly in therapeutic doses, were found to induce skeletal, eye, and brain anomalies in the human fetus. The main defects

were microcephaly and mental retardation, microphthalmia, cataract, iridal defects, and skeletal anomalies [23].

There is concern about the carcinogenic effects of irradiation on the developing embryo and fetus. Several epidemiological studies have demonstrated an increased risk of childhood leukemia and other childhood tumors [23]. The overall additional risk is estimated to be about 40%.

It is recommended to avoid high-dose irradiation during pregnancy as it may induce central nervous system, eye and skeletal anomalies, impaired growth, and mental retardation. At any point during the pregnancy, maternal exposure (to the abdomen) of less than 0.10–0.20 Gy does not seem to cause teratogenic effects, although in utero exposure to radiation causes 40% increased risk of childhood leukemia and other tumors. If there was very early or low-dose exposure to radiation, these do not justify termination of the pregnancy [23].

Studying the teratogenicity of cancer chemotherapy is usually based on animal models. However, the chemotherapy doses used in humans are often lower than the minimum teratogenic doses applied in animals. Therefore, it is difficult to extrapolate data from animal models to humans [107]. Cytotoxic drugs are often used in multidrug regimens, which make it difficult to estimate the exact effect of each drug.

Due to the rarity of pregnancy-associated cancer, there is little expertise in the field. There is a critical need for multicenter cooperation to facilitate better epidemiological studies and improved long-term follow-up.

## Conclusion

Reproductive health after cancer is increasing in importance as the number of cancer survivors multiplies and the length of their survival also improves. Interventions that prevent or reverse the reproduction problems will greatly improve the quality of life of patients.

There is a tremendous demand for the provision of reproductive care for survivors of cancer treatment including fertility options, management of pregnancy, and other needs such as contraception and sexual dysfunction. Such demand is without doubt increasing every day with more successful outcomes of cancer treatment and availability of new effective modalities to satisfy fertility and reproductive needs.

A large minority of male and female cancer survivors have unmet needs related to reproductive health, even when treated in a comprehensive cancer center. Although fertility-sparing treatment is allowing more patients to have children after cancer, the gains are minimal compared with the elevated rates of childlessness among cancer survivors. As Cvancarova et al. [108] points out, the need for more effective fertility preservation for girls and young women is particularly pressing. Controlling cancer is necessary but not sufficient to ensure a satisfying quality of life for our patients.

Current evidence suggests that pregnancy does not appear to be detrimental, but individualized counseling regarding prognosis and risk of relapse based on their age and pathological features of the cancer is required before patients can make informed decisions regarding future childbearing. There is a growing recognition of the importance of developing a "survivorship plan." Multidisciplinary teams including reproductive medicine specialists and gynecologists would be needed.

The keys to successful preservation of fertility are to mitigate the risks whenever possible and to initiate planning for fertility treatment as soon as possible in order to prevent unnecessary delays in cancer treatment.

Reasonable, evidence-based recommendations regarding the effect of cancer treatment on human fertility are needed to counsel patients during their cancer diagnosis, treatment, and follow-up, including the various options for fertility preservation.

During the last three decades, oncologists have seen explosive developments of prophylactic and therapeutic techniques to prevent post-treatment infertility in cancer patients. Although many problems still remain, in particular for

female cancer patients, the risk of posttreatment infertility can be minimized if the responsible physician is aware of this progress. Adequate pretreatment counseling of young patients, based on today's knowledge about the technical possibilities, is the part of good clinical practice.

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# Menopause Symptoms

18

Debra Barton

## Introduction

The menopause transition is triggered by senescence of ovarian follicular function resulting in decreased estrogen and progesterone production. It is fully ushered in with follicular depletion. This usually occurs at a mean age of 51 years, although for cancer survivors due to treatment effects, it can happen at a much younger age [1, 2]. According to the last state of the science meeting on menopause symptoms at the National Institutes of Health, symptoms clearly associated with menopause include hot flashes, night sweats, vaginal dryness with or without dyspareunia, and perhaps sleep disturbance [3]. The consensus of the panel was that symptoms with limited or insufficient evidence to associate their cause with menopause included mood disorders, cognitive changes, pain, fatigue, joint and muscle aches, urinary symptoms, and libido [3].

Like all life's experiences, natural menopause is associated with psychosocial events and psychological meaning. It signifies the end of childbearing years; it is a time when children are grown and beginning independent lives; it can be accompanied by increased job demands and stresses; it may require care of parents and is accompanied by sometimes subtle but apparent changes in body image [4]. For cancer survivors, menopause can occur prematurely as a result of cancer treatment including the need for bilateral oophorectomy as well as chemotherapy that can impact follicular life [5, 6]. Early menopause as a cancer survivor can be associated with different meaning than menopause that occurs naturally at an older age. It can be a reminder of the cancer diagnosis and may be associated with more distress since it can occur years before the woman's peer group experiences this phenomenon. There is also the potential for more severe sequelae due to the number of years a woman may live with estrogen depletion as well as the fact that endocrine-related treatments are associated with various menopause-related symptoms [7].

Specific examples of endocrine-related side effects include hot flashes and vaginal discharge from tamoxifen [8] and bone loss, arthralgias and myalgias, and hot flashes (though to a lesser extent than tamoxifen) with aromatase inhibitors (AIs) [7, 9–11]. Knowledge about the incidence and management of side effects related to endocrine therapy is critically important now as women may benefit from taking these medications for a longer period of time, e.g., 10 years, and the role that side effects may play in adherence to these drugs [12].

In addition to sharp decreases in estrogen and progesterone, menopause related to cancer treatment may also signify decreases in other hormones such as androgens. It is not known to what

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extent other ovarian functions are disturbed by chemotherapy. In postmenopausal women, the ovarian stroma is a source of androgen production [11]. When a woman has had a bilateral oophorectomy, her testosterone concentrations can be half of that of women experiencing natural menopause [13]. One descriptive study found that women who had a bilateral oophorectomy were more likely to experience moderate, severe, and daily hot flashes compared to women experiencing natural menopause [14]. It is not clear whether, or how much, androgen production is decreased postchemotherapy, nor what impact androgen deprivation may have on hot flashes, bone changes, or vaginal health when coupled with estrogen deprivation. Decreases in androgen may well be a contributor to the plethora of menopausal symptoms experienced by female cancer survivors, and this needs further study.

Since the gold standard of treatment for bothersome menopausal symptoms, estrogen replacement therapy, is contraindicated for many female cancer survivors with hormone sensitive cancers, other treatment options are needed. There has been a fair amount of research evaluating nonestrogenic, nonhormonal, and nonpharmacologic interventions for a variety of menopausal symptoms over the past decade or so. This evidence base will be presented in this chapter, along with a brief description of what is known related to the physiology of the symptoms of hot flashes/night sweats, osteoporosis, and vaginal symptoms associated with vulvovaginal atrophy, now often referred to as genitourinary syndrome of menopause [15]. Each section will conclude with evidence-based practice recommendations.

Evidence-based practice consists of treatment recommendations based on the best available evidence which integrates both patient characteristics and provider expertise. Things that providers need to consider in developing symptom management recommendations with their patients include their own experience with patients' symptom expressions and responses to interventions; the specific attributes of a patient's symptom expression; a patient's preferences for types of interventions, including lifestyle factors; as well as various types of evidence, from randomized controlled trials to pilot data to case studies. It is important to also determine, with the patient, what is the most distressing or problematic symptom. Since people generally experience more than one side effect and can have multiple chronic symptoms, prioritizing them for successful treatment will be necessary. All of these elements have a role in the final decision of what types of interventions should be used first line and second line to manage a patient's symptoms.

Sleep disturbances, though an important symptom, will not be addressed in this chapter as it is covered in Chap. 4 of this book.

## Hot Flashes and Night Sweats

### Definition and Incidence

Hot flashes are a sensation of heat that often begins in the neck and the face and can encompass the entire body, particularly the chest [1, 16]. The warmth may or may not be accompanied by sweating and red skin. Night sweats are periods of perspiration, mild to profound, which occur during one's sleep which can disrupt the sleep cycle. Hot flashes are the most prevalent symptom of menopause, experienced by up to 75% of women, having a significantly negative impact on daily activities [1]. Women with a history of breast cancer are thought to experience more severe symptoms and can experience symptoms for longer periods of time due to endocrine-related treatment for cancer [5, 17].

### Physiology

The physiologic mechanisms that cause or perpetuate a hot flash are not definitively known; however, more about hot flash physiology is being uncovered. It has been shown that core body temperature rises as much as 10 min before a hot flash begins [18]. In addition, it is thought that hot flashes are triggered by central nervous system activity resulting in an imbalance of serotonin and norepinephrine [19, 20]. More recently, data evaluating heart rate variability during hot

flashes points to the hypothesis that hot flashes are associated with increased sympathetic activity and vagal withdrawal, providing another potential target, sympathovagal balance, for interventions [21, 22]. Further, it is believed that estrogen withdrawal results in changes in the hypothalamus, causing less flexibility in the body's ability to respond to temperature changes [23, 24]. This is referred to as a narrowed thermoregulatory zone. Therefore, one hypothesis about hot flash perpetuation is that as a person is confronted with stress, environmental conditions, or other factors that increase the core body temperature or further upset neurotransmitter balance, a hot flash can ensue.

### Evidence-Based Prevention and Treatment

There have been many clinical trials done, which provide a rich evidence base for the use of many nonestrogenic-based pharmacologic as well as nonpharmacologic interventions.

## Pharmacologic Treatment Options

There are a variety of pharmacologic agents that have been found to reduce hot flashes in phase III placebo-controlled trials. Classes of agents that are found to be effective include antidepressants; selective serotonin reuptake inhibitors (SSRIs), i.e., paroxetine (10 mg/day or 12.5 mg CR), fluoxetine (20 mg/day), citalopram (10 or 20 mg/day), and escitalopram (20 mg/day); serotonin/norepinephrine reuptake inhibitors (SNRIs), i.e., venlafaxine (75 mg/day extended release) and desvenlafaxine (100 mg/day); anticonvulsants, i.e., gabapentin (300 mg TID) and pregabalin (75 mg BID); and anticholinergics, i.e., clonidine (0.1 mg/daily) [25–28]. Studies to date have not found differences in any of these agents based on whether a woman has hot flashes from natural, surgical, and cancer treatment-induced menopause or from endocrine treatment-related side effects. Currently, there is only one FDA-approved nonhormonal drug for moderate to severe hot flashes associated with menopause, and that is paroxetine mesylate (Brisdelle by Noven Therapeutics), a selective serotonin reuptake inhibitor, and as with Paxil (GlaxoSmithKline), it should not be used with tamoxifen as it may decrease its efficacy.

Of the antidepressants found to be beneficial, the mechanism of action has included serotonin modulation. Venlafaxine and paroxetine have been found to reduce hot flashes by about 55–60% in phase III trials, while citalopram and fluoxetine have been found to reduce hot flashes by about 50% in similarly designed trials. The antidepressant, sertraline, although also a serotonin modulator, did not prove to be quite as helpful (less than 40% reduction) in reducing hot flashes as other agents in its class have been found to be [29]. It is not clear why this might be so. Interestingly, pilot trials investigating the efficacy of other types of antidepressants, such as dopamine, and pure norepinephrine modulators, such as bupropion and desipramine, respectively, were found to reduce hot flashes only 20–30%, which is consistent with a placebo effect [30, 31].

A second class of agents, anticonvulsants (gabapentin and pregabalin), was found to reduce hot flashes by 60% and 50%, respectively, in phase III trials. Finally, clonidine, either orally or transdermally, provides about a 40% reduction in hot flashes [32].

Side-effect profiles related to the doses found effective for hot flashes with these agents are relatively mild and well tolerated. For the antidepressants, the most common side effects include nausea, appetite increase or decrease, and dry mouth [32, 33]. Theoretically, SSRIs can be accompanied by sexual function changes such as lack of orgasm. However, long-term studies at the low doses used for hot flash management have not been done to describe the actual effects on sexual function from these agents when used for hot flashes. The anticonvulsants are associated with a few more side effects such as drowsiness, dizziness, trouble concentrating, trouble sleeping, blurred vision, and coordination troubles. Gabapentin can also cause changes in albumin/total protein resulting in a generalized edema [32]. Clonidine is associated with side effects of

drowsiness, dry mouth, constipation, and, if using a transdermal patch, pruritus as well as a skin rash.

## Herbs and Supplements

Several herbal agents and dietary supplements have been studied for hot flash reduction, including vitamin E, various soy products, black cohosh, and flaxseed. All of these agents have been studied in large, randomized, placebo-controlled trials, and none have been shown to be effective against hot flashes [34–42].

Other herbs such as red clover, licorice, chaste berry, hops, and dong quai have also been popularly touted in the complementary therapy literature to be effective for hot flashes. However, none of these have been studied in large, placebo-controlled trials, and some of these herbs may have the ability to bind with estrogen receptors and promote cell proliferation. Therefore, until more research is done to understand their biologic properties as well as effect on hot flashes, it is recommended that women who must avoid estrogen should not take these particular herbs.

## Nonpharmacologic Interventions

Yoga is a popular intervention studied for menopausal symptoms based on the general health benefits it is believed to bestow. There are many types of yoga, but most involve a combination of breathing, focus of attention, postures, movement, and balance. A recent review article provided a systematic review of seven trials evaluating yoga for menopausal symptoms [43]. None of the randomized control trials resulted in a benefit of yoga in reducing hot flashes compared to the control. Uncontrolled trials did show favorable effects, however. The types of yoga studied were varied and included Iyengar yoga as well as restorative and Sahaja yoga and other forms that were not specified. Therefore, while the risk associated with yoga is low, there are little compelling data at this time to recommend yoga specifically for hot flash management. Despite this, overall health benefits compared to risks may be favorable for this intervention, and yoga may be a helpful adjunct to other hot flash treatments.

There are behaviors that can assist in keeping core body temperature low and, therefore, decrease the advent of hot flashes. These include wearing open weave, layered clothing, keeping air moving with a fan or open window, sipping on cool liquids or even ice or popsicles, and avoiding spicy foods and alcohol or other foods/drinks that can act as a hot flash trigger by resulting in increased body temperature [33].

There has been a Cochrane review as well as a more recent systematic review [44] about the use of exercise for menopausal symptoms, specifically hot flashes. Although some association studies provide data to hypothesize that decreased physical activity is associated with more menopause symptoms, at least one association study in over 500 perimenopausal and postmenopausal women found that women classified as highly active were more likely to have moderate to severe hot flashes than women classified as minimally active [45]. Randomized controlled trials evaluating walking and moderate aerobic activity have either found no benefit or small effect sizes (<0.20) [44]. It is scientifically plausible that exercise may improve hot flashes based on endorphin release; however, this benefit might be offset by an increase in core body temperature from exercise that can precipitate hot flashes. The role of lifelong exercise in preventing moderate or severe menopause symptoms versus managing existing symptoms needs to be studied and clarified.

Acupuncture is another popular treatment for hot flashes and related menopausal symptoms that is getting much research attention. Several systematic reviews and/or meta-analyses have been done citing 8–11 randomized clinical trials, and all authors conclude the data to remain inconclusive [46–48]. Trials have used various types of sham control arms consisting of shallow needling, the use of nonacupuncture points, and no needling. In most trials, the control arms were about as effective as the active arms. When nontreatment comparison groups were included in

study designs, more often than not the active and sham acupuncture arms were significantly better in reducing hot flashes than the control arm [46]. Acupuncture research faces a couple of important methodologic challenges, namely, lack of an appropriate "placebo" control arm based on the knowledge of the mechanism of action of acupuncture as well as the individualized nature of the diagnosis and intervention. Current research methods do not readily allow for acupuncture to be evaluated in the way it is used clinically. Novel research in this area continues to be an important gap.

Stress is considered a precipitating factor for hot flashes, and methods to reduce stress have been evaluated for hot flash management. Two of these, thought to impact serotonin much like an antidepressant, are paced breathing and cognitive behavioral therapy incorporating relaxation strategies. Controlled trials evaluating slow, deep abdominal breaths, practiced for 15 min twice daily, have provided evidence that paced breathing/relaxation can reduce hot flashes by about 40% [49], less than the desired minimal effect of 50% and also not significantly different than control groups using usual breathing [49, 50]. This reduction is equal to clonidine without any adverse effects, however. Future research may evaluate a simple stress-reducing strategy such as paced breathing as an adjunct to low-dose pharmacologic treatment.

Cognitive behavioral therapy (CBT) with relaxation strategies is another stress-reducing intervention proposed to reduce hot flashes. Originally, the CBT intervention consisted of six weekly 90-min group sessions that addressed information about hot flashes, emotional and physiologic aspects, paced breathing, sleep, anti-anxiety strategies, and behavioral reactions to hot flashes. This intervention was later adapted to be a self-guided intervention over 4 weeks with only two contacts by a clinical psychologist. In both randomized controlled trials [51, 52], the perception of hot flash bothers or as a problem was significantly reduced. These results were also replicated in another trial using a similar group intervention [53]. However, CBT did not reduce the actual frequency of hot flashes [51, 52]. Therefore, key CBT strategies may be able to enhance effects of very low-dose antidepressants and could be studied further.

A newer strategy that has been evaluated for hot flashes and included as a strategy in a nonhormonal clinical practice guideline [54] is hypnosis. Hypnosis involves a deep relaxed state involving mental imagery. There have been two large randomized trials published evaluating hypnosis for hot flashes [55, 56]. One study was completed in women with a history of breast cancer using a usual care control [55] and the other was in women without breast cancer using an attention control arm [56]. Both studies were consistent, demonstrating a reduction of over 65% in hot flash frequency and severity without unwanted side effects [55, 56]. In a very small unblinded randomized trial, hypnosis reduced hot flashes more than did 300 mg TID of gabapentin [57]. Research is needed to determine how best to scale this intervention for broad dissemination.

Research is also being done to evaluate an invasive procedure, stellate ganglion block (SGB), in women with severe, intractable hot flashes. Preliminary evidence has been positive demonstrating large reductions in hot flash frequency over a period of 12 weeks after the procedure [58, 59]. SGB is a procedure where bupivacaine is injected next to the stellate ganglion to produce a sympathetic block. It is a procedure that has been used by anesthesiologists and invasive pain therapists for years for various problems such as atypical facial pain, complex regional pain syndrome, and severe migraines [60]. Treatment with SGB is consistent with the idea that hot flashes are related to sympathetic activation. More research is needed in this area, but this may be an option for women with very severe symptoms.

## Assessment and Evidence-Based Practice

It is critical to do a thorough assessment regarding the hot flash/night sweat experience in order to develop the best clinical practice plan. It is, of

course, important to get an idea of the number and severity of hot flashes the woman is experiencing on an average day. In addition, though, it is important to evaluate to what degree the hot flashes are causing night awakenings as well as interference with activities of daily living such as job or care-taking demands. It is helpful to evaluate the degree of distress or bother associated with the hot flash experience. A thorough history of behaviors and pharmacologic agents that have been tried to alleviate hot flashes should be taken, along with as much detail as possible regarding dosing, length of time used, and degree of response. The clinical plan for hot flash management should reflect the degree of interference the hot flashes are causing in one's life (Fig. 18.1). Nonpharmacologic interventions may take longer to see an effect than pharmacologic ones; therefore, if a woman has been without sleep for months, starting her on a pharmacologic treatment to get some relief and then incorporating a nonpharmacologic intervention would be an optimal strategy.

The goal of therapy is to reduce the hot flashes maximally with minimal to no side effects. If using an antidepressant, it is important to titrate patients on and off these medications slowly. Additionally, if mood disturbances are part of a woman's experience of symptoms, antidepressants may be an optimal choice based on the ability to modulate mood as well as impact hot flashes. Small studies have shown that if one agent is not effective in reducing hot flashes, a woman can try another agent, even in the same class such as an SSRI, and may, indeed, obtain needed relief. Randomized trials have clearly shown that within 2 weeks, nice reductions in hot flashes are realized and there is generally a plateau of effect in 4–6 weeks [61]. Using the lowest dose possible to achieve the desired reductions would also be important. Of note, there is no data to support the fact that physiology gets "reset" and that treatment with antidepressant agents can be withdrawn in such a way that hot flash relief can continue [28, 62]. If medications are stopped, hot flashes may reoccur or increase.

Research has also demonstrated that gabapentin and an antidepressant are not synergistic or additive with respect to hot flash reduction; therefore, there is no benefit to using both pharmacologic interventions together. Finally, one last very important consideration is drug interactions. If women are taking tamoxifen, pharmacologic agents that inhibit CYP2D6 metabolism are not to be used as they will inhibit the conversion of tamoxifen into its active metabolite, thus reducing efficacy with regard to breast cancer management [63]. Agents that are known to inhibit CYP2D6 metabolism that are effective for hot flashes include paroxetine, sertraline, and fluoxetine [64].

There are some additional clinical considerations to think about when choosing a pharmacologic intervention for hot flashes. Side effects such as dizziness and drowsiness can be more of problem in an older population with gabapentin. Titrating this agent beginning with 300 mg at bedtime, increasing to 300 mg three times daily over a week, may not always be possible, and women may require a longer titration beginning with 100 mg daily. Gabapentin requires dosing three times a day due to its short half-life, and some people may find it difficult to take the midday dose [65]. Pregabalin has the advantage of being able to be dosed twice a day but is associated with a few more side effects such as trouble concentrating [26]. Finally, owing to the different side-effect profiles and dosing schedules, women should be engaged in the decision about which medication to try and follow-up to determine tolerability, and benefit should be evaluated within 2–3 weeks.

If night sweats are the main issue, there are a couple slightly different strategies to consider. The first is the use of gabapentin 300 mg at bedtime alone. Gabapentin can cause some drowsiness which can help with sleep and has already been shown to help with hot flashes. The relatively short half-life makes it a good candidate to use right before bed to help with hot flashes/night sweats during the first several hours of sleep. Additionally, the antidepressant, mirtazapine, has been used as a sleep aid. In an open-label phase II trial, mirtazapine was studied for its effect on hot flashes as well as its effect on sleep [66]. Hot flashes were reduced by about 53% on 15 mg of

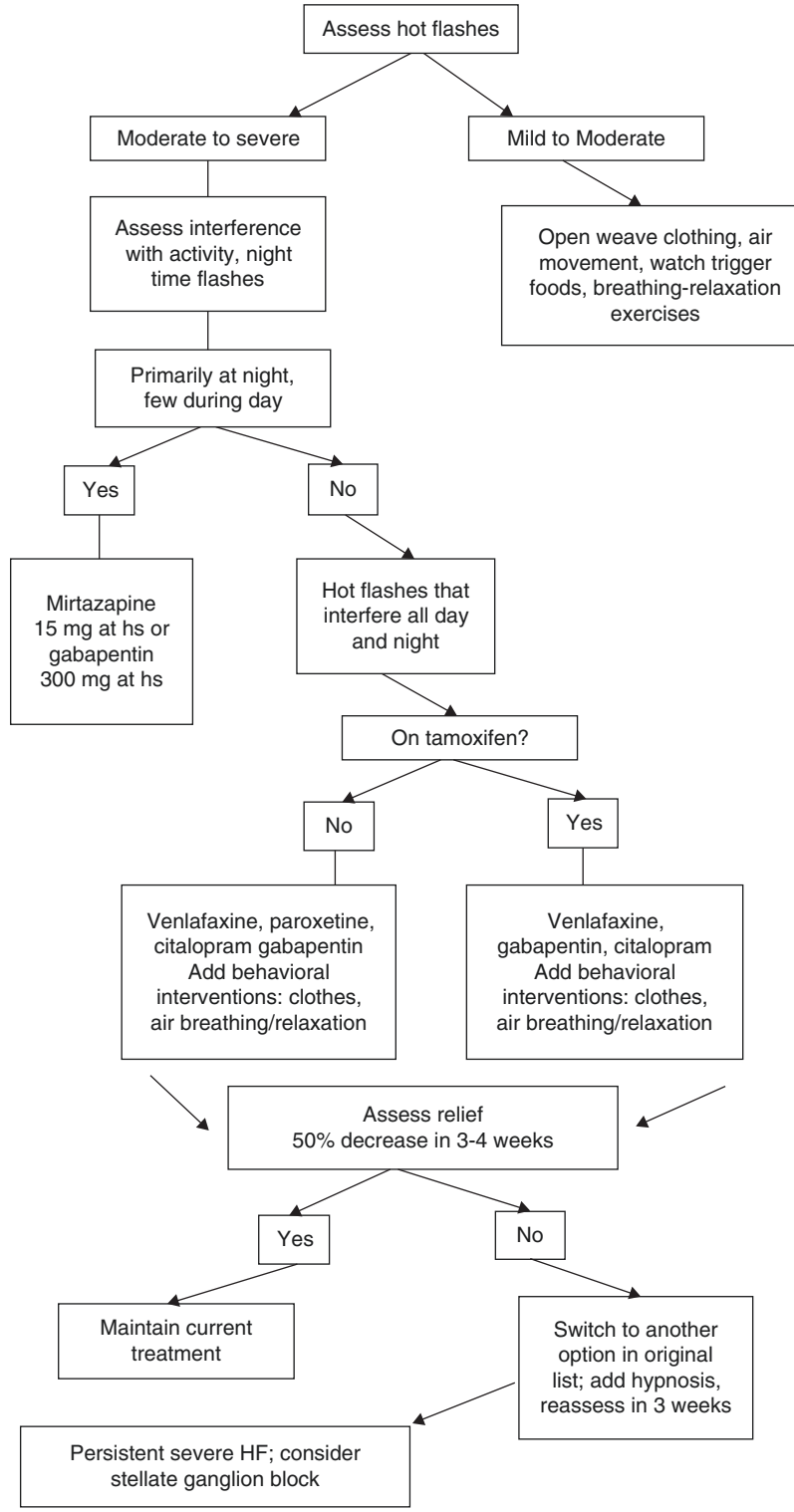


**Fig. 18.1** Hot flash assessment and treatment algorithm

mirtazapine per night. Sleep was also improved. Some women did feel that they had residual drowsiness in the morning; however, if sleep disorders and night sweats are the primary bothersome symptoms, this may be a reasonable option to try.

## Osteoporosis

### Definition and Incidence

Osteoporosis is a skeletal disorder characterized by low bone mineral density (BMD) and poor bone quality, resulting in reduced bone strength and increased risk of fractures [67, 68]. The World Health Organization defines osteoporosis as a bone density that is 2.5 standard deviations (expressed as a *t*-score) below peak bone mass or the mean bone density for young white adult women. Osteopenia, or low bone mass, is defined as a *t*-score of −1 to −2.5 [68]. Bone density peaks in women in the third decade of life and thereafter begins to decline. Risk factors for osteoporosis include smoking, body mass index (BMI) <20 kg/m$^2$, oral corticosteroid use >6 months, prior fracture history, family history of fracture, and advanced age [69, 70].

In premenopausal women being treated for hormone sensitive cancers, estrogen depletion may occur as a result of chemotherapy or direct ovarian suppression via surgical (oophorectomy) or medical (goserelin) intervention. In postmenopausal women with breast cancer, AIs are often initiated to further reduce estrogen levels [71]. Several studies have shown that both steroidal (exemestane) and nonsteroidal (anastrozole and letrozole) AIs increase bone loss and fracture risk [72]. Tamoxifen protects against bone loss in postmenopausal women but has been linked to decreased bone density in premenopausal women due to its agonist/antagonist properties at different tissue receptors in various hormonal milieus [72, 73]. Overall, breast cancer survivors are at an increased risk as a result of having undergone chemotherapy, surgical or medically induced ovarian suppression, and the use of AIs, all of which result in a more rapid decline in bone density. In the Women's Health Initiative (WHI) study, breast cancer survivors had a 31% increased risk of fragility fractures compared with the general population [74], and estimates are that bone loss associated with AI therapy is more than twice that experienced by an age-matched postmenopausal population [70, 72].

### Physiology

Healthy bones are in a continuous state of turnover. Osteoporosis occurs when there is an increase in bone destruction (via osteoclast activity) relative to bone formation (via osteoblast activity) [75]. Estrogen regulates key cytokines involved in the development of osteoporosis including interleukin-1 (IL-1), tumor necrosis factor (TNF), transforming growth factor β (TNF-β), and osteoprotegerin [76]. All these play a role in the inhibition of NFκB receptor (RANK), and its ligand (RANKL), which represents an important signaling pathway for osteoclast differentiation, maturation, and functional activity [76].

During menopause, estrogen levels decrease, and bone resorption increases. After menopause, residual estrogen aids in maintaining bone density, and cancer treatments that further deplete estrogen can have a negative effect on bone [69].

### Evidence-Based Prevention and Treatment

#### Behavior and Dietary Supplements

Several studies have looked at the contribution of calcium, vitamin D, and exercise in maintaining bone health [70, 77, 78]. Although the evidence clearly suggests a role for all these behaviors, they are not seen as primary treatment, particu-

larly with respect to the high risk of bone loss related to treatments for breast cancer. Very large studies and meta-analyses have found fairly consistent benefits for calcium and vitamin D when used together, in reducing fracture risk, with higher doses of vitamin D providing more benefits [77]. One large study that did not show a decrease in fracture risk used only 400 IU of vitamin D3 [79] as opposed to other positive studies using 700–800 IU of vitamin D3 [77] along with calcium.

For exercise, most of the research points to the maintenance of bone in natural menopause and slowing effects on bone loss for women with an increased risk of bone loss as in breast cancer survivors. The summary in a recent Cochrane review [78] states that there are data to support that weight-bearing exercise increases bone density but there has not been enough research to determine whether this translates to decreased risk of fracture.

It would be reasonable to conclude that the role of calcium, vitamin D, and exercise is most appropriate as lifelong behaviors to decrease risk factors and maintain bone health [80]. Phytoestrogens, known as plant estrogens, have also been a popular topic of study for bone health. Isoflavones are one of the categories of phytoestrogens, and soy is a major source of these dietary substances [81]. Isoflavones are structurally and functionally related to 17B-estradiol and may act like natural selective estrogen receptor modulators (SERMs), having both estrogen agonist and antagonist properties depending on what tissue/receptor they associate with. The isoflavones, genistein, daidzein, and glycitein, need to be metabolized in the gastrointestinal system, and some of these are dependent on the microflora. Much of the evidence about soy and bone health comes from association studies and reviews which conclude that there are insufficient data to support the use of soy products for maintaining bone health [82].

### Bisphosphonates

Bisphosphonates reduce bone resorption by inhibiting osteoclast activity [73] and subsequently may indirectly decrease bone formation since osteoclasts have some role with osteoblasts in bone formation [83]. This group of agents is the broadest with respect to options and research in osteoporosis management. While a variety of oral and IV bisphosphonates have been FDA approved for the treatment and/or prevention of osteoporosis in postmenopausal women (Table 18.1), research in populations treated with hormone deprivation therapy and also research evaluating fractures as an outcome is more sparse. Large randomized controlled trials have evaluated both intravenous and oral agents, listed in the table below, in postmenopausal women receiving adjuvant treatment for breast cancer and have demonstrated the ability to improve bone mineral density, mostly in the lumbar spine and total hip, with up to 5 years of follow-up [84]. Treatment was given from 1 to 5 years, depending on the agent. Longer-term outcomes such as effects on bone fracture and safety have not been well addressed to date [73]. With the exception of risedronate, these agents are approved for both men and women. Finally, a European panel recommends bisphosphates as adjuvant therapy in early breast cancer based on the growing evidence about the biologic activity of bisphosphonates on tumor cells or on the immune environment [71], but NCCN guidelines await further research in this area [73].

While bisphosphonates are generally well tolerated, 10–30% of patients will experience fever and myalgias with their first dose. Osteonecrosis of the jaw has been linked to IV bisphosphonate use, and clinicians should be aware of the risk and avoid administering bisphosphonates to those undergoing dental surgery [75]. The more common side effects of oral bisphosphonates are mostly gastrointestinal such as abdominal pain, diarrhea, indigestion, nausea and vomiting, backache, headache, influenza-like symptoms, fatigue, and constipation. Rare but serious side effects include hypersensitivity reactions, esophagitis, and gastric ulcers [85].

**Table 18.1** Current bisphosphonates available for osteoporosis

| Generic | Trade name/ company | Dose | Administered | FDA approval related to osteoporosis |
|---|---|---|---|---|
| Alendronate sodium (generic available) | Fosamax® (Merck) | 5 mg daily<br>35 mg/weekly | Oral on empty stomach; 30 min before eating; follow with 6–8 oz plain water | Prevention of postmenopausal osteoporosis |
| Alendronate sodium (generic available) | Fosamax® (Merck) Comes with vitamin D also, 5600 IU | 10 mg daily<br>70 mg weekly | Oral on empty stomach; 30 min before eating; follow with 6–8 oz plain water | Treatment of postmenopausal osteoporosis; also corticosteroid induced |
| Ibandronate sodium | Boniva® (Roche) | 2.5 mg daily<br>150 mg monthly<br>3 mg every 3 months | Oral<br>Oral<br>All oral, 60 min before eating, follow with water, no mineral water<br>IV | Treatment of postmenopausal osteoporosis; oral is approved for prevention |
| Risedronate sodium | Actonel® also comes with calcium (Procter and Gamble) | 5 mg daily<br>35 mg weekly<br>75 mg for two consecutive days monthly<br>150 mg monthly | Oral; 30 min before eating; follow with 6–8 oz plain water | Prevention and treatment postmenopausal osteoporosis; corticosteroid induced as well |
| Zoledronic acid | Reclast® (Novartis) | 5 mg once yearly<br>5 mg every 2 years | IV<br>IV | Treatment of osteoporosis in postmenopausal women also corticosteroid induced<br>Prevention of postmenopausal osteoporosis also corticosteroid induced every 12 months |

Bisphosphonates not FDA approved for osteoporosis are etidronate disodium (Didronel, Procter & Gamble), pamidronate disodium (Aredia, Novartis), and tiludronate disodium (Skelid, Sanofi-Aventis)

## Selective Estrogen Receptor Modulators

A newer class of agents that have been evaluated for bone health includes selective estrogen receptor modulators (SERMs), namely, raloxifene, bazedoxifene, and lasofoxifene. Raloxifene was the first oral FDA-approved SERM for osteoporosis prevention and therapy in postmenopausal women as well as a preventive agent for breast cancer in high-risk women [86]. SERMs are an attractive class of agents for bone and breast health based on their ability to differentially impact various tissues in the body, inhibiting proliferation in some areas (such as the breast) and promoting activity in others (such as bone and lipids). Studies with these agents have been positive for decreases in markers of bone turnover and increases in BMD [86–91]. However, there is less research in populations of women with breast cancer on various treatments, and these agents are not without unwanted side effects such as hot flashes, night sweats, trouble sleeping, leg cramps, and possible thromboembolic events [73]. In fact, in one study evaluating tamoxifen (another SERM) in combination with the aromatase inhibitor, anastrozole, disease outcomes were less favorable with the use of anastrozole alone [92]. Hence, NCCN and ACS/ASCO guidelines caution against the use of SERMs in women on AIs until further research is completed [69, 73]. Furthermore, bazedoxifene and lasofoxifene are currently only approved in Europe.

## RANKL

Denosumab is a fully humanized monoclonal antibody that inhibits the interaction of RANKL and RANK and is FDA approved for postmeno-

pausal osteoporosis and treatment-related bone loss with AIs and androgen deprivation therapy [73]. Studies evaluating 60 mg administered subcutaneously every 6 months over 3 years have showed increases in BMD and reductions in fracture risk over placebo in postmenopausal women [93] without increasing the risk of cancer or hypocalcemia. There were no cases of osteonecrosis of the jaw. Denosumab is also approved for patients with solid tumor-related bone metastasis to prevent skeletal-related events at a dose of 120 mg each month.

## Novel Agents

The development of novel agents for osteoporosis, based on the known physiology of bone modeling and remodeling, is an active area. Currently, these agents are not being evaluated in women or men with a history of cancer. Some treatments that have been known to have efficacy for some time, such as parathyroid hormone, have been continued to be studied using new delivery systems such as transdermal and through a wireless microchip [94, 95]. There are two forms of parathyroid hormone that have been studied for bone health, a form of anabolic therapy that enhances bone formation [83]. One is approved by the FDA in the USA, teriparatide (I-34) (20 μg subcutaneously daily) (Forteo, Lilly) [96], and the other is a synthetic form, I-84 (100 μg subcutaneous daily) [97]. With regard to women, teriparatide is approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture as well as for glucocorticoid-induced osteoporosis in both men and women. Studies have shown that these parathyroid-related agents can decrease new vertebral fracture risk by over 60% after 18 months [96, 97]. Side effects from these agents include hypercalcemia, nausea, joint aches and pain, dizziness, and depression, and teriparatide includes a black box warning for osteosarcoma, which was seen in rat studies. It has not been studied in people with cancer and is to be avoided in people who have risks for osteosarcoma (i.e., Paget's disease, skeletal radiotherapy) [73].

Other new agents under development include bone resorption inhibitors. These include inhibitors of Wnt signaling, specifically sclerostin (a protein produced by osteocytes) and also inhibitors of cathepsin K (a protease expressed in osteoclasts that is important in bone degradation) [83, 98]. Odanacatib was in the process of completing phase III trials [99], and plans were to take it through the FDA approval process in the next year or so. However, development of this agent has been stopped due to the risk of stroke. Time will tell if other drugs with similar mechanisms arise. Drugs targeting the inhibition of sclerostin are in phase II studies, such as romosozumab, which is administered subcutaneously once a month. A phase II international dose-finding study with romosozumab compared to a subcutaneous placebo or open-label oral alendronate or subcutaneous teriparatide demonstrated increases in bone mineral density that were significantly greater than placebo and larger than the open-label-approved agents [100, 101]. There were also no concerning safety issues. Studies have not yet been done in the cancer population since FDA approval for postmenopausal osteoporosis is still pending but currently on track, and long-term outcomes and safety are not yet demonstrated.

## Assessment and Evidence-Based Practice

Early identification and management are critical in reducing the risk of fractures in this population. Osteoporosis will continue to be a problem for cancer survivors, both male and female, as hormone deprivation therapy remains a long-term successful anticancer therapy. In fact, the main significant toxicity in the study evaluating an additional 5 years of letrozole versus a placebo was bone related with those taking letrozole having more bone pain and fractures and newly diagnosed osteoporosis [12].

Guidelines currently recommend a baseline dual X-ray absorptiometry (DXA) for breast cancer survivors who are postmenopausal, women with chemotherapy-induced early menopause,

those who are about to begin AI therapy, premenopausal women taking therapy to suppress ovarian function, or those on tamoxifen [69, 73]. Repeat DXA scans are then recommended every 2 years or more often if risk factors significantly change. These recommendations are currently in line with most insurance reimbursement. BMD measurement alone is not sufficient to detect women at risk for fracture. Providers need to carefully evaluate risk factors and develop a broader fracture risk perspective. A National Osteoporosis Risk Assessment (NORA) study revealed that women with osteopenia were almost twice as likely to suffer a fracture than women without osteoporosis. These results suggest that women with BMD in the osteopenic range (*t*-score −1.0 and −2.5) are at increased risk of fracture, and treatment may be necessary even before women become osteoporotic (*t*-score less than −2.5), particularly if there are additional risk factors [102].

The American Society of Clinical Oncology (ASCO) recommends all women beginning AI therapy to receive calcium and vitamin D supplementation. General lifelong recommendations to maximize bone health include adequate calcium, with much being from food sources (1200 mg/day), and vitamin D intake (600–1000 U/day), weight-bearing exercise, and avoidance of smoking [69].

Guidelines for the administration of bisphosphonate therapy are based upon expert advice in healthy women. Clinicians should consider individual risk factors in determining the optimal treatment approach. Adequate calcium and vitamin D concentrations should be evaluated and ensured before beginning and while on bisphosphonate therapy. Several algorithms are available to evaluate fracture risk [73, 103], and numerous guidelines exist to assist in determining when to start therapy. Guidelines differ a bit with respect to when interventions should begin, but in general, women with BMD $\leq -2.0$ should receive bisphosphonate therapy. The use of bisphosphonates in women with osteopenia and known risk factors is somewhat more controversial. However, it is generally accepted that any patient initiating or receiving AI therapy with a *t*-score less than −1.5 or with multiple risk factors (2 or more) should receive bisphosphonate therapy. While oral bisphosphonates are currently a common treatment related to osteopenia or osteoporosis, poor bioavailability and patient compliance may limit their efficacy. Therefore, an important aspect of managing osteoporosis includes the assessment of adherence and barriers to taking oral medications (such as unwanted side effects, intolerance, or lifestyle) as well as barriers to incorporating exercise into one's life. Providers should facilitate problem-solving against the challenges of maintaining healthy behaviors. Further, the optimal duration and long-term safety of bisphosphonate therapy are not known. Most experts recommend 3–5 years of treatment followed by a drug holiday accompanied by reevaluation of risk [73]. Data demonstrate that the effects of bisphosphonates can continue for 3–5 years after treatment has stopped [104, 105].

Based on the black box warning of osteosarcoma, the use of teriparatide in women with a history of breast cancer is not generally recommended. People who are at higher risk for bone cancers including those with previous radiotherapy to the bone, Paget's disease, and other metabolic disorders of the bone (besides osteoporosis) should also avoid the use of teriparatide [73].

## Vaginal Symptoms of Dryness and Dyspareunia

### Definition and Incidence

Genitourinary syndrome of menopause (GSM), previously known as vulvovaginal atrophy, is often one of the later issues to emerge during the transition to menopause, but it is one (similar to bone loss) whose associated symptoms are not subject to spontaneous or adaptational improvement [106]. The longer a woman is estrogen depleted, the worse vaginal symptoms of dryness and dyspareunia are likely to get. Symptoms generally associated with GSM which can cause distress are vaginal dryness, itching, burning, and irritation, urinary frequency and/or urgency, and pain with intercourse, dyspareunia. Negative

overall sexual health and satisfaction can then occur due to decreased sexual activity and intimacy. An aging vagina can also increase one's susceptibility to urinary tract infections by increasing vaginal pH [107]. Overall, in the general female population, 1 international descriptive study involving over 4200 postmenopausal women provides data to support that about 40% of women report symptoms related to vaginal aging, with slightly higher numbers in the USA and Finland compared to Canada [108], while other reviews state the prevalence is as high as 57% [15].

The most common symptoms reported include dryness, itching/irritation, and dyspareunia. Studies of the general population report that slightly more women experience dryness (55%) as opposed to dyspareunia (44%) or irritation (37%) [109]. Women on aromatase inhibitors, in one study, reported higher frequencies of dyspareunia (62%) versus vaginal dryness (42%) [110], and even women with a history of colon or rectal cancer reported experiencing vaginal dryness (28% and 35%, respectively) and dyspareunia (9% and 30%, respectively) [111]. Similarly, in ovarian cancer survivors, a report of descriptive data of a heterogeneous group of 329 epithelial ovarian cancer patients at a single institution cites that among women who were sexually active, 80% had trouble with vaginal dryness (40% "very much"), 62% had dyspareunia (20% "very much"), and 75% had trouble reaching orgasm with 50% of those expressing this occurred 90% of the time[112]. Cancer survivors, particularly breast and gynecologic, can experience the hypoestrogenic state much earlier than natural menopause, setting the stage for more prevalent and severe atrophic effects due to the duration of hypoestrogenism.

After cancer diagnosis, changes in the vagina and vulva that can result in associated symptoms of dryness or pain can occur as a result of a treatment-induced hypoestrogenic state, as in premature chemotherapy-induced menopause, or due to medications such as aromatase inhibitors that seek to keep estrogen concentrations as low as possible, or it can result from radiation therapy to the pelvis [113] or surgery in the pelvic or anal area such as in gynecologic or colon and rectal cancer [111]. All of these populations of women can also experience psychosocial and surgical challenges that can impact self-image and their relationships with themselves and their partners. Hence vaginal changes can also be impacted by changes in behaviors such as less sexual activity that further decreases circulation and negatively affects tissue health.

## Physiology

Estrogen and estrogen receptors play a major role in vaginal architecture [107]. The vaginal wall contains a squamous epithelium, a lamina propria, a smooth muscle layer, and a covering membrane, all of which are very much influenced by estrogen [107]. Estrogen maintains the fluid film that separates the vaginal walls. Estrogen also keeps the epithelium dense, resulting in more superficial cells than basal or parabasal layer cells. Estrogen keeps vaginal smooth muscle functional and contributes to tissue elasticity through the regulation of fibroblasts that make collagen. Additionally, estrogen is responsible for vasodilatation in the lamina propria and promotes the expression of various neurotransmitters that ultimately result in increased blood flow [114].

Without estrogen, the vagina decreases in both size and function, and changes occur in the vaginal epithelium. The epithelial cells decrease, and parabasal cells become the major cytology. Collagen, blood flow, and lubrication decrease resulting in an inflexible network of dry cells with a higher pH, increased susceptibility to infection, and itchy, uncomfortable sensations. The smooth muscle becomes less functional, challenging orgasm, and intercourse becomes painful with fragile tissues that are subject to bleeding and trauma.

## Evidence-Based Treatment

Although there have been a good number of studies evaluating various treatments for GSM, very few of them have been done in women with a

history of breast, gynecologic, or any other types of cancer. A summary of what is known about the evidence to date is provided below.

## Vaginal Versus Systemic Treatment

Experts recognize that if the primary concerns are vulvar and vaginal symptoms (e.g., not accompanied by hot flashes), the most efficient way to impact those symptoms is to focus on local, vulvar and vaginal interventions as opposed to a systemic pharmacologic approach [115, 116].

## Vaginal Estrogen

When there are no contraindications, low-dose vaginal estrogen may be the best, most effective treatment for vaginal atrophy, and several forms are available: rings, tablets, and creams [116]. The product with the lowest dose of estrogen that has been proven effective for the treatment of vaginal estrogen is the ring, with 7.5 μg of estrogen [117–120]. Systemic absorption is related to dose, but it is not yet clear what the lowest effective dose might be. Higher doses of vaginal estrogen have been shown in studies to be systemically absorbed sufficiently to alleviate nonlocal symptoms such as hot flashes [118, 121]. However, it should be noted that, to date, there has not been a product that has been shown to be effective for vaginal atrophy that has had no systemic absorption. Data have shown that even with 7.5 μg of vaginal estrogen, there is an increase in systemic concentrations initially, followed by a decrease, but not in all women [122, 123]. In addition, the literature is limited by the fact that in most laboratories, serum estradiol assays do not reliably measure very low concentrations and may therefore miss small increases. Increases in systemic absorption may be insignificant statistically and remain in the postmenopausal range but may have biologic activity at distant target receptors (such as lipids, bones, or breast), some of which may be unwanted and even result in increasing a woman's risk of cancer or its recurrence [122]. More research is needed regarding the clinical significance of short-term increases in systemic estrogen as well as the impact on distant target tissues with various doses of vaginal estrogen.

## Vaginal Lubricants and Moisturizers

Nonhormonal local treatment options include vaginal lubricants and moisturizers. Lubricants are used during the time of sexual activity to improve lubrication and can be made with various types of bases including water, oil, or silicone. They typically act immediately and provide very short-term benefit by reducing friction and irritation. Over-the-counter lubricants can also contain additives such as perfumes, propylene glycol, warming agents, spermicides, or sweeteners, which may not be specifically labeled and could cause irritation or infections [15, 124]. Water- and silicone-based lubricants break down in warm, soapy water, while petroleum-based lubricants can damage latex condoms and may increase vaginal infections similarly to glycerin-based products [124].

Vaginal moisturizers are different in that they are intended to hydrate the vaginal tissue and can improve vaginal pH. Moisturizers are not used at the time of sexual activity but, rather, are recommended to be used at bedtime to allow the maximum absorption [124]. The optimal frequency of moisturizer use is not known, particularly on a long-term basis, but it makes sense that the degree of the severity of the symptoms, and thus state of atrophy of the vaginal tissue, should guide the dosing. For example, it would be prudent to use a moisturizer as much as 5 days a week initially, at bedtime, and as symptoms improve over the next 4–8 weeks, reducing the frequency to three times per week and then perhaps maintaining hydration with twice weekly use. Randomized trials involving a polycarbophil-based moisturizer, Replens, have evaluated its effects comparing it to both dienoestrol cream as well as a placebo water-based lubricant [125–127], demonstrating relief of symptoms generally regardless of what product is used. Moreover, a large randomized controlled trial found that 12 weeks of daily and nightly use of a moistur-

izer significantly improved dryness and dyspareunia in women with a history of breast or gynecologic cancer [128]. Be sure to also treat the vulva as this can be a source of discomfort.

## Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a prohormone and an endogenous hormone produced by the adrenal glands [129], and a vaginal ovule containing DHEA, called Intrarosa (Prasterone-Endoceutics, Inc.), has been approved by the FDA for moderate to severe pain during sexual intercourse. The ovule that was approved contains 6.5 mg of prasterone and is to be used once daily at bedtime. DHEA has a sulfate ester form (DHEA-S), which is interconvertible with DHEA. Both DHEA and DHEA-S are inactive forms of androgen and must be converted or synthesized to active metabolites [129]. Much of the conversion of DHEA is believed to be done in peripheral tissues at target sites [130] and not diffused into the general circulation. There are target sites for DHEA in the vaginal epithelium [130].

Several studies have been completed in postmenopausal women to evaluate the effect of vaginal DHEA on vaginal symptoms of dryness and/or dyspareunia. The seminal phase III, randomized controlled study in 218 women evaluated three doses of vaginal DHEA [131]. Postmenopausal women were randomized to receive one of three doses of vaginal DHEA by ovule (0.25%–3.25 mg, 0.5%–6.5 mg, 1.0%–13 mg) or placebo for 12 weeks. The primary outcome was the improvement in atrophy symptoms consisting of a decrease in parabasal cells and vaginal pH, increase in superficial cells, and improvement by self-report of the most bothersome symptoms: dryness, itching/irritation, or dyspareunia. All the primary outcome measures were significantly improved, some beginning at 2 weeks into the study [131]. Women reported significant improvements in their most bothersome symptom, be it dyspareunia, vaginal dryness, or itching/irritation as well as general measures of sexual function with DHEA over placebo. Parabasal cells decreased by 29% in the 0.25% DHEA dose and about 36% with the two higher doses compared to a small increase in parabasal cells in the placebo by the second week. At 12 weeks, the decrease was even more pronounced in all doses of DHEA, while there was no change in the placebo group. Vaginal pH was also improved, showing significant decreases with each dose of DHEA at each data point compared to placebo [132]. Sex steroid hormone concentrations were not significantly increased and were similar among the placebo arm and the two lower doses of DHEA [133]. Prasterone has not been studied in women with a history of cancer. However, a compounded vaginal DHEA product was evaluated in 441 women with a history of breast or gynecologic cancer and at least moderate vaginal symptoms of dryness or dyspareunia and compared to a compounded vaginal moisturizer [128]. Results of this study did not demonstrate statistically significant differences in the most bothersome symptom at 12 weeks between the arms; however, the vaginal DHEA improved symptoms more quickly with significant improvements at 8 weeks compared to the moisturizer and also was significantly better than the plain moisturizer for many of the secondary outcomes [128, 134].

## Selective Estrogen Receptor Modulators (SERMs)

SERMs were developed and are novel-acting agents for the prevention of breast cancer as they act to block estrogen's effects on cell growth in the breast while having estrogenic effects on other types of cells, such as the vagina. As such, the idea that they may help prevent vaginal aging and keep vaginal tissue healthy is something worth pursuing. However, not all SERMs are created equal, and they have differential effects on vaginal tissue [135]. Therefore, data with vaginal endpoints have been mixed with at least one SERM not having a positive effect on vaginal symptoms [136] with others having a positive effect on tissue maturity [137, 138]. Most of the research to date has been with ospemifene, which

was approved by the FDA in 2013 for moderate to severe dyspareunia due to menopause. Studies that have been done have excluded participants with a history of cancer. Overall, however, if the primary concern is vaginal symptoms, taking a systemically active agent that has the potential for side effects will likely not rise to the level of a high-priority treatment.

## Miscellaneous Treatments: The Good, the Bad, and the Promising

Numerous types of products have been studied, topical and vaginal, to try to address the unmet need of nonestrogenic treatment for vaginal symptoms. Most of these interventions have had very limited research; so many unanswered questions remain as well as a lack of information about definitive effectiveness. However, as some of these interventions may end up providing some benefit, they are briefly reviewed.

Pilocarpine—Based on an interesting hypothesis and some preliminary data that pilocarpine, a cholinergic parasympathomimetic agonist, could stimulate increased secretion by exocrine glands including in the vagina, a phase III randomized placebo-controlled trial was completed. This four-arm trial evaluated 5 mg twice a day versus 5 mg four times per day of pilocarpine versus matching placebo dose arms on patient reports of vaginal dryness over 6 weeks. The results indicated no benefit of pilocarpine at either dose over placebo to improve vaginal dryness [139].

Fractional microablative CO2 laser—This laser procedure is used to remodel tissue, being used in dermatologic and plastic surgery, to improve collagen and elasticity in places such as the face and neck. Uncontrolled studies from Europe in postmenopausal women, including breast cancer survivors, using a vaginal probe to deliver laser beams to atrophic vaginal tissue, report improvement in vaginal tissues, sexual functioning, and sexual satisfaction [140, 141]. More research is needed to better define risks versus benefits around this procedure.

Topical lidocaine—For women with a history of cancer who have dyspareunia related to pain or tenderness in the vulvar vestibule, topical 4% lidocaine applied to that area for 3 min was shown to significantly improve some measures of arousal, orgasm, and pain as measured by the Sexual Function Questionnaire over a placebo at 4 weeks [142, 143]. The sample in this small randomized trial was selected specifically based on a response to lidocaine for their vulvar pain; hence, this would appear to be a very specific solution to a specific problem but may indeed be helpful for women with a vulvar pain issue.

Estriol and *Lactobacillus*—Consistent with the knowledge that estrogen is the most effective treatment for vaginal tissue repair and with the desire to use the lowest dose of estrogen possible, one phase I study has been done with the weakest type of estrogen, estriol (E3), in combination with *Lactobacillus acidophilus* to repopulate the vaginal flora. This study, completed in 16 postmenopausal women who were on aromatase inhibitors, evaluated a vaginal tablet containing 0.03 mg estriol and *Lactobacillus* for effects on various endpoints, pharmacokinetics, sexual experiences, and vaginal microflora characteristic [144–146]. The preliminary findings are that more women returned to sexual activity, reported decreased dryness and dyspareunia, had improved markers of the vaginal microflora, and did not experience increases in estradiol or estrone, only estriol, and this was transient. More research in this area would likely be of benefit to cancer survivors.

Testosterone and hyaluronic acid—Very small preliminary studies have been completed, one open-label vaginal testosterone without a comparator [147] and one randomized between estradiol vaginal tablets and hyaluronic acid sodium salt vaginal tablets [148]. Both demonstrate benefit of pH and vaginal tissue maturation and self-report of dryness and dyspareunia for all arms. The open-label testosterone study was completed in women on aromatase inhibitors. More research is needed to better understand the potential mechanisms and risks versus benefits of these agents on vaginal cells and, in particular, in women with a history of cancer.

Vaginal dilators—A Cochrane review published in 2014 did not find any randomized controlled trials or any experimental studies that provide data to support the use of vaginal dilators to improve sexual satisfaction as an outcome [149]. However, based on excluded studies, the authors conclude that vaginal dilator therapy may be used to improve vaginal stenosis and to help prepare women for sexual activity after radiation therapy. The idea of using dilator therapy in cancer survivors to help women move more comfortably into engaging in intercourse is echoed in a very practical review by colleagues working in sexual health who also suggest dilators may improve blood flow and prevent fibrosis in those who have stenosis or scaring as a result of pelvic surgery [124]. Care must be taken by providers to obtain the knowledge required to evaluate how women can safely and appropriately use this therapy as it can cause vaginal trauma and psychosocial distress [149].

## Assessment and Evidence-Based Practice

In summary, there are several proven effective treatments for vaginal symptoms; however, none have been adequately studied nor approved for women with a history of cancer. Approved options in general menopause include vaginal estrogen for both dryness and dyspareunia, vaginal dehydroepiandrosterone for dyspareunia, ospemifene for moderate to severe dyspareunia, and vaginal moisturizers mostly for vaginal dryness, but some women also get benefit related to dyspareunia. Moisturizers are thought to have more transient relief, but their efficacy and magnitude of effect have not been fully evaluated in a controlled trial using the frequency of use likely needed for symptoms related to a very atrophic vagina as in hormone-deficient cancer survivors. Preliminary evidence from well-designed trials indicates that with frequent use (up to daily), women do experience symptom relief.

Assessment of vaginal changes and discomfort with accompanying unwanted sexual symptoms should be part of good health care for cancer survivors. Health-care providers might consider asking their patients about their experience by stating something like "A decrease in estrogen, as in menopause, can cause changes in the cells in the vagina. Some women report dryness, itching, burning, or pain, particularly with sexual activity. Have you experienced any of those symptoms which have impacted your life in a negative way?" thus setting the stage for women to vocalize their concerns in this area. Information related to vaginal infections such as whether the woman has experienced malodorous secretions, burning, and pain on urination should be solicited. Alternatively, providing a checklist of concerns to the patient that includes various sexual-related concerns, specifically vaginal symptoms, may be a way to open up the dialog with those who acknowledge a problem in this area [150]. When possible, physical inspection of the vagina should be done. An atrophic vagina will have a thin, pale, parched epithelium, and it will appear shorter, with a loss of rugae and elasticity and decreased secretions [107].

Treatment options based on the evidence cited above should be reviewed. According to the position statement of the North American Menopause Society on treating symptomatic vulvovaginal atrophy, nonhormonal therapies such as vaginal moisturizers are considered first-line therapy [151]. Education, regarding the regular use of moisturizers or lubricants, increased foreplay to improve blood flow, and the degree to which vaginal symptoms are distressful and/or impact one's quality of life is part of a comprehensive evaluation. Adequate blood flow is an important factor in enhancing vaginal health. Dyspareunia leading to decreased sexual activity further complicates vaginal health due to lack of blood flow to the vagina. Maintaining at least a modicum of sexual activity is one of the best ways to optimize blood flow and help maintain vaginal health.

For women who are deeply bothered by vaginal symptoms or who experience multiple infections, dialog regarding the risks and benefits of very low-dose vaginal estrogen (if not contraindicated) or DHEA can be initiated.

## Conclusions

There are very clear sequelae experienced by women related to estrogen depletion. Due to the important role of sex steroid hormones on various tissue receptors throughout the body, a clear understanding of the extent to which estrogen ablation treatment impacts symptoms and broader aspects of quality of life is needed. A fair amount of research is available in the areas of hot flashes and osteoporosis, providing a menu of options in treating and, in the case of bone loss, even preventing these unwanted menopausal symptoms. Less research exists with regard to vulvar and vaginal symptoms in cancer survivors, particularly with regard to long-term safety.

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# Part VII

# Hematological

# Thrombosis and Bleeding in Cancer Patients

19

Wolfgang Korte

## Introduction

The writings of Virchow in 1856 were the first descriptions on the way to the understanding of the pathogenesis of thrombosis [1]. Hypercoagulability is a frequent phenomenon in cancer patients. Published knowledge dates back to Armand Trousseau, who described a tendency to "spontaneous coagulation" in two patients with phlegmasia alba dolens and gastric cancer [2]. Since these observations, much progress has been made; it has become clear that activation of blood coagulation not only is a result of the presence of malignant cells; rather, it makes part of the malignant process [3]. Recent years have shown that the pathophysiology is likely to be different in different types of cancer [3, 4]; for example, specific genetic alterations associated with increased thrombogenicity in myeloproliferative diseases, different from solid tumors, have been identified [5]. In general, however, cancer patients display a procoagulant phenotype [6]. But cancer patients are also prone to bleeding due to the properties of the tumor, during interventions or when a disseminated intravascular coagulation [DIC] occurs [7, 8]. This chapter will review the important issues of thrombosis and bleeding in cancer patients from a practical point of view.

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## Epidemiology of Hypercoagulability in Cancer Patients

There is ample evidence that cancer patients frequently show increased biochemical markers of plasmatic and platelet coagulation activation (increased prothrombin fragment 1 + 2 and thrombin-antithrombin complex), generation of soluble fibrin (increased fibrinopeptide A and B), fibrin generation and degradation (increased fibrin degradation products, D-dimer), and surrogates of continued platelet activation [9–11]. Such markers of overall coagulation activation prove the procoagulant phenotype [12, 13] in cancer patients. Besides, some of these markers such as fibrin monomer or D-dimer have been shown to be associated with tumor spread [14] as well as progression, response to therapy, and survival [15–17]. In addition, certain genotypes of coagulation proteins seem associated with survival and response to therapy (e.g., PAI-1 in testicular cancer [18] and TFPI in breast cancer [19]), although this is, for now, not part of a management algorithm.

Depending on the type of cancer and the state of the disease, increased surrogate markers of



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coagulation activation can be found in up to 90% of patients. However, one has to recognize that coagulation proteins and markers of coagulation activation make part of a dynamic phenomenon: even largely increased markers of coagulation activation are not predictive of the occurrence of a thromboembolic event in the single patient, although the relative risk is increasing with increasing activation marker concentrations [10, 16, 20–22]. On the other hand, it is well documented that cancer patients have a high prevalence of clinically silent thrombi, as shown by the fact that cancer patients have a high prevalence of thrombi that are detected at autopsy only [23–25].

Venous thromboembolism (VTE) that is cancer associated can precede cancer diagnosis. The highest risks for VTE before a cancer diagnosis is made are found in acute myelogenous leukemia (AML), non-Hodgkin lymphoma (NHL), and renal, ovarian, and pancreatic cancer (approximately three- to fourfold increased risk); the overall risk in cancer patients to develop a VTE as a sign of (the still undetected) cancer is approximately 1.3 [26]. In the first 2 years after a VTE diagnosis is made, the greatest risks for being diagnosed with cancer are found for lymphoma (approximately fivefold) and ovarian cancer (approximately sevenfold) [27]. Prospective studies have also confirmed the association between overt malignancy and VTE. A prospective case-control study of 3220 patients with VTE revealed an overall sevenfold increased risk in patients with cancers. Hematologic malignancies had the highest risk (OR 28), whereas solid tumors had ORs from 2 to >20 [28]. Comparable results for VTE in lymphoma, leukemia, and plasma cell dyscrasias were described in other studies [29]. Besides, various additional comorbidities, including various forms of cancer, are associated with an increased risk of dying in patients admitted to the hospital for VTE [30].

The tumor itself is able to induce (mainly) procoagulant changes, but such changes are also found in relationship to cancer treatment. In a US study, 8% of 66,000 (neutropenic) cancer patients hospitalized were found to develop thromboembolic events (5% venous, 15% arterial events during first hospital admission) [31]. The highest incidence for VTE was found in leukemias and lymphomas and pancreatic, brain, endometrial, or cervical cancer; on the other hand, arterial thrombosis was most commonly seen in hematological malignancies and prostate, lung, and bladder cancer [32]. Immunomodulatory therapy in multiple myeloma is associated with an increased risk for VTE [33]. These observations are well in line with those in other patient cohorts of chemotherapy in solid cancer with an incidence of VTE of 7% within 3 months after chemotherapy and an annual incidence of 11% [34].

Besides its overall predictive properties in hospitalized patients [30], VTE is a significant predictor of a 2-year mortality in breast cancer patients with the greatest effect in patients with local- or regional-stage (hazard ratio 3.5–5) breast cancer [35]. These and similar observations [26] suggest that survival is worse the closer VTE and cancer diagnosis come together. This might be due to a more advanced cancer stage in such situations.

## Pathogenesis of Thromboembolism in Cancer Patients

According to Virchow, the main reasons for the occurrence of a thrombosis are changes in blood flow, vessel integrity, and composition of the blood [1]. Aberrant blood flow is frequently observed in situations associated with hyperviscosity, which can derive from both fluid and cellular blood components. As perfusion problems due to hyperviscosity frequently occur in small vessels first, it is easy to understand from a mechanistic point of view that the brain, the heart, the lungs, and the kidneys are frequently affected, with the resulting clinical manifestations [36]. Laboratory tests for hyperviscosity are infrequently performed. Therefore, the recognition of hyperviscosity usually depends on clinical suspicion and supporting laboratory data, e.g., increased monoclonal proteins in multiple myeloma [37]. These can affect flow characteristics via several mechanisms [38]; as hyperviscosity is also a function of the size of the molecules

involved, it is most common with IgM paraproteins [39]. Other (rare) reasons for hyperviscosity can be light chain disease as well as cryofibrinogenemia and cryoglobulinemia [40]. Fibrinogen, which significantly influences blood viscosity and is frequently increased in cancer patients [41], is, as are other hemostatic markers, dependent on the course of the malignant disease [16].

Further important reasons for hyperviscosity are massively increased cell counts [42]. A high hematocrit can convey hyperviscosity, as can be deduced from the thromboembolic risk that is well documented for polycythemia vera (P. vera) patients; thromboembolism is the most frequent cause of death in P. vera [43]. Other factors seem to play important roles, too, such as platelet activation (increased thromboxane formation) [44]) and JAK-2 mutations, shown to be involved in the development of myeloproliferative diseases; specifically, the incidence of thromboembolism seems to depend on the number of alleles affected, but the exact mechanism remains to be elucidated [4, 45–47].

Leukostasis can occur within the microcirculation of the central nervous and respiratory system when hyperleukocytosis is present. It can occur in chronic leukemias, especially chronic myeloid leukemia, but it is rather seen in AML variants with increased blast adhesiveness [48]. Leukostasis is much less frequently seen in lymphoid leukemias: lymphocytes are smaller and seem to have a lower adherence to vasculature, specifically in chronic lymphocytic leukemia (CLL) [49]. Different from myeloid leukemias, leukostasis in lymphoid leukemia might need additional risk factors such as a concurrent infection to upregulate adhesive cell surface molecules in order to precipitate clinical symptoms.

Thrombocytosis is associated with an increased risk for VTE in cancer patients as well: patients with a platelet count of >350 G/l have a significantly increased risk [50, 51]. Also, there is evidence that physical properties such as mean platelet volume (MPV) [52] as well as the degree of platelet activation [21] are associated with the risk for thrombosis in cancer patients.

As most solid tumors or affected lymph nodes grow expansively at some point in time, vessel compression is a further potential reason for the occurrence of VTE in cancer patients. However, the classical example for this situation, the superior vena cava syndrome (SVCS), is probably much rarer than perceived. In a large retrospective cohort of more than 34,000 patients, only 6 had SVCS thrombosis and most had to be attributed to central lines [53]. Any vein might be subject to external compression, thus a reason for VTE [54]. Cancer patients are often immobilized or have to undergo surgery; both situations result in impairment of regular circulation, inducing an additional risk factor (besides the cancer itself). That this risk is severe can be deduced from a prospective cohort in which up to 50% of the deaths early after cancer surgery were due to VTE [55].

As mentioned, direct tumor-associated vessel impairment increases the risk for VTE. Besides outside vessel compression, direct tumor cell invasion of the vessel wall might result in increased risk for VTE; also, the tumor induces tissue factor (TF)-dependent angiogenesis, thereby increasing the exposition of the blood volume to tumor-derived procoagulants [56]. The tumor itself might present as an intravascular mass that induces additional adjacent accumulation of blood cells and fibrin. Emboli directly deriving from tumors are rare but do occur, most frequently in gastrointestinal cancers [57]. This phenomenon might, for example, explain the reduced survival in hepatocellular carcinoma with portal vein tumor thrombi (3-year survival 20% with vs. 56% without [58]), with the extent of the portal vein thrombus likely also being important [59]. Other tumor entities have been found to show similar phenomena.

It is well known that the procoagulant phenotype in cancer is at least partially related to cytokine trafficking from cancer cells, endothelial cells, and peripheral blood cells [60, 61]. This can lead to tissue factor (TF) (over-) expression (e.g., on monocytes), upregulation of procoagulants, downregulation of anticoagulants, platelet activation [62], or neovascularization through proangiogenic signaling [63]. Neutrophils can activate platelets via cathepsins, can produce elastase to degrade the endothelium, can expose

thrombogenic subendothelium [64], and can bind to platelets via various mechanisms [65]. It was recently shown that generation of neutrophil extracellular traps (NETs) in malignancy links the neutrophils to the generation of a prothrombotic state [66], while neutrophilia is associated with an increased risk of VTE in cancer patients with chemotherapy [67].

Tumor cells produce several factors that induce the prothrombotic state in cancer. TF is increased in cancer patients [68] with DVT [69], especially in leukemia and lymphoma [70]. On the other hand, increased profibrinolytic activity might also be encountered in leukemia patients [71] as well as patients with solid tumors [8].

PAI-1 levels are frequently increased in cancer patients, which is associated with an increased risk for VTE in both cancer and non-cancer patients [72]. Whether the 4G/4G polymorphism has direct or indirect (through VTE) influence on the outcome remains to be elucidated [18].

Apoptosis of (tumor) cells results in a prothrombotic state as observed with different malignant and benign cell lines; thrombin generation seems to parallel the degree of apoptosis [73], resulting in increased prothrombotic risk. This offers a mechanistic explanation for the hypercoagulablity observed in tumor lysis syndrome as well as the increased risk of VTE during tumor therapy [74].

Very small membrane fragments are known as microparticles (MP); they derive from normal cells (platelets, blood cells, or endothelial cells) but can also be derived from malignant cells. Microparticles carry TF and may—through the provision of phospholipids—be involved in facilitation of complex formation and thus increased thrombin generation. Recent clinical studies have shown MP to be increased in cancer patients with different tumors [74, 75]. Procoagulant microparticles devoid of TF activity have also been described ([76] see also below).

Cancer patients can acquire a resistance against activated protein C (APC resistance) [29, 77–80], but the exact contribution of this potentially prothrombotic mechanism to the VTE phenotype is difficult to define, given the other prothrombotic mechanisms present in cancer patients.

The antiphospholipid syndrome (APS) is characterized by thromboembolism and the presence of antiphospholipid antibodies (APA, by definition against cardiolipin or β-2 glycoprotein I or a lupus anticogulant; to fulfill the diagnostic criteria for APS, the antibodies have to be found in two separate investigations at least 12 weeks apart). In lymphoma patients, APA seems not infrequent (up to 27%, with an annual rate of thrombosis of 5.1% in patients with APA and 0.75% in those without [81]), well in line with other findings [82]. As in non-cancer patients, the presence of antiphospholipid antibodies in cancer patients seems to be associated with an increased risk of thromboembolism [83, 84]. Although overall causality of the malignant process for the presence of APA seems unlikely [85, 86], some data suggest that antiphospholipid antibody-associated VTE might be the first manifestation of malignancy [84, 87]; whether or not chemotherapy modulates the VTE risk associated with APA is unclear.

Factor V Leiden is the most frequent inherited thrombophilia, also in cancer patients [88]. It confers an approximately 7-fold increased risk for DVT in heterozygotes and an 80-fold increase risk in individuals being homozygous. Overall, its presence seems to add an additional risk factor for VTE in cancer patients besides the cancer itself [89]. The prothrombin 20210A mutation causes increased prothrombin levels and is associated with a relative thrombotic risk of three in heterozygotes. It seems possible, however, that the VTE risk mediated through these most frequent congenital thrombophilias is different in different cancer patient populations [88, 90–92].

## Iatrogenic Factors

Chemotherapies and tumor surgery frequently induce a hypercoagulable state [93, 94]. Therefore, cancer patients (and specifically those undergoing chemotherapy) have a high risk of developing thromboembolic events [95]. A special situation is encountered with the use of asparaginase in lymphoproliferative diseases; the initial phase with early reduction in protein synthesis is followed by a phase of hypercoagulability as procoagulants

recover earlier than anticoagulants (mainly antithrombin); this is associated with an increased thrombin generation throughout therapy [96]. Corticosteroids, often used in conjunction, also might increase the prothrombotic risk [97]. Other chemotherapeutic regimens with procoagulant effects include cisplatin, which seems able to induce a TF-independent procoagulant response mediated through generation of (TF free) microparticles from endothelial cells [76]. Thalidomide and analogues such as lenalidomide are also prothrombotic. When used for single-agent therapy in myeloma, less than 2% of patients will develop thromboembolism [98]. In combination with steroids (dexamethasone), however, the rate increases markedly [99] [100]. Cohort studies suggest, however, that prophylaxis with low-molecular-weight heparin (LMWH) can significantly reduce the VTE risk in these patients [101].

Central venous catheters (CVC) are frequently used in order to provide a secure and reliable way for repeated access to the venous system during IV-based therapies. CVCs are believed to be thrombogenic due to the vessel injury to begin with but also because of changes in blood flow as well as provision of an artificial surface in the setting of hypercoagulability from the underlying cancer [102]. Underlying congenital thrombophilia might be an aggravating factor [103], and prevalence might differ with different access sites [104]; prospective data are missing, however. Also, data on the frequency of CVC-related venous thrombosis are not homogeneous [105–108]. In a registry of 2945 cancer patients, deep venous thrombosis (DVT) in the upper extremities overall occured in 6.7%; association with a CVC occured in 3.5% [109]. Other trials suggested ovarian cancer to induce a specific risk for CVC-related DVT [108] and thrombocytopenia to be somewhat protective in this setting.

## Management of Hypercoagulable States

As mentioned above, VTE is frequent in cancer patients [6, 110] (with an estimated prevalence of 4–20%) and is the second greatest cause of mortality in cancer. In the past, a prospective randomized clinical landmark trial has clearly demonstrated that long-term use of daily subcutaneous LMWH is more efficient than vitamin K antagonists to prevent recurrent VTE in cancer patients [111], but a recent trial failed to confirm this [112]; a potential explanation for this outcome, besides other things, might be that cancer therapy has considerably changed over the decade that has elapsed between these trials. Various national and international guidelines [113–116] recommend the use of LMWH for 3–6 months for treatment and secondary prophylaxis of VTE in cancer patients. Despite convincing data that effective pharmacological antithrombotic prophylaxis is relevant, many caregivers still seem not to have yet modified their clinical practice [117]. This problem is of significance [118], as there is evidence that up to 40% of patients that developed VTE did not receive the thromboprophylaxis necessary [95, 118]. And this is despite the fact that LMWH long-term use appears well tolerated and may, in some instances, positively influence overall response to therapy [119]. Palliative care patients might be preferring LMWH injections over warfarin or compression stockings, but physicians' preferences also seem to have an important influence on the respective decisions [120–124].

The exact rate of VTE or arterial thromboses [125] with the use of thalidomide and its analogues probably depends on the therapeutic regimens chosen (especially in combination with dexamethasone, see above) and therefore still remains some matter of debate [33, 126], but the frequency of VTE is high enough to suggest that pharmacological thromboprophylaxis, probably preferably with low-molecular-weight heparin, should be used [127, 128].

Pneumatic compression stockings seem to work well for thromboprophylaxis in cancer patients, but randomized controlled studies on their use, specifically in comparison to other pharmacological antithrombotic therapies, are rare [117, 129–131].

At the time being, there is still no unequivocal evidence that antithrombotic prophylaxis will prevent catheter-associated thrombosis in cancer

patients, but available data strongly suggest a rational for the use of antithrombotics [106, 132, 133].

The potential use of direct oral anticoagulants (DOACs, also still referred to as NOAC for "new oral anticoagulants" or "non-VKA oral anticoagulants") in cancer patients is of utmost interest and seems in a transition phase at the time being. The phase III studies for VTE therapy and secondary prophylaxis for dabigatran, rivaroxaban, apixaban, and edoxaban all included patients with VTEs that were later on found to be related to a malignancy. Such patients within these trials (subgroup analyses) as well as "real-world patients" (cohort studies) were separately evaluated; no sign was found that the use of DOACs showed evidence for decreased efficacy or increased toxicity as compared to non-DOAC, standard anticoagulant therapy in the setting of cancer-associated thomboembolism [134–142]. However, as patients with active cancer were excluded from the respective phase III studies, a formal evaluation of the use of DOACs in cancer patients is needed [143]. Such studies are underway. Meanwhile, in VTE found to be cancer associated, our approach is to continue DOACs in patients that were started on it if therapy has been effective and well tolerated. If a malignacy is already known when VTE occurs, we currently still suggest to start therapy with LMWH according to the current guidelines. But as mentioned before, a transition phase is taking place. Should the formal studies confirm the positive initial clinical experience with DOACs in cancer patients, these substances will be an important addition to the current selection of antithrombotic therapies in patients with cancer. Specifically, these substances will likely reduce the need for the subcutaneous application of antithrombotics in many, if not most, cancer patients and thus also increase their quality of life.

Despite being frequently used, aspirin cannot be generally considered as an adequate prophylaxis for primary or secondary prophylaxis of venous thromboembolism in cancer patients [144]. However, in situations where plasmatic antithrombotics are contraindicated and aspirin is not, its use might be considered rather than completely withholding antithrombotic therapy [115].

In hypercoagulable states due to acquired anticoagulant deficiency such as antithrombin deficiency with asparaginase therapy, replacement therapy should be taken into consideration although randomized controlled trials are needed to clarify this question [145, 146].

In patients with hyperviscosity due to paraproteins [37, 80], plasma exchange or plasmapheresis might be the most appropriate way to treat, at least for the short-term benefit. High protein concentrations, however, tend to "rebound" due to the high protein concentrations present in the extravascular space (especially with IgG) [147]. Other reasons for hyperviscosity in cancer patients might exist and thus necessitate different and/or continued therapeutic prophylactic approaches [41]. Recently, this was recognized specifically for JAK-2-positive hematological diseases [148, 149].

Vena cava filters might be an option for the prevention of thromboembolism in patients with manifest thrombosis or very high risk for thromboembolism and bleeding risk with antithrombotic therapy (such as chemotherapy-induced thrombocytopenia) or contraindication to anticoagulation [115], but the consideration itself is a sign of poor prognosis [150]. CVC filters may be associated with device-related thromboembolic complications in nearly 10% of patients [151]; however, in the absence of randomized trials, results from different reports are difficult to compare as survival times of the patients might greatly differ [152]. From a hemostaseological point of view, IVC filters are almost never needed and frequently create more problems than they solve [153].

## Pathogenesis of Bleeding

Besides thromboembolic events, cancer patients show also evidence of a bleeding tendency. This can be related to various, seemingly separate pathologies; however, recent research suggests that bleeding might occur, in fact, as the result of an interplay of various different pathologies [154–156].

## Thrombocytopenia

Drug-induced thrombocytopenia is a frequent finding in cancer patients undergoing chemotherapy [157]. It is common knowledge that thrombocytopenia increases the risk of bleeding, both in cancer and non-cancer patients [158]. In thrombocytopenic patients, additional risk factors for bleeding are infection, antithrombotic therapy, signs of renal dysfunction, and anemia [159]. In acute leukemia, the degree of thrombocytopenia correlates well with the risk and degree of bleeding. Fever and infection not only increase the bleeding risk but also reduce the response to platelet transfusion [160]. There is some well-based evidence that platelet substitution in AML induction chemotherapy can be lowered to trigger levels of 10 or 20 G/l [161]; the same group performed a randomized clinical trial indicating that a non-prophylactic approach *outside* induction or reinduction therapy for acute leukemia might be reasonable if the staff involved is sufficiently experienced [162].

Although bleeding does occur during treatment for solid cancers such as lung cancer, it seems that thrombocytopenic bleeding in solid cancer patients is rather rare [163]. Defining the exact need for platelet transfusion seems relevant as treating patients in this setting consumes considerable resources, with approximately half of the therapy courses inducing the additional financial burden [164]. It is important to preemptively consider the need for platelet support in advanced cancer patients on a case-by-case basis; this should allow to provide the therapy necessary and, at the same time, to reduce the strain on the resources available [165, 166].

## Platelet Dysfunction

The potential reasons for platelet dysfunction are manifold; most frequently, platelet dysfunction is drug induced [167], including anticancer drugs such as tyrosine kinase inhibitors [168]. Unexplained GI bleeding is frequently associated with nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulants [169]; NSAIDs impair mucosal healing or directly induce mucosal toxicity, both properties that will increase the risk for bleeding, e.g., in the gastrointestinal tract [170]. In that respect, COX-2 inhibition could be an attractive target in cancer patients with pain [171]; however, as COX-2 inhibitors may be associated with increased cardiovascular risk [172], the decision to use them should be carefully evaluated and be taken on a case-by-case basis.

## Tumor Infiltration

Bleeding in cancer patients might be due to direct infiltration of the respective vessel, as it can be encountered, for example, in gastric lymphoma; here, therapy has shifted away from primary surgery. But if bleeding occurs, early surgical intervention needs to be considered [173]. Radiation therapy might be an appropriate approach to control bleeding that comes from direct tumor infiltration [174]; rarely, however, radiotherapy can aggravate or induce bleeding in sensitive tumors, especially when applied in combination with chemotherapy [175].

## Fibrinolysis

Many malignancies might be associated with an increased fibrinolytic activity [8, 176]. Along with elevated levels of plasminogen activators in many hematological malignancies, excessive fibrinolysis can increase the risk of bleeding [177]. In DIC (with increased fibrinolysis), the extent of bleeding correlates with fibrinolytic activity [178], as is probably the case in acute promyelocytic leukemia [71]. The increased fibrinolytic response in APL might have to do with the increased expression of uPA [179] and Annexin II [180], a receptor for tPA and plasminogen. Annexin II has been found to be highly expressed in in cerebral endothelial cells [181], which may explain why intracranial hemorrhage in APL seems frequent and provides a rational for the prophylactic use of antifibrinolytics. Annexin II might also contribute to bleeding in other acute leukemias [180]. The

standard use of antifibrinolytics seems helpful to reduce bleeding and thus the use of blood products [182], but requires careful consideration of the concurrent thrombembolic risk.

Rarely, coagulation factor inhibitors are found in cancer patients; in this situation, bleeding complications can be severe [183] (see also "Paraproteins" below).

## Perioperative Bleeding Problems in Cancer Patients

Perioperative coagulopathies continue to be a diagnostic and therapeutic dilemma, especially in cancer patients. The pathophysiology behind unexplained intraoperative coagulopathies is of great variety and complexity as all aforementioned mechanisms can occur [154, 184–187]. If the pathophysiology is known, therapy should be directed accordingly. We showed in prospective studies that patients with "unexplained" intraoperative coagulopathy have significantly less factor XIII per unit thrombin available at any point in time [188], resulting in the loss of clot firmness and increased intraoperative blood loss. These patients have less cross-linking capacity to begin with, explaining their preoperatively increased fibrin monomer concentration, which can be used for preemptive risk stratification [189]. Importantly, the relative (compared to the amount of thrombin generated) acquired FXIII deficiency shows clinical relevance with surgical stress even if deficiency is moderate, which differs from the experiences in patients with inborn FXIII deficiency. There is proof of principle that the use of FXIII in high-risk patients (high preoperative fibrin monomer) leads to maintenance (vs. loss) of clot firmness and significant reduction in blood loss [190].

## Adverse Effects of Therapies

Drugs used for oncologic therapies frequently induce myelosuppression, which can cause thrombocytopenia and thus induce bleeding [191]. In addition, other mechanisms might include direct or indirect influences on platelets (such as tyrosine kinase inhibition [168], see above) and coagulation factors: L-asparaginase, used for the treatment of acute lymphocytic leukemia, induces a depletion in L-asparagine, leading to an impaired protein synthesis that also extends to procoagulants, anticoagulants, and fibrinolytic proteins. The lowering of various procoagulants induces a transient hypocoagulable state that is at least partially balanced due to the parallel decrease of anticoagulants [96, 192]; however, replacement of coagulation factors in high-risk situations might be appropriate and needs to be decided on a case-by-case basis.

## Paraproteins

High levels of paraproteins can interfere with hemostasis in various ways: they can inhibit polymerization of fibrin monomers, interfere with platelet aggregation, or inhibit clotting factor activity [193, 194]. As already described for hyperviscosity, bleeding problems in such patients might improve with plasmapheresis (but also might rebound with redistribution). Although this can be a clinically important in single patients, it is a rare problem.

### Conclusions

Hypercoagulability in cancer patients not only is an attendant phenomenon but in fact is part of the problem. Therefore, the stringent evaluation of the need for thromboprophylaxis or continued use of anticoagulant therapy in every cancer patient is a must, especially as recent data suggest that the use of low-molecular-weight heparin might improve clinical outcome, whereas at the same time, not all patients in need of thromboprophylaxis will receive it.

On the other hand, our knowledge of the use of blood products in cancer patients has evolved (e.g., platelet transfusion in leukemia patients) and should thus allow us to make better use of the available resources, avoiding unnecessary burden and risk to the patient and economic strain to the healthcare system.

Studies in recent years have advanced our understanding of thromboembolism and bleeding complications in cancer patients. The next important step to come will be to define the adequate use of direct (or "novel") oral anticoagulants in cancer patients. Other issues such as specific problems and therapies with disease-specific approaches (e.g., JAK-2-positive diseases) are on the horizon, indicating that we will need to continue prospective controlled trials to generate further evidence-based knowledge.

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# Anaemia in Cancer Patients

20

Matti Aapro

## Introduction

Anaemia and iron deficiency are frequently observed in patients with solid tumours or haematological malignancies and more so when they are treated with chemotherapeutic agents [1, 2]. Fatigue, impaired physical function and reduced quality of life (QoL) are a consequence of anaemia [3].

There are many reasons for anaemia: blood loss due to cancer or surgery, impaired erythropoietic activity and disturbed iron homeostasis related to inflammatory cytokines, malnutrition and rarely vitamin B12 or folate deficiency [4].

Chemotherapy-induced anaemia (CIA) can be treated with erythropoiesis-stimulating agents (ESAs), iron preparations for intravenous (i.v.) or oral administration, red blood cell (RBC) transfusions and combinations of these treatments [4].

Since the publication of the European Society for Medical Oncology (ESMO) anaemia treatment guidelines in 2010 [5] and the last review of the European Organisation for Research and Treatment of Cancer (EORTC) (anaemia treatment and other guidelines [6]), clinical experience with ESAs and iron preparations including in myelodysplastic syndromes have increased considerably [7, 8].

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## Erythropoiesis-Stimulating Agents

ESAs have been shown to increase Hb levels and to reduce the need for RBC transfusions in cancer patients receiving chemotherapy and are approved for the treatment of CIA since 1993 [9]. Furthermore, a meta-analysis of 23 studies that reported QoL results and included 5584 patients showed a statistically significant difference between patients treated with ESAs and controls when combining QoL parameters and fatigue as well as anaemia-related symptoms [10, 11].

ESAs have to be used according to label. However dose escalations in patients who do not respond within 4–8 weeks are not recommended (except for epoetin theta's low starting dose to be doubled after 4 weeks if Hb response is ˂1 g/dL) [6]. There is no evidence of differing efficacy among ESAs. Because of possible safety issues, we recommend that products should not be used interchangeably without adequate traceability and without notifying the treating physician.

In the late 2000s, the safety of ESAs was discussed when single studies and some meta-analyses suggested that ESA treatment could harm some cancer patients particularly if target Hb levels exceeded 12 g/dL [12]. The most recent Cochrane review has included subgroup analyses and shown statistically significant on-study mortality only in patients with baseline Hb > 12.0 g/dL but not for Hb categories Hb < 10 g/dL and Hb = 10–12 g/dL that correspond to the currently



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approved cut-off for initiation and the target Hb range of ESA therapy [11]. A retrospective analysis of 47,342 chemotherapy-treated patients from the SEER-Medicare database showed similar OS with or without ESA [13]. In November 2014, these data led the National Institute for Care and Health Excellence (NICE) in the UK to indicate that ESAs (epoetin alpha, beta, theta and zeta and darbepoetin alpha) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are receiving chemotherapy. If different ESAs are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used [14]. Overall, there is currently no clinical evidence (neither single studies nor meta-analyses) indicating an effect of ESAs on stimulating disease progression or relapse when used within label and following recommendations for the treatment of chemotherapy-induced anaemia [11].

Some reports have suggested a potential role of the EPO receptor (EpoR) on tumour cells in tumour progression, but there is, after review of all the available data, no confirmation of those data [7]. Venous thromboembolic events (VTEs) are a known risk of ESA and transfusion use in cancer patients [15], and the risk of a VTE with ESAs is increased 1.6-fold on top of baseline. The most important risk factors of a VTE are high haematocrit, older age, prolonged immobilisation, malignant disease (pancreatic cancer, some drugs used in multiple myeloma treatment), major surgery, multiple trauma, a previous VTE and chronic heart failure [16]. In the absence of prospective randomised studies showing that antithrombotic therapy reduces the risk of VTEs in ESA-treated patients, prophylactic antithrombotic treatment is not recommended, and the existing guidelines on VTEs should be followed [17, 18].

## About Iron

Iron deficiency (ID) can be absolute (depleted iron stores) or functional (reflecting insufficient availability of iron despite adequate iron stores). Iron homeostasis in cancer patients can be impaired via the release of pro-inflammatory cytokines and upregulation of hepcidin [19]. Guidelines recommend iron treatment for the correction of ID before the initiation of ESA therapy [5]. ID is reflected by low transferrin saturation (TSAT < 20%) and can be further characterised as absolute ID (depleted iron stores, serum ferritin <30 μg/L) or functional ID (adequate iron stores with normal or increased serum ferritin) [4]. Circulating ferritin levels are used for distinguishing between absolute and functional ID in clinical practice. In noninflammatory conditions, a serum ferritin level <30 μg/L is indicative of absolute ID, while higher levels usually reflect appropriate iron stores. However, in cancer and other conditions with an activated inflammatory cascade, ferritin follows the path of inflammatory cytokines. Hence, the cut-off levels should be raised to 100 μg/L in patients with inflammation or cancer.

Randomised trials investigating iron usage in ESA-treated anaemic cancer patients have shown that IV iron supplementation (total doses in the range of 1000 mg of iron) significantly improved the haematological response to ESA treatment versus ESA alone [10]. If the iron preparation to be used allows for it, administration of a single 1000 mg iron dose may be more convenient for patients than multiple lower doses [10].

With IV iron, no increased risk of infection or cardiovascular morbidity or tumour progression has been observed [10]. However, IV iron should not be given to patients with an active infection, and administration of IV iron and at the same time cardiotoxic chemotherapy should be avoided. The European Medicines Agency (EMA) no longer recommends administration of a test dose to predict/prevent allergic reactions (mainly observed with iron dextrans [20]); however, the EMA recommends that IV iron should only be administered by staff trained to evaluate and manage anaphylactic and anaphylactoid reactions and only when resuscitation facilities are immediately available. Patients should be observed closely for symptoms of hypersensitivity reactions for at least 30 min following each IV iron administration [20].

## RBC Transfusions

RBC transfusions are not a simple treatment of anaemia in cancer patients. They should be prescribed only in case of absolute need for a rapid haemoglobin response. Strict precautions have improved the general safety of RBC transfusions over time. Nevertheless, there remains the risk of transfusion reactions, of transmitting unknown or emerging pathogens and an increased risk of infections due to transfusion-related immunosuppression [21]. Furthermore, stored allogeneic blood can elicit prothrombotic as well as inflammatory responses (referred to as 'storage lesion') [22]. In the oncology surgery setting, large population-based studies and a meta-analysis suggest independent associations between RBC transfusions and an increased risk of mortality, morbidity and cancer recurrence, respectively [23]. Analysis of studies with a restrictive Hb threshold <7 g/dL has shown significant reductions in total and in-hospital mortality, rebleeding, acute coronary syndrome, pulmonary oedema and bacterial infections, compared with a more liberal strategy [24]. Many anaemia treatment guidelines recommend transfusing only the minimum number of RBC units that is required to relieve severe anaemia symptoms or to return the patient to a safe Hb range (e.g. 7–8 g/dL in stable, noncardiac in-patients) [25, 26].

## Biosimilars and Follow-on Products

rHuEPO and recombinant G-CSF were the first biotechnological medicinal products used in haematology. Only products that are approved, produced and distributed according to a strict biosimilar guidance of a regulatory authority such as the EMA or the Food and Drug Administration (FDA) should be considered as biosimilar and be differentiated from products that are not manufactured and quality controlled in compliance with the biosimilar guidance or even counterfeit medicines.

### Conclusions

Treatment of chemotherapy-induced symptomatic anaemia is well-documented with ESAs. ESAs are relatively safe except for an increased risk of VTE. Outside approved indications, these agents have been linked with increased mortality.

IV iron has been shown to significantly enhance the activity of ESAs, and as a sole therapy, IV iron improves anaemia in cancer patients with ID, but representative, randomised studies and long-term data are lacking.

Based on findings from studies in non-oncology populations and cancer patients undergoing surgery, RBC transfusions are best reserved for patients with Hb levels below 7–8 g/dL and situations when rapid improvement of severely symptomatic anaemia is required.

The FDA recently determined that the ESA Risk Evaluation and Mitigation Strategy (related to the use of ESAs to treat patients with anaemia due to associated myelosuppressive chemotherapy) was no longer necessary to ensure that the benefits outweigh the risks of shortened OS and/or increased risk of tumour progression or recurrence in patients with cancer [27]. In addition, the FDA's Oncology Drugs Advisory Committee has recommended approval of a biosimilar to epoetin alpha [28].

In Europe, recently published German guidelines have reached similar conclusions about the adequate safety and appropriate use of ESAs [29].

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# Lymphedema in Cancer Patients

21

Patricia O'Brien

## Introduction

As we review the new information on supportive lymphedema care for our cancer patients, we need to reflect on the many new treatments that have been developed to treat the cancer. Comprehensive cancer therapy and the support to the survivor have also changed. As cure rates rise, there is more of an emphasis on the cancer survivors and their quality of life. Survivorship care is a growing area of specialty care in oncology. When deciding on a cancer treatment option, some patients now ask about long-term side effects of treatment before embarking on the therapy. Some patients come into their cancer experience aware of lymphedema and are hoping to be able to prevent it. This increased awareness of lymphedema has helped some patients get more education on how to prevent it or if they do develop it, how to get treatment early. Access to information about lymphedema and treatment remains highly variable. Ongoing professional education and advocacy continues to be needed so that more patients receive appropriate education on and treatment of lymphedema.

Lymphedema remains a low priority in many parts of the world. Patients in countries with good access to health care expect to be informed of potential complications of their cancer therapy. In other parts of the world, patients are much more worried about access to the cancer treatment than the side effects of the treatment. Funding is a key part of any health-care policy changes. As was true in 2000 when the journal of Clinical Cancer Care published a review article on "Lymphedema: Current Issues in Research and Management … as with other quality of life and nonlethal conditions, it receives less research funding and attention than do many other areas of study" [1].

Despite this lack of funding and support, lymphedema care is improving in recognition, quality, and new research efforts. Lymphedema advocates around the world are working to improve access to lymphedema care. In the United States, the Lymphedema Treatment Act has been introduced in the Senate, and advocates from many nonprofits are working to get this passed to improve access to care [2]. Public health-care reform to expand lymphedema care is an international effort. In Australia alone 19 groups have come together to form the Lymphedema Action Alliance (LAA 2016). In many parts of the world, patients do not have access to all the tools needed to give good compression or access to information about their disease. In the United States the Lymphedema Advocacy Group is working to change insurance coverage for tools to help treat lymphedema [3].

The research and advocacy efforts are international and are working to improve access to care

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from many different angles. A recently published study "Self-Management of Secondary Lymphedema: a Systematic Review" detailed the many challenges of lymphedema care in resource-poor communities where patients have little access to education, tools, or treatment options [4]. In the 2016 spring issue of Lympho News, the International Lymphoedema Framework welcomed multiple new countries into their membership [5]. This need to look globally at the disparities in lymphedema care is expanding, as is the advocacy to expand cancer treatments throughout the world. The differences in access to health care between resource-rich countries and resource-poor countries are very significant on many levels. Global public health advocates and lymphedema experts have looked at these ongoing challenges [6].

Due to the growing advocacy and awareness, the tools of treatment are slowly changing. In general, the treatment of lymphedema continues to revolve around the basic components of complete decongestive therapy (CDT) followed by compression. How this is accomplished continues to expand as new techniques for drainage are researched, new tools are developed for compression, new research is published on exercise, and new skin care methods are tried. New drugs are being researched in clinical studies. As the population of cancer survivors grows, the demand for lymphedema care products grows. New companies have come into the marketplace with updated tools to make lymphedema care easier. More cancer centers have developed survivor centers to help patients cope with their burden of side effects. Lymphedema is a common side effect of many cancer treatments. Ideally these survivor-oriented centers will provide better access to referrals for lymphedema diagnosis and treatment.

## Cancer and Cancer Treatments as the Risk Factors for Lymphedema

As with any chronic disease, prevention and/or cure would be the ideal goal. There are many risk factors for development of lymphedema. Lymphedema can be due to the tumor itself or due to the cancer treatments. As cancer treatments constantly keep changing, so will the risk factors to develop lymphedema. It is important to review the physiologic cause of each risk factor for lymphedema so that prevention interventions can be focused to each patient.

Some patients may present to oncology with lymphedema at the time of the diagnosis. This may be due to bulky disease blocking pathways or microscopic disease blockages. Occasionally patients may have primary lymphedema or secondary lymphedema due to other causes such as obesity. Obesity at the time of diagnosis or developing obesity at any time will increase the burden on the lymphatic system and increase the risk of lymphedema [7].

Surgical methods continue to change dramatically in the treatment of cancer. Advancement of the sentinel node procedure for many types of cancers has allowed surgery to do less invasive procedures and has successfully prevented many axillary and inguinal dissections. Reverse mapping has also been used to guide the surgeon to preserve key lymphatic structures. Invasive deep dissections are associated with not only more direct damages to the lymphatic system by removal of additional lymph nodes, but it is also associated with more localized infections, wound complications, and drainage issue. These infections and post-op complications can further damage the lymphatic system.

## Radiation Therapy as a Risk Factor for Lymphedema

Radiation is being used to treat many types of cancer, and the way the radiation is delivered is constantly changing. Radiation therapy always changes the tissue, but these changes may not be evident at the time of the exposure. Tissue changes should be put into two categories—those that are immediate and obvious and those that are delayed. During radiation therapy or immediately after radiation exposure, patients will often develop acute erythema and local swelling. This is typically mild, and short lived, and requires

only topical treatment and occasionally mild pain medication. Occasionally acute radiation treatments will be associated with more severe tissue damage and ulceration that can require delay or discontinuation of the planned intervention, and local wound care needs to be initiated. Typically, even with more severe wounds, only local care is needed, but occasionally there can be secondary infections and more life-threatening complications. These acute reactions complicate the burden on the lymphatic system, and there is often a transient increase in lymphedema and lymphatic congestion, and there may be a need for acute lymphatic therapy intervention.

In the 2007 Seminars in Radiation Oncology, Delanian leads with the comment "Tissue of irradiated cancer survivors always bears the trace of the radiation therapy … some are asymptomatic … some of them develop late clinical complications in normal tissue that affect organ function and may even be life threatening …" [8]. The late effects have the common histologic characteristic of radiation-induced fibrosis (RIF). The fibrosis is felt to be irreversible, but treatments can address the symptoms of this fibrosis. In the case of lymphedema, the goal is to treat the lymphedema and its effect on the patient's quality of life. It is important for patients and therapists to understand that the fibrosis itself is not reversible and may be progressive.

Animal research has shown that even just radiating one lymph node will cause a change in lymphatic flow. Irradiation of one popliteal node in a rabbit impaired the lymph transport and increased the pressure required to maintain flow in the lymphatic system. These pressure changes then lead to the compensatory mechanism of new vessel formation and growth of lymphatic venous anastomoses [9]. Clinical evaluation in humans has also shown increased lymphedema in patients that received lymphatic irradiation. Breast cancer patients that received axillary radiation as part of their therapy plan had a greater risk of lymphedema, than those that just received radiation to the breast or chest wall [10]. Patients receiving radiation therapy for rectal cancer showed considerable long-term effects on local tissue that impacted QOL [11]. Although we generally consider lymphedema as being a sign of radiation-induced vascular changes, it is not always present. In a 2016 review of radiation-associated angiosarcoma (RAAS) in breast cancer patients, none of these patients had developed lymphedema [12].

Radiation late effects are dependent on many factors including the dose and the volume of tissue radiated. Patients developing lymphedema years after radiation treatment cannot go back in time and change these risk factors, but there are factors that the patient and therapist can work to change. Obesity, inflammation, further trauma, and infection are all important burdens to try to prevent on this already "at-risk" tissue [13].

## Lifestyle Risk Reduction Controversies

Lymphedema research is full of many controversies. Every clinician would like to be able to help our patients prevent a chronic problem like lymphedema. Risk reduction lifestyle measures remain controversial, but these should be discussed with each patient so that patients can be informed and make their own choices. Many cancer patients have looked for information online about lymphedema and have unfortunately found frightening pictures of patients with advanced elephantiasis. These pictures may have psychologically burdened these patients who may already have been dealing with fears about their cancer. Many breast cancer patients have received lists of all the "never do" activities that they should avoid after treatment to avoid lymphedema. Instead of scaring our patients, perhaps we need to try harder to help them live well and follow a healthy well-balanced lifestyle.

You don't have to look hard to find literature for breast cancer survivors telling them they should avoid having their blood pressure taken on the affected side or that they should avoid all injections and IVs on that side, they should not lift weights or carry a pocket book on that side, or they should always wear a compression sleeve when flying. Some tell women who have had a bilateral mastectomy to never get her blood

pressure checked in her upper extremities and that they should now get her blood pressure checked in their legs. These well-intended risk reduction recommendations can potentially do harm. We need to encourage our patients to keep their blood pressure under control and have it checked at regular intervals and that a standard cuff that is removed after measurement has not been found to be a problem. People need to be active and get exercise but should understand to build up their exercise and activity slowly after surgery or radiation. The Journal of Clinical Oncology published an excellent article in the March 2016 issue reviewing these topics in the breast cancer population, but we need to think of these practical recommendations for all our "at-risk" cancer patients [14].

Dr. Judith Nudelman, a physician and a survivor, published an excellent "counterpoint" guest editorial in Lymphatic Research and Biology [15]. She passionately advocates for individualized education for patients at risk for lymphedema so that they can be empowered to make their own informed choices about their lifestyles. Education of patients on their individual risks takes time, and teaching patients about healthy choices takes time, but ultimately as health-care providers, we need to develop health-care systems that do provide these services. Cancer treatments do put people at risk for a variety of long-term complications. Lymphedema is only one of many long-term potential problems of which cancer survivors need be aware. Survivorship clinics may help solve some of these issues. They may be able to do the individualized education for each cancer survivor to understand their "postcancer treated" body and how to best take care of it. Patients will need information about lymphedema pretreatment so that they are making informed choices about their care after treatment is completed and again as they move into survivorship care. How much they understand and can cope with may be very different at each stage in their continuum of care.

Obesity and risk for lymphedema clearly are related. This has been well documented for years. The National Lymphedema Network has been advising obese patients to work to lose weight as part of their evidence-based guidelines as have many other patient advisory groups [16]. Even relatively minor amounts of weight gain have been documented to increase the risk for lymphedema [17]. Good nutrition and exercise are going to be part of a balanced approach for the cancer survivor to try to keep their weight under control and lower their risk for lymphedema. Comprehensive oncology rehabilitation programs that help patients focus on diet and exercise are needed to help patients' lead long healthy lives.

Breast reconstruction is a very personal issue. Patients have been told that any surgery that cuts more lymphatic pathways and disrupts more natural lymphatic pathways may be putting them at increased risk for lymphedema. Some research has shown that this additional surgery does not put the patient at increased risk [18]. Patients will need information on these controversies and will have to make these choices based on the best possible information.

There is very interesting research that indicates that women may be at risk for developing lymphedema even before they have any of these cancer treatments done or have any lifestyle adverse behaviors. Some women have been found to have "constitutively enhanced lymphatic pumping" that affects their risk for developing lymphedema. This infers that some people may have higher lymphatic pump pressures at baseline and that a population of people is predisposed [19].

## Lymphedema Treatments
(See Fig. 21.1)

Some cancer patients present with lymphedema at the time of their diagnosis. Dealing with lymphedema is not their primary concern once they learn the cause of this swelling. For these patients they want to get their cancer treatment treated and cured as quickly as possible. Other patients do not develop their lymphedema until after their cancer treatment. For them lymphedema is often a chronic burden after an acute life-threatening burden. They may already be

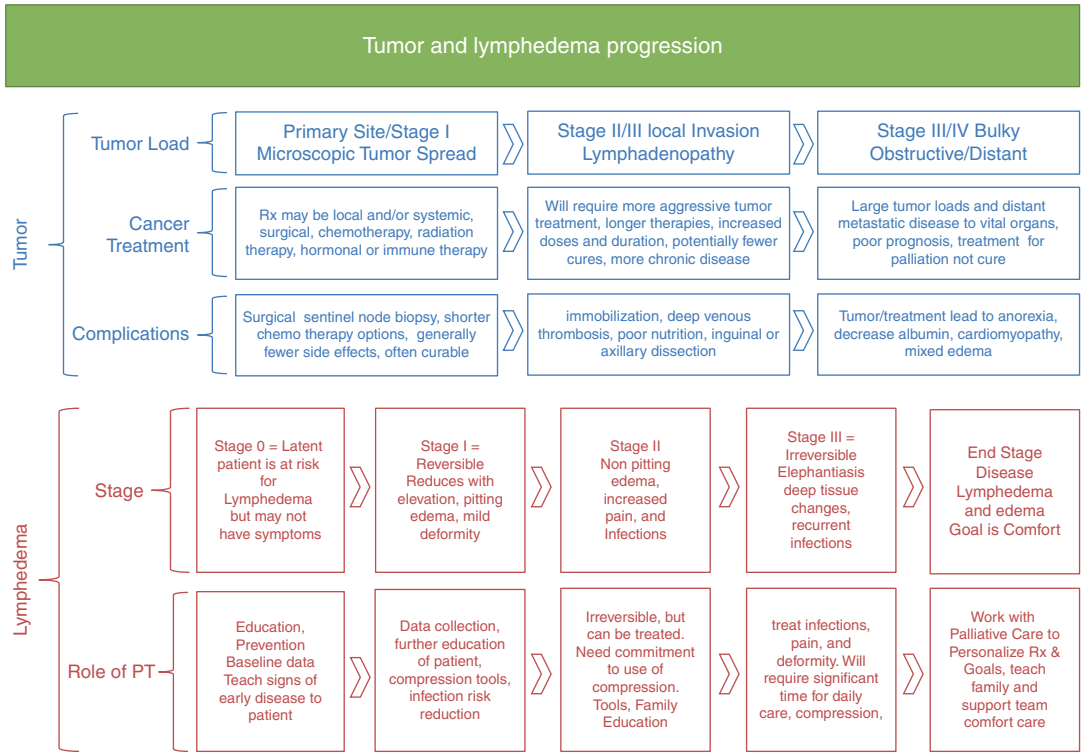


**Fig. 21.1** Shows the relationship between treatment of the tumor and treatment of the lymphedema as related to the tumor. Cancer and lymphedema treatments are both based on the stage of the disease process

exhausted physically, emotionally, and financially from all their cancer treatments to treat their primary tumor. When treating the patient with lymphedema secondary to cancer, it is important to take this into consideration and plan the lymphedema interventions to match the needs of the patient and the tumor status.

Lymphedema treatment goals are to decrease the swelling, enhance functional status, relieve discomfort, and improve quality of life. There are typically two phases of lymphedema care, the first is to reduce the volume of the edema, and then the second is to maintain this decreased volume. Again it is important to consider the stage of the cancer patient and their prognosis. The patient with advanced end-stage disease may never decrease their volume but will ideally be able to get pain relief. The patient that has been treated for cure will ideally be motivated to try to prevent the development of chronic disease complications from that treatment. The approach needs to be individualized. All lymphedema patients should be taught to take excellent care of their skin to avoid infection. High-volume lymphedema increases the risk of skin and wound infection. Infection prevention is a key goal for all patients with lymphedema or risk factors to develop lymphedema.

In the first phase of treatment, patients are usually treated with manual lymphatic drainage by a trained therapist. The patient and/or family can then be taught to continue this massage independently when possible. The manual drainage is a very gentle massage that patients typically find very relaxing and comfortable. A trained lymphedema therapist will outline what drainage pathways have been damaged by the tumor or the treatment for the tumor and then design a drainage program to utilize alternative "watershed" pathways. These "watershed" pathways are the pathways that are assumed to be "open" and should provide an alternative route based on standardized lymphatic circulatory pathways. The therapist may evaluate the response to the

treatment to continually update the planned intervention [20].

Patients with high tumor loads may not get much of a change in volume with treatment but may get a nice relaxation response and relief of pain. Other patients may get a dramatic response to this treatment and move measurable volumes. Often patients will need to urinate within an hour of starting the drainage massage.

An exercise program can be utilized to promote enhanced lymphatic circulation. Muscle movement also enhances lymphatic pumping and can promote improved drainage. The active patient will be given an exercise program designed to utilize this. Deep breathing, moving the diaphragm muscle, is also used to promote pelvic lymphatic pumping. By changing the pressures within the intra-abdominal cavity, lymphatic pumping is enhanced. Even very debilitated patients can be taught to do this and again often find it relaxing and comforting.

Multiple types of tools can then be used to treat lymphedema. Most garment tools are designed to maintain this volume reduction. Compression bandaging programs can help reduce the volume of lymphedema fluid. Customized tools can be used to provide various levels of compression. For some patients they may require use of custom compression garments. This compression can be achieved through a wide variety of products. These products can range from custom-made high-grade medical compression garments that can tend to be very expensive to much cheaper over-the-counter products. The lower range of compression can often be provided by non-prescription simple sportswear. The amount of compression needs to be individualized to the patient's needs. It is important to have the patient with a chronic disease understand the goals of therapy and have choices in how to manage their disease. For example, a young teenager with lower extremity mild edema may not want to wear a pair of panty hose, which looks very medical, to school around their peers. That same patient might be more compliant with layered athletic-looking compression for public events but willing to bandage at home or use a compression pump at home while doing homework. Chronic disease interventions need to be individualized to the patient's physiological and psychological needs. As the population of cancer survivors increases, the choices in options are improving, and lymphedema therapists need to problem solve for each individualized patient.

Intermittent pneumatic compression therapy is helpful for some patients allowing them to have treatments in their own homes. A variety of pump designs are on the international market. Most pumps have sequential chambers that attempt to replicate the flow of the lymphatic system. The sequencing is intended to try to replicate a wave motion to move fluid from distal to central circulation. Many pumps treat the quadrant of disease, so that if it is for an arm, it also treats the trunk. Some pump designs include the ipsilateral lymphatic nodes and the regional nodes. So, for example, in a pump for a patient who has right upper extremity lymphedema, the pump will work on the right-sided inguinal nodes and the left axillary nodes. For patients with bilateral lower extremity lymphedema, pump design may include a full pant-like design or a method to compress the bilateral inguinal nodes, and some even use bilateral axillary nodes.

Surgical intervention for treatment of lymphedema has significantly expanded in the last 5 years. Multiple types of procedures are available at tertiary centers. The excisional surgical options include debulking or liposuction. Microsurgical techniques include lymph node transfers, lymph node flap transfers, lymphovenous shunts, and lymph node reanastomosis. The field of autologous lymph node transfer research is very exciting and is already helping many patients with severe lymphedema. In her invited review article in the *Journal of Reconstructive Microsurgery* 2016, Dr. Corinne Becker MD presents excellent cases of patients with severe advanced fibrosis and lymphedema. The review discusses long-term outcomes data. In her case presentations, Dr. Becker shows pre- and postoperative lymphoscintigraphy [21]. Not only is this exciting field of research expanding but multiple international teams are also

experimenting with adding growth factory therapy to these lymph node transfers. Growth factors such as VEGF-C/VEGF-D have been used in animal studies [22].

Drug treatment options for lymphedema remain very limited and experimental. Diuretics are useful in patients with edema. In a patient with a presentation of edema and lymphedema, careful diuretic use may be helpful but will require close monitoring as dehydration can complicate lymphatic function.

Platelet-rich plasma (PRP) is an autologous concentrated preparation of human platelets contained in a small volume of plasma. These preparations have been used to promote tissue regeneration in multiple areas of tissue healing. A team led by Dr. Ahmet Akgul MD in Turkey has been researching this as an intervention for lymphedema. Their interest is to use this PRP preparation to regenerate lymphatic tissue [23].

New targets for lymphedema drug intervention are being researched. Lymphedema and inflammation are closely linked, research is exploring these relationships, and anti-inflammatory agents may someday be targeted for lymphedema. Patients may hear of various food supplements that will help treat lymphedema. Caution is encouraged as coumarin, once popular for treatment, was found to be toxic to the liver. A healthy diet that encourages a normal BMI may be much better than supplements with little research verification. Patients should be encouraged to always report all supplements and over-the-counter drugs they are taking to all their health-care teams.

Acupuncture has been found in some small studies to be helpful in the treatment of lymphedema, and larger studies are being done. Some studies have used the needles on the affected tissues; other studies have not. As infections can be a major risk factor for persons with lymphedema, any use of needles in the swollen tissue needs to be done very cautiously. These preliminary studies did not report an increase in the episodes of cellulitis after needle insertion in the affected extremity, but it should be noted that these are small studies with limited numbers of patients and limited follow-up.

Antibiotic use for infections continues to be a very important tool in the treatment of lymphedema. Untreated cellulitis can lead to progression of disease. The type of antibiotic, dose, and duration will depend on the location of the infection, surgical procedure, patient tolerances and a host of other factors. Cellulitis can become a life-threatening problem if not treated quickly. Patients should be educated to be able to identify the symptoms of an infection and should understand to seek medical attention. Patients with a history of recurrent infections often keep antibiotics at home for quick intervention.

Lymphedema treatments can be a financial cost to cancer patients after they have already coped with the strain of cancer treatment. Effective lymphedema treatments can overall save costs by preventing further disabilities, infections, and hospitalizations. Insurance coverage for lymphedema treatment and tools is highly variable. International health-care systems have highly variable coverage for cancer care and for lymphedema care. Advocacy is needed internationally to improve access to care.

## Special Attention for Patients with Lower Extremity Lymphedema

Much of the lymphedema research has been done on the patient with breast cancer and upper extremity lymphedema. I encourage oncology providers to pay special attention to their patients at risk for lower extremity lymphedema. Cancer patients coping with lower extremity lymphedema may have very different needs than the patient dealing with upper extremity lymphedema [24]. Quality-of-life studies and treatment outcomes research in this population show that these patients may have much more distress than previously appreciated [25]. These patients may have much larger volumes of lymphatic overload, and this high volume of fluid needs to be considered with interventions [26]. Intensive treatment can move large volumes, and it is generally well tolerated even in patients with elephantiasis [27]. Lower extremity lymphedema and survivorship research needs to be expanded so that care

guidelines can be updated. This is a patient group that needs much more advocacy.

## Wound Care

Fistula formation or the non-healing wound can be a major complication for a cancer patient. Lymphedema drainage may be a part of this complex syndrome. When a patient with a compromised lymphatic system is not able to move the lymphatic fluid out of the area, the fluid may build up and break open the skin. This can then become a chronic draining wound or a fistula. Ideally this complication is avoided by drains placed at the time of surgery or drainage placed as needed in areas of tissue breakdown. The cancer patient may have poor nutritional status, so the wound healing is delayed, and tissue breakdown susceptibility is high. These patients present multiple challenges, but good lymphedema care may be a part of helping them heal. A lymphedema care plan that attempts to use watershed lymphatic pathways to move the fluid out of the area may be helpful. There have been significant improvements in the types of drainage that can utilized. Wound drainage pumps and improved wound care can help to decrease the risk of infections.

## Diagnostic Testing

The diagnosis of lymphedema in a cancer patient is typically done clinically and is often a diagnosis of exclusion. After all other causes of swelling are ruled out such as deep venous thrombosis, tumor progression, or infection, the swelling is labeled as lymphedema. The patients' disease is then put into one of the three groupings or clinical stages. Patients are categorized as having stage I, II, or III disease based on the physical findings. Stage I is reversed with simple elevation of the limb, shows pitting edema, and is early mild disease. The next step in the spectrum is stage II disease that is no longer reversible with elevation alone and has a component of fibrosis and texture changes. Stage III is elephantiasis with advanced tissue changes, inflammation, infection, and deformity. All of our cancer patients might be considered to have stage 0 disease or latent lymphedema. Education of patients at risk for the disease will help with early identification and early treatment.

In order to better delineate lymphedema and more subtle changes in the patient, further measurement tools are needed. The most basic and widely used system to monitor the volume of the lymphedema is the circumference method. For many clinicians, they simply use a tape measure to measure the circumference of a limb at a specific part of the anatomy such as at the wrist, the ankle, or other joints. This is a quick, inexpensive way to get a sense of volume of fluid in an extremity. Some therapists use a more detailed method of calculating a volume by measuring the extremity at every 2 cm using a standardized system taught in most of the lymphedema training programs. This method of measurement is so commonly used that cell phone apps are now available for patients or therapists to use to make this calculation quickly and easily. There are obvious inherent problems with this, as it does not take into consideration all the other tissue changes that can cause a change in circumference such as muscle loss or gain. Although this may help in the clinical setting, some researchers believe that it should not be used in the research setting due these inaccuracies [28]. The same concept can be done also using an electric Perometer tool which is much faster. This is often used in the research setting but is expensive and not typically found in most cancer centers.

Portable ultrasound can also be used to measure the skin thickness and the dilation of the lymphatic vessels and allows the observer to look at lymph nodes and other structures. Training in ultrasound measurement of lymphedema is not as widely used. Texture analysis of the skin changes with lymphedema has also been used in research; again this is rarely used and requires specialized software [29]. A Belgian rehabilitation team recently did an excellent review of the use of ultrasound as a tool to diagnose and stage lymphedema more accurately. This was published in the Lymphatic Research and Biology journal. They advocate that these techniques are clinically relevant and could improve staging and early diagnosis [30].

Bioelectrical impedance analysis (BIA) has become the method of choice for detection of early lymphedema at the Lymphedema Research Unit in Australia [31]. This method uses a harmless electrical current to measure the impedance to flow through the body. This methodology is now available throughout the world. Like every methodology it has limitations, for example, it is not useful for advanced lymphedema and fibrosis. Some clinics use bioimpedance measurement preoperatively and then use this as a method to measure for early lymphedema after surgery and as a guide for early intervention and treatment of lymphedema. Impedance technology and research are a growing field, and more clinics are using this internationally. Magnetic resonance imaging is a safe, noninvasive radiologic technique that allows detailed visualization of soft tissue changes associated with lymphedema. Lymphedema causes distinct patterns of structural changes in the subcutaneous tissues. MRI-related research shows cancer-related lymphedema in the adipose tissue, fluid accumulation in the fibrous septa, and fat globule hypertrophy. This is an excellent tool for research as it allows very detailed information. The cost is a major limiting factor [32].

Lymphoscintigraphy is widely used throughout the world. There are a variety of techniques and protocols. There are two main types of preparations used for this, either macromolecules or colloidal suspensions that are attached to a radiolabel. A qualitative lymphoscintigraphy aims to image the morphology of the lymphatic system. A quantitative study may be a port-sensitive method of diagnosing impairment in flow [33]. Lymphoscintigraphy is a highly useful tool for documentation of lymphedema in the patient when the etiology of the swelling needs further investigation. It can help guide the diagnosis and disease staging and guide interventions when appropriate.

## New Directions

"Big data" is a buzz term in many areas of research. Using new data collected from multiple studies and bringing this information together in new ways are hopefully going to advance the world of lymphedema research. Lymphology researchers will be able to link everything from genetic profile to outcomes data from large studies directed at other end points. It is hoped that by utilizing big data in new ways, science will move forward faster. Lymphedema has been referred to as an "orphan disease," and research in the field has been limited by lack of funding. Tools to precisely measure the disease in large populations of patients with similar disease have also been a challenge to the research. In many aspects of cancer research, it is hoped that "big data" will advance our understanding of the disease and help find cures. As yet, the movement toward collection of large data sets is behind in the field of lymphedema, but as cancer and precision medicine initiatives move forward, there may be more large databases that lymphedema research may be able to build on [34].

As large databases are used to research the safety of radiation therapy, then there will be improved documentation of the side effects of radiation therapy. Lymphedema and fibrosis can be long term side effects of radiation therapy, and can happen late in the course of cancer survivorship. These side effects can get worse, not better with time. It is important to follow cancer survivors for long periods of time, and monitor their lymphedema so that we can better understand the burden of complications from cancer therapies [35]. The large surgical studies needed to show that lymph nodes did not need to be taken out, collecting the first large-scale data on the surgical complications of axillary dissection. The rates of lymphedema with various surgical treatments were finally collected so that the problem could be better addressed [36]. Big data analysis is the future of medicine and cancer care. Lymphedema care providers will be asked to participate in this future by using standardized data collection so that they can participate in long-term clinical studies that monitor the side effects of various cancer treatments [37]. Radiation therapy side effects such as lymphedema and fibrosis tend to be late in the course of the cancer survivor. Big data research will help in the analysis of this "bystander" effect. This side effect research may help improve data on lymphedema and other complications [38].

## Lymphedema Case Studies

Discussing cases is often a good way to transition from abstract information about a disease to the actual clinical issues that confront the clinician and patient. As with many diseases, lymphedema presents a spectrum of severity. The disease can progress, and the patient can develop progressive symptoms and require more intensive care. Other patients may respond to treatment and stabilize. Both spectrums of the disease will be discussed. Stage 0 lymphedema is also referred to as latent lymphedema. For the cancer patient this often means that the patient had an early cancer, they presented with no edema, and the surgery done to cure the cancer did not cause any edema. They are considered to have latent lymphatic disease. The lymphatic system has been injured by the cancer treatments, but there is no evidence of actual edema. The second case will be of advanced end-stage lymphedema in a patient with metastatic disease. The chart below gives a sense of how the disease intervention needs to match the actual disease. Each level of lymphedema treatment will need to match the needs of the patient.

### Case 1

JC is a young man that presented with a mole that was changing on his calf. On biopsy it was found to be melanoma. He had a wide excision and a sentinel node procedure. The node in the inguinal area was found to be negative, and no further surgical investigation was done. The patient never developed any swelling at the ankle or distally. He had minor swelling at the site of the surgery and the sentinel node procedure. The swelling at both sites was resolved quickly and was gone by the post-op visit when the bandage was removed. He continued to receive local skin care and dressing changes at the calf and inguinal sites but had no postoperative infections or swelling.

Depending on where in the world this patient was being treated, a variety of interventions might have been done to try to prevent his development of lymphedema. In some surgical centers, he would have been seen before surgery for baseline measurements that could have included circumference data on the whole lower extremity, photographic documentation, and baseline bioelectric impedance data collection. The surgeon doing the sentinel node procedure would typically have done an ultrasound of the inguinal area, and these images would be collected, and the lymphatic vessels might have been measured and analyzed.

This baseline data would not be collected at all facilities and is presently not the standard of care. Some surgical centers would have moved on with the sentinel node procedure prior to any lymphedema data collection. Then in some centers a physical therapy session would be set up to collect the data and do some preoperative education. The patient at that point might or might not be given a stocking to use for postoperative compression to try to prevent excessive swelling. Some patients are routinely given prescriptions for compression; it is not a policy of all institutions. Some patients get extensive education on lymphedema risk reductions; some patients are not told about lymphedema unless they develop this complication. These prevention and educational efforts are highly variable with each cancer center utilizing different protocols. During the ideal education session, the patient would receive risk reduction information which typically would include avoiding infection, keeping his weight normal, and avoiding trauma and how to monitor for swelling. The patient would learn how to monitor for cellulitis and how and when to seek medical attention for a possible infection.

Typically medical and/or surgical oncology would monitor this melanoma patient for recurrent cancer. Ideally when he came back in for his cancer follow-up, they would also monitor for lymphedema. If he did develop swelling later, he would be typically referred back to physical therapy for evaluation and treatment. His lymphedema tools should be checked once a year at a minimum, and his leg would be measured annually even if he felt it was "under good control." Ideally he would know how and where to seek lymphedema assistance and reevaluation at any time if he felt his leg was swelling.

### Case 2

This is a case of a woman with progressive breast cancer. As her disease progressed over several years, she developed severe lymphedema and

ulcerations. She eventually went on to hospice care. She passed away with massive uncontrolled lymphedema despite ongoing aggressive attempts to treat the lymphedema. There are two sets of images. The first set shows the advanced disease as she presented to the clinic for palliative lymphedema physical therapy. The second set is from her at autopsy. This type of side-by-side image shows the deformity that advanced lymphedema can cause despite intensive treatment. It is important to understand from this case that despite very dedicated lymphedema care, it is not always possible to control the swelling. At the end of life cancer patients may have massive deformities that are painful and may require a comprehensive team to manage these symptoms.

In Fig. 21.2, the pictures on the left were done in physical therapy. Her therapy consisted of intensive manual lymphatic therapy, daytime and nighttime compression, and use of a compression pump as well as wound care, antibiotic treatment of infections, and constant adaption as her condition progressed. Despite all of these compression and treatment methods, the volume of her lymph-


**Fig. 21.2** The first picture shows the patient in custom compression garments while in treatment; the second picture shows the extent of lymphedema and tissue necrosis at time of autopsy. This patient was in significant pain related to her lymphedema and metastatic disease at the time of end-of-life transfer to hospice care

edema continued to progress. This was due to ongoing progression of the tumor. Her pain medications were continually being adjusted as the lymphedema progressed.

Other methods of intervention that could have been employed would have been to create a fistula for artificial drainage or potentially to use a suction wound vacuum. Due to her hospice status, personal choice, and a variety of issues, these options were not pursued but might be considered in other patients with draining wounds on hospice. Topical antibiotics were used to try to control the infected wound and odor from the wound. The International Lymphedema Framework has done an excellent job of reviewing all of the information on advanced lymphedema at the end of life. This position paper can be found at their website: www.lympho.org. The type of services that patients can access at end of life is highly variable. Not all hospice programs are trained to provide lymphedema care. More education, advocacy, and support are needed to expand these services to the patients who need end-of-life lymphedema services.

## Conclusion

Care of the patient with lymphedema is constantly changing as more resources and attention are being paid to the quality of life of the cancer survivor. As the treatment of cancer is constantly changing, ideally more patients are achieving long-term cures with less morbidity from their treatments. Ideally as more patients receive preoperative or pretreatment education about possible lymphedema complications, more lymphedema can be prevented. Earlier attention to lymphedema may prevent some deformities or the clinical burden of lymphedema. As the basic science knowledge is advanced, other mechanisms to prevent injury or to treat injury will be pursued. Until then each of us providing care to patients at risk for lymphedema will need to develop teams to care for these patients. These teams will vary depending on the country we live in, the funding, and the health-care environment. We will each need to be informed advocates to make sure our patients receive comprehensive care.

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# Infections and Cancer

22

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## Introduction

Infections are major causes of morbidity and mortality in cancer patients. The risk of infection is determined by the intensity and duration of chemotherapy. It is essential to know the patient's quantitative and qualitative defects predisposing to infection and to stratify the risk for specific pathogens in the context of the history, physical examination, and radiological and laboratory data. This chapter will deal with infections associated with malignancy in general with a special emphasis on the predisposing factors and with the management of the patients with febrile neutropenia.

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## Factors Predisposing to Infection in Patients with Cancer

Cancer patients comprise a very heterogeneous population, both in terms of the underlying malignancy as well as the level of predisposing factors to infection; multiple predisposing factors may exist in a single patient.

Bacterial infections are, by far, the most common cause of infection in cancer patients, and therefore it should be stressed that we are facing a major challenge with the continued emergence of multiresistant microorganisms; that threat is very serious and can lead us back to the pre-antibiotic era. The possibility of that scenario is made worse by the relatively slow development of new agents during the past years.

Local epidemiology and patterns of resistance are crucial for the selection of the most appropriate agents to be used for the management of these fragile patients. Furthermore, present measures to improve the management of infection in cancer patients encompass antimicrobial stewardship, early detection of sepsis, and use of valid tools for clinical assessment [1].



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## Infections in Patients with Hematological Malignancies

In patients with hematological malignancies, the underlining malignancy itself may be associated with immune defects. These patients with hematological malignancies associated with defective immunoglobulin production have an increased susceptibility to encapsulated bacteria and other pathogens, leading to recurrent sinopulmonary infections, septicemia, and disseminated infection.

- Chronic lymphocytic leukemia: This is frequently associated with hypogammaglobulinemia, and the low levels of immunoglobulin (IgG) increase the risk of severe infections in these patients [2].
- Multiple myeloma and other related plasma cell dyscrasias: These patients are often functionally hypogammaglobulinemic, despite the fact that the total level of immunoglobulin production is elevated as the antibodies produced are inadequate.

Early reports by Savage et al. [3] noted a biphasic pattern of infection among multiple myeloma patients. Infections by *S. pneumoniae* and *Haemophilus influenzae* occurred early in the disease, while patients responding to chemotherapy had a higher incidence of bacterial infections mainly by *Staphylococcus aureus* and gram-negative organisms. This occurred more commonly in advanced disease and during neutropenia. Therapy with bortezomib, carfilzomib, and ixazomib increases the risk for reactivation of the herpes simplex and herpes zoster viruses. Stem cell transplantation has broadened the spectrum of infection to include those caused by *Clostridium difficile*, cytomegalovirus (CMV), and opportunistic molds [4]. Other new therapies for multiple myeloma, such as lenalidomide, can also induce a significant risk of febrile neutropenia.

- Hairy cell leukemia: Infections are a major cause of morbidity and mortality in patients with hairy cell leukemia, presumably due to neutropenia and monocytopenia. The infections seen may be due to unusual pathogens, including *Mycobacterium* and *Listeria* [5].
- Hodgkin disease: Patients with untreated Hodgkin disease have significant immune abnormalities that persist in the majority of long-term survivors [6]. Such patients are at increased risk for toxoplasmosis, nocardiosis, pneumocystosis, cryptococcosis, mycobacterial infections, and herpes zoster. Most opportunistic infections occur with uncontrolled malignancy when patients are treated with corticosteroids, chemotherapy, or both [7].
- HIV-related non-Hodgkin lymphoma (NHL): This represents another subset of cancer patients at risk of opportunistic infection [8].

## Infections in Patients with Solid Tumors

In solid tumors, anatomical factors may predispose patients to infection. In addition, tumors that overgrow their blood supply become necrotic and infected.

- Head and neck tumors may cause erosion through the neck and floor of the mouth.
- Esophageal cancer may increase the risk of aspiration pneumonia.
- Endobronchial lung tumors are associated with recurrent postobstructive infections.
- Abdominal tumors may obstruct the genitourinary or hepatobiliary tracts, predisposing to pyelonephritis and cholangitis, respectively.
- Tumor invasion through the colonic mucosa is associated with local abscess formation by enteric flora. Colon cancer is associated with a significant incidence of bacteremia (endocarditis) caused by *Streptococcus bovis*, *Clostridium septicum*, and other pathogens.
- Breast cancer patients have an increased risk of abscess formation, usually by *S. aureus*. Breast cancer implants can be complicated by bacterial, mycobacterial, or fungal infections [9].

## Effect of Radiation Therapy

Local radiotherapy is associated with loss of epithelial integrity, necrosis, and loss of blood supply, resulting in poor wound repair. Oral mucositis resulting from radiation therapy, chemotherapy, or the combination of both represents a portal of entry for pathogens. Prevention, namely, through the use of soft laser irradiation, is essential to decrease that risk and reduce the pain and malnutrition associated with that condition [10].

Visceral complications include radiation pneumonitis, esophagitis, and enteritis.

Actually, the mucosal linings in the gastrointestinal, sinopulmonary, and genitourinary tracts constitute the first line of host defense against a variety of pathogens. The physical protective barrier conferred by the epithelial lining is damaged by radiotherapy, thus allowing access to colonizing microflora. Possibly defects in mucosal immunity can also be jeopardized by radiochemotherapy. In BMT patients, chronic graft-versus-host disease (GVHD) further affects mucosal immunity.

## Intravenous Devices

Implantable intravenous devices and ports used for administration of chemotherapy are major potential sources of infection [11].

## Effect of Neutropenia

Neutropenia may develop independently of chemotherapy in patients with advanced chronic leukemia, non-Hodgkin lymphoma, and myelodysplastic syndromes. In these conditions, the marrow may be replaced with malignant cells, and patients develop neutropenia. Patients rendered neutropenic by myeloablative chemotherapy are likely to be at greater risk for life-threatening infections due to the concomitant disruption of epithelial mucosal barriers by such agents.

The relationship between circulating leukocytes and risk of infection was established by Bodey et al. in patients with acute leukemia [12]. It has been established that the frequency of severe infections was the highest when the absolute neutrophil count (ANC) was less than 100/μL and proportionately less frequent at 100–500/μL and 500–1000/μL. This relationship was sustained independent of the disease status (relapse or remission); however, the overall risk of infection was greater during relapse. Most disseminated fungal infections and septicemias occurred when the ANC was less than 500/μL.

The risk of invasive fungal infection is also directly related to the duration of neutropenia, namely, in patients with leukemia [13]. Invasive fungal infection is also a major mortality cause in patients with persistent neutropenia in the bone marrow transplant (BMT) setting [14].

The diagnosis of infection in granulocytopenic patients may be delayed by the lack of typical signs and symptoms, but fever remains the reliable surrogate of infection in neutropenic patients. However, in patients with similar infections, physical findings of infection were less frequent in neutropenic than in nonneutropenic patients.

## Immunosuppressive Agents Not Related to Neutropenia

### Corticosteroids

Corticosteroids have profound effects on the distribution and function of neutrophils, monocytes, and lymphocytes. They induce a neutrophilic leukocytosis by accelerating the release of neutrophils from the bone marrow and by inhibiting the egress of neutrophils from the circulation. Corticosteroids reduce the adherence of neutrophils to the endothelium, thus inhibiting migration to inflammatory sites [15].

Corticosteroids elicit a peripheral blood monocytopenia. In addition, the following impaired monocyte functions have been documented: (1) chemotaxis, (2) bactericidal activity, (3) production of interleukin-1 (IL-1), and (4) tumor necrosis factor-alpha (TNF-alpha).

Corticosteroids also inhibit T-cell activation and peripheral lymphocytopenia. This redistribution

predominantly involves T cells. At high doses, corticosteroids also inhibit immunoglobulin generation by B cells.

In patients with cancer, corticosteroids are used in high doses and often in combination with other immunosuppressive agents. These patients are highly susceptible to a broad spectrum of bacterial, fungal, viral, and protozoal pathogens.

### Monoclonal Antibodies and Other Targeted Therapies

Rituximab is an antiCD20 monoclonal antibody that has demonstrated efficacy in patients with various lymphoid malignancies [16].

The use of rituximab was associated with a significant increase in the incidence of hypogammaglobulinemia between 12 and 24 months post stem cell transplant (SCT). Other studies have reported the occurrence of unexplained peripheral blood cytopenia, particularly neutropenia following rituximab treatment [17]. A concern associated with the prolonged administration of rituximab maintenance is viral reactivation. Several cases of hepatitis B reactivation have now been reported with the use of this agent. Other viral reactivations that have been reported with rituximab use include adenovirus, CMV, and varicella-zoster virus (VZV) [18].

Alemtuzumab is a humanized monoclonal antibody against CD52, an antigen found on the surface of normal and malignant lymphocytes. It is approved for the treatment of B-cell chronic lymphocytic leukemia. Successive courses of treatments may have an adverse effect on patients' immune responses to certain bacterial, fungal, and viral infections [19].The field of target therapy and immunotherapy, namely, the checkpoint inhibitors, is presently rapidly expanding. The risk of infections with these drugs appears limited (<10%) [20]; however, the available experience has been obtained from patients included in clinical trials who may not represent "real life" situations. Therefore, clinicians should have a high level of suspicion when fever occurs in patients receiving these novel therapies and proceed, in those cases, to a comprehensive work-up of a possible infectious process.

### Splenectomy

The spleen is a reservoir in which rapid antigen presentation occurs, leading to the production of opsonizing antibodies by B cells. Splenic macrophages remove both opsonized and nonopsonized particles from the blood stream. The removal of nonopsonized bacteria is a particularly important function to protect against encapsulated bacteria to which the patient is not immune.

Asplenic patients are primarily at risk for overwhelming sepsis by encapsulated bacteria. The most common pathogen is *S. pneumoniae*, but other pathogens include *H. influenzae* and *Neisseria meningitidis* [21]. Asplenic patients should be advised to seek medical attention when fever occurs.

### Bone Marrow Transplantation

The spectrum of pathogens to which BMT recipients are most susceptible follows a time line corresponding to the predominant immune defects observed at different periods. In the early stage of BMT, neutropenia is the principal host defense defect. These patients are at risk for the same spectrum of bacterial and fungal infections that affect nontransplant patients who have been treated with potent myeloablative therapy. Severe mucocutaneous herpes simplex virus infection is also commonly observed in the first month of transplantation in association with chemotherapy-induced mucositis. After myeloid engraftment, fever and mucositis typically resolve, and the risk of serious bacterial and fungal infections decreases, but a qualitative dysfunction of phagocytes persists due to corticosteroid therapy, other immunosuppressive agents, and the presence of graft-versus-host disease (GVHD). The risk of infection by filamentous fungi and viral pathogens during this period is strongly associated with the severity of GVHD and the requirement for potent immunosuppressive regimens [22].

## Infection in Non Neutropenic Cancer Patients

There is relatively limited information about infections in non-neutropenic cancer patients compared

to what we know about neutropenic patients. These infections occur mainly in patients with solid tumors and the primary or metastatic cancer disease often serves as a portal of entry. The urinary tract and the abdomen are the most frequent causes of infection, with obstructive phenomena frequently associated with them; cholangitis is the most recurrent source of these infections. Aerobic gram-negative bacilli, with increasing rate of multiresistance (see below), are the leading cause of infections in patients with solid tumors, often associated with various anaerobes [23]. These considerations support the need for an early surgical approach in those patients when obstruction is present and the mandatory use of anti-anaerobic average in many cases. Otherwise the management of these cancer patients without neutropenia is not fundamentally different from that recommended in noncancer patients: clinical and microbiological diagnoses of the type of infection should precede and guide the choice of antimicrobial therapy. Prolonged fever of unknown origin may be a diagnostic challenge in those patients; in some, fever can be due to the cancer itself such as lymphomas, colon cancer, kidney cancer, or extensive liver metastases (±10%); but, in most cases, it is related to an occult infection most often associated with an obstructive phenomenon. Opportunistic infections (e.g., tuberculosis) and noninfectious causes unrelated to the tumor (e.g., drug fever) should be considered as well. Modern imaging techniques (CT, MRI, PET) can be of great diagnostic value [24].

## Evaluation and Management of Febrile Neutropenia

Patients with cancer and neutropenic fever either have an established or an occult infection, and bacteremia is documented in approximately a quarter of these patients. Patients with febrile neutropenia often do not have classical symptoms or signs of infection as a result of decreased inflammatory reactions due to the lack of neutrophils. The manifestation of infection may only be fever and neutropenia following chemotherapy treatment. Due to the potential for the possible rapid progression of febrile neutropenia to severe sepsis, prompt initiation of empiric antibiotics is indicated. The risk of bacteremia is related to the intensity (with an ANC of less than 100/μL carrying the greatest risk) and the duration of neutropenia. A rapid decrease in the neutrophil count may also be a risk factor for infection, whereas evidence of bone marrow recovery even if the neutrophil count is still less than 500/μL is a positive prognostic factor.

Neutropenic fever is defined as:

1. A single oral temperature of greater than 38.3 °C (101 °F) or greater than or equal to 38.0 °C (100.4 °F) over at least 1 h
2. ANC less than 500/μL or less than 1000/μL with predicted rapid decline to less than 500/μL

The evaluation of a patient with febrile neutropenia begins with a careful history and physical examination.

Certain clinical settings are important to identify in patients with febrile neutropenia. Recent colitis caused by *C. difficile* should raise a suspicion of recurrent infection in a patient presenting with neutropenic fever and diarrhea. Patients undergoing corticosteroid treatment are at risk of various opportunistic infections (such as *Pneumocystis carinii*). Mucositis may occur following chemotherapy treatment. Severe mucositis may be very difficult to distinguish from herpes infection or oral candidiasis. In patients with prolonged neutropenia, or those patients who are undergoing concomitant high-dose corticosteroid therapy, fungal infection of the palate (*Zygomycete* or *Aspergillus* species) may occur; a black necrotic region is the most common sign of such infections.

Besides the standard physical examination, specific aspects of the clinical examination of a febrile neutropenic patient include: (1) ophthalmologic and anterior sinuses examinations, (2) detailed inspection of the skin and the nails (inspection of the skin and nails may reveal lesions suggestive of systemic infection such as ecthyma gangrenosum caused by *Pseudomonas aeruginosa* or erythematous papules caused by

disseminated candidiasis), (3) inspection of catheter sites and surgical wounds and biopsies, and (4) inspection and palpation of the perineum and perianal regions. An ENT specialist consultation may be warranted in some cases.

The initial laboratory evaluation should include the following: complete blood cell and differential count and differential serum chemistry including liver function tests, two sets of blood cultures from different sites (including one from each lumen of the central venous catheter), a urine culture, and a chest radiograph. Details of potential sites of infection, such as skin lesions or sputum, should be obtained before starting antibiotic therapy.

## Empiric Antibiotic Regimes

Febrile neutropenia should be considered a medical emergency, and prompt initiation of empiric antibiotics should not be delayed if culture material is not immediately available [25]. It is critical to reevaluate the patient regularly to monitor the response to therapy and to identify evolving signs of infection that were not present during the initial evaluation.

In the early 1970s, Schimpff and colleagues conducted a study of patients with cancer and febrile neutropenia who were treated empirically with carbenicillin and gentamicin. Treatment of patients with *P. aeruginosa* infection had dramatic survival improvement compared with historic controls. This study was the basis for empiric antibiotic therapy [26].

Combination therapy increases the likelihood that at least one antibiotic will have activity against the isolate before the availability of susceptibility data. In addition, the beta-lactam plus aminoglycoside combination has a synergistic bactericidal activity in vitro. Since this early study, typical combination regimens for neutropenic fever have included an antipseudomonal penicillin plus an aminoglycoside.

Actually, recent data analysis has shown that the prompt empirical usage of broad spectrum beta-lactam antibiotics with antipseudomonal activity is usually sufficient as an initial antibiotic therapy for febrile neutropenic patients. Meta-analyses have shown that the usage of a combination treatment with a broad spectrum of beta-lactam antibiotics with antipseudomonal activity and aminoglycoside antibiotic resulted in increased toxicity and similar survival [27]. The addition of aminoglycoside antibiotics is now often limited to patients who are hemodynamically unstable. Fluoroquinolones may be an important alternative to aminoglycoside antibiotics in this setting (as part of a combination regimen), particularly in those patients with impaired renal function.

In the 1980s, there was a shift in the relative prevalence of specific pathogens afflicting neutropenic patients with cancer. Whereas in the 1960s and 1970s, gram-negative bacterial pathogens (*Enterobacteriaceae* and *P. aeruginosa*) were the principal causes of bacteremia, in the 1990s and 1980s, gram-positive bacterial pathogens became predominant. Vancomycin was added to the standard combination to cover these changes [28].

The rationale for adding vancomycin to an empiric regimen for neutropenic fever stems from the increased proportion of infections by gram-positive bacteria. Occasionally, one might need to use new gram-positive antibiotics for pathogens not sensitive to vancomycin. Some examples include tigecycline, daptomycin, and telavancin, but none of these has been used extensively in this setting [29].

Catheter-associated infection was the main cause of emergence of gram-positive infections in neutropenic patients; these are usually caused by coagulase-negative *Staphylococci*. Among the common gram-positive infections in neutropenic patients, the following are typically resistant to cephalosporins: MRSA, coagulase-negative *Staphylococcus* species, and *Enterococcus* species.

Numerous studies have evaluated single and multiple drug regimens with and without vancomycin. In the largest study, ceftazidime plus amikacin with and without vancomycin were compared in patients with febrile neutropenia in Europe and Canada [30]. The addition of vancomycin to the empiric regimen was not associated with any benefit with regard to duration of fever

or morbidity or mortality related to gram-positive infections but higher toxicity and increased cost.

Today, with the availability of highly effective monotherapy for neutropenic fever regimens such as meropenem, cefepime, and piperacillin plus tazobactam, initial empiric biotherapy regimens may be most appropriate in unstable patients and in institutions in which multidrug-resistant pathogens are frequently encountered [31].

## Persistent Fever in the Neutropenic Patient

The patient should be very closely observed after selection of an initial empiric regimen for neutropenic fever. Physical examinations should be performed at least daily throughout the duration of neutropenic fever. Signs and symptoms should be systematically evaluated on a daily basis. Modifications of the initial antibiotic regimen should be made on the basis of new physical examination findings (pointing to a previously not apparent focus of infection) and radiographic and culture data. Patients with persistent fever and a positive blood culture before or during the start of empirical antibiotic therapy for febrile neutropenia, or those with venous catheter sepsis, should be considered candidates for anti-gram-positive antibiotic treatment with vancomycin or linezolid, if resistant to vancomycin.

Antibiotic therapy should be continued for the whole duration of neutropenic fever.

## Common Scenarios in this Setting Include

- Biopsy and culture may be necessary if a new erythematous papular lesion develops, as this may be indicative of cutaneous or disseminated bacterial or fungal infection.
- Catheter sites, surgical wounds, and biopsy sites should be carefully examined for signs of infection. Fever and local tenderness may be the only signs of infection in the neutropenic patient.
- A diffuse maculopapular rash may be suggestive of a drug etiology; cultures should be performed to exclude infection, namely, fungal or viral.
- Blurred vision is an important clinical sign. It may represent a central nervous system (CNS) process or could be indicative of keratitis or endophthalmitis caused by a bacterial, viral, or candidal infection. Careful ophthalmologic examination by a specialist may be needed to establish the diagnosis. A magnetic resonance imaging (MRI) scan of the brain with or without a lumbar puncture may be indicated.
- In patients receiving high doses of corticosteroids, upper respiratory tract symptoms in a persistently neutropenic patient (longer than 10 days) may be indicative of a fungal infection. A computerized tomography (CT) scan is more sensitive and provides superior evidence of disease compared to a chest radiograph. Aspiration or biopsy of lesions should be performed where possible, especially in patients with persistent radiological evidence of pulmonary infiltration. The use of serial serum galactomannan in combination with chest CT might be useful to detect early aspergillosis [32, 33]. False-negative results are common especially in patients already receiving antifungal agents. The β-D-glucan test also has false-positive and false-negative results [34].
- In cases of suspected bowel or perianal infection, the antibiotic regimen should have broad-spectrum activity against anaerobes, such as metronidazole.
- Should persistent fever be present, blood cultures from different sites should be obtained frequently to avoid a delay in adjusting the antibiotic regimen.

## Empiric Antifungal Therapy

Before standard implementation of empiric antifungal therapy, there was a high mortality in

patients with cancer due to fungal infections (frequently found at autopsy). Randomized prospective studies demonstrated that empiric amphotericin B was associated with fewer fungal infections in antibiotic-treated neutropenic patients with persistent fever [35]. Because fungal infections are uncommonly encountered in the first 7 days of neutropenic fever, empiric antifungal therapy is typically begun between days 4 and 7 of neutropenic fever and should be continued for the duration of neutropenia. Liposomal amphotericin B's (L-AmB) efficacy is similar to that of conventional amphotericin for empiric therapy but with fewer adverse events. Another approach is preemptive antifungal therapy. This attitude takes into account the relatively low (± 25%) frequency of invasive fungal infection in persistently febrile and neutropenic patients as well as the cost and toxicity of antifungal therapy. A recent meta-analysis of nine studies evaluated the empirical versus preemptive approaches and their cost. Compared to empirical antifungal therapy, preemptive strategies were associated with lower antifungal exposure without an increase of mortality related to fungal infection and of overall mortality. The preemptive approach was also less costly [36].

Because the overall success rate of voriconazole was lower than that of L-AmB in a study in febrile neutropenic cancer patients, and because noninferiority was not demonstrated, voriconazole did not receive FDA approval as empiric therapy. Voriconazole remains however the standard treatment for proven aspergillar infection [37]. It should be considered that Zygomycetes can occur as a superinfection in patients treated with voriconazole and would require therapy with amphotericin B or caspofungin [38].

In a randomized, comparative trial of caspofungin versus L-AmB in cancer patients (<10% HCT) with febrile neutropenia, the agents were comparable in overall response, breakthrough IFI, and resolution of fever during neutropenia, although caspofungin was superior for baseline infection resolution, survival through 7 days of follow-up, and discontinuations as a result of toxicity [38].

## Outpatient Antibiotic Therapy for Neutropenic Fever

Historically febrile neutropenia was associated with a high morbidity and mortality, and urgent treatment with systemic antibacterial therapy and hospital admission were regarded as necessary. Inpatient observation was typically continued until resolution of neutropenia. More recent studies have shown that patients with febrile neutropenia can be stratified according to their risk of developing major or life-threatening infectious complications.

In terms of risk assessment, the MASCC has pioneered work in this field and developed an index that predicts for high risk or low risk of severe medical complications [9].

The index consists of seven independent prognostic factors with an assigned integer value. The index consists of the sum of these integers. Patients with a MASCC risk index equal to or greater than 21 are identified as low-risk patients with a positive predictive value of 91% (specificity 68% and sensitivity 71%) (see Table 22.1). The index has been validated by other institutions

**Table 22.1** MASCC scoring system

| Characteristic | Weight |
|---|---|
| Burden of illness: no or mild symptoms | 5 |
| No hypotension | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumor or no previous fungal infection | 4 |
| No dehydration | 3 |
| Burden of illness: moderate symptoms | 3 |
| Outpatient status | 3 |
| Age < 60 years | 2 |

Points attributed to the variable "burden of illness" are not cumulative

The maximum theoretical score is, therefore, 26

From doi: 10.1200/JCO.2000.18.16.3038 Journal of Clinical Oncology 18, no. 16 (August 2000) 3038–3051 [39]. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved

in their respective patient populations and clinical settings [39, 40].

Patients with a risk index greater than 21 may be candidates for outpatient antibiotic therapy for febrile neutropenia. The greatest concern about early hospital discharge or outpatient management of neutropenic fever relates to the possibility of life-threatening complications that may be reversible if detected early, and appropriate interventions are immediately implemented (e.g., intravenous fluid, vasopressors, broadening of antibiotic coverage).

The results of most outpatient antibiotic therapy studies are encouraging about the safety of outpatient antibiotic therapy for low-risk patients with neutropenic fever [41–44]. However, important limitations exist and this approach cannot be considered routine standard care. Further studies are required to define more precisely patients for whom outpatient management of neutropenic fever is safe and to further delineate optimal antibiotic regimens (oral vs. parenteral) for different patient subgroups.

Key issues for outpatient management include the observation of low-risk patients by adequate staff who are experienced with this patient population, and in such approaches, the facility must be in a geographic location, in proximity to a facility having adequate infrastructure for emergency management.

## Management of High-Risk Patients

Patients with severe sepsis or septic shock, or signs making this situation likely, should be hospitalized and treated aggressively with fluid resuscitation and prompt administration of broad-spectrum intravenous antibiotics. It has been clearly established that in such patients any delay in starting antimicrobial therapy is detrimental for survival. These patients should be rapidly identified in the emergency room and managed according to their clinical status. If the MASCC score is very low ($\leq 15$) or if there are signs of cardiovascular instability, admission to the intensive care unit may be appropriate. Antifungal therapy should be strongly considered early in the course of management. Modifications of the antibiotics should be made as soon as the culture results and sensitivity data are available. Infectious diseases experts and other specialists, as indicated, should be consulted.

## Prevention of Febrile Neutropenia

The use of prophylactic granulocyte-colony stimulating factors (G-CSFs) has shown benefits in terms of reducing the time to neutrophil recovery and the duration of fever and hospitalization. However, the prophylactic usage of G-CSF is costly, and the reduction in treatment-related mortality is controversial. It remains that the reduction of the incidence of febrile neutropenia in patients receiving G-CSF by at least 60% decreases significantly the morbidity and possibly reduces the cost of the management of these patients. Moreover, it allows, in a significant proportion of chemotherapy-treated individuals, to administer the treatment without dose reduction or delays, which is crucial when chemotherapy is given with a curative intention (e.g., neoadjuvant or adjuvant treatments). Among the guidelines for the prophylactic use of G-CSF, those of ASCO (American Society of Clinical Oncology) [45] and of EORTC (European Organization for Research and Treatment of Cancer) [46] are most authoritative. The EORTC recommendations are summarized in Fig. 22.1. They are based on the risk of febrile neutropenia as linked to the aggressiveness of the administered chemotherapy. Patients with a risk >20% should receive G-CSF; for those with a risk between 10% and 20%, the decision to give prophylactic G-CSF should take into account the age of the patient and the possible presence of a series of comorbidities. There are several recent reviews about the use of prophylactic G-CSF including a recently updated set of recommendations by ESMO (European Society of Medical Oncology) [47].

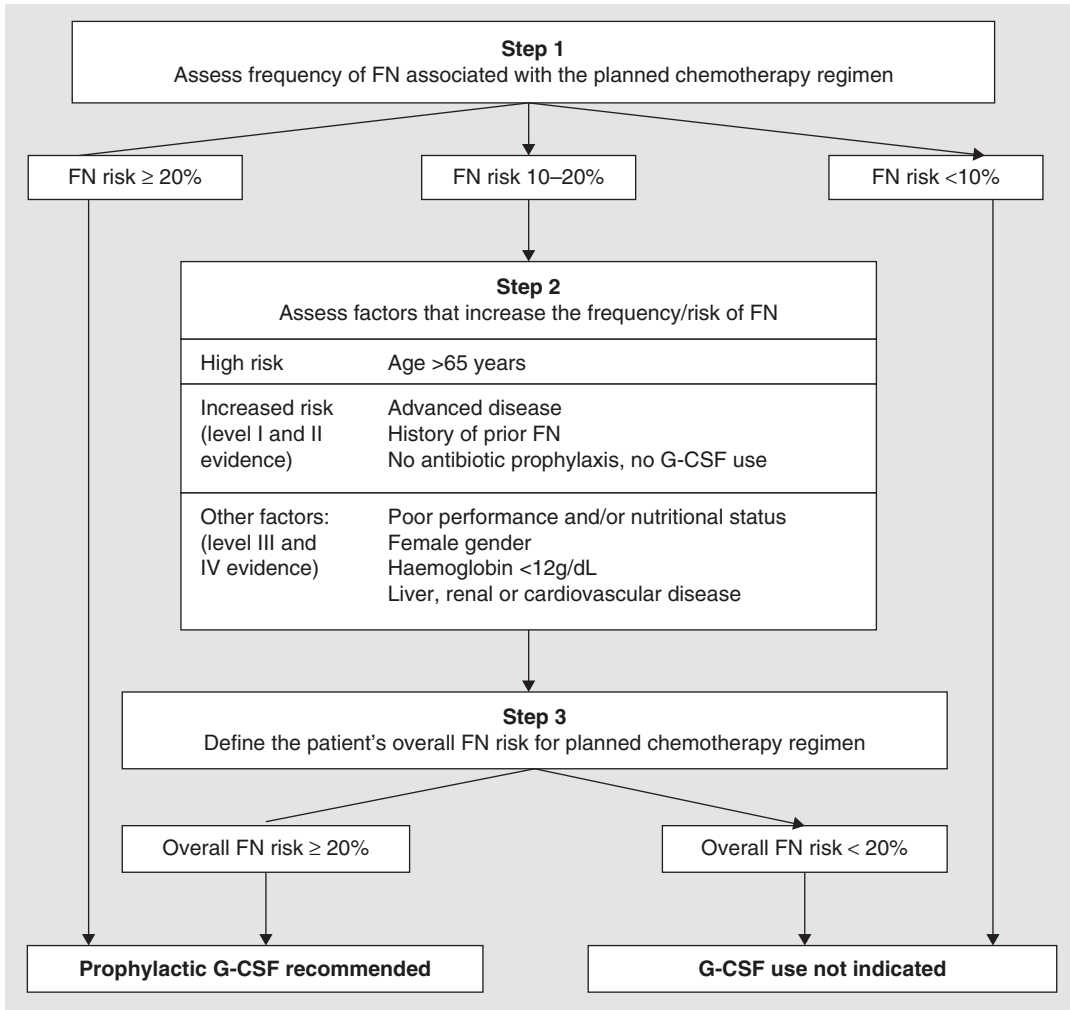


**Fig. 22.1** EORTC guidelines for the prophylactic use of G-CSF [45]

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# Part VIII

# Gastrointestinal

# Cancer Cachexia and Anorexia

# 23

Vickie E. Baracos and Neil MacDonald

*The beginning of wisdom is to call things by their right name*

Chinese Proverb

Clinicians and their patients benefit when the condition treated is clearly defined. Alas, this has not been the case for the cancer anorexia–cachexia syndrome. The presence of multiple concurrent but different definitions is an impediment to clinical care and to clinical cachexia research, and this incited a significant recent focus on reaching a consensus definition.

A generic definition encompassing cachexia in all disease conditions was proposed recently by a group of experts [1]. This definition of cachexia notably makes a distinction between the behavior of skeletal muscle and of adipose tissue: "….cachexia, is a complex metabolic syndrome associated with underlying illness and *characterized by loss of muscle with or without loss of fat mass*…" Importantly, this definition recognizes that skeletal muscle wasting can be hidden within the bulk of body weight and body weight change and underscores the recent recognition of severe muscle depletion (i.e., sarcopenia) as a clinically important phenomenon [2].

More recently, an international group of experts conducted a Delphi consensus process to provide a definition and conceptual framework specific to cancer-associated cachexia [3]. This consensus definition was "*Cancer cachexia is a multifactorial syndrome [of involuntary weight loss] that is defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and that leads to progressive functional impairment. The pathophysiology of cachexia is characterized by a negative protein and energy balance that is driven by a variable combination of reduced food intake and abnormal metabolism*." This definition underscores the point that loss of skeletal muscle is related to functional impairment, cancer-related mortality, treatment-related complications, and poor quality of life. Unlike simple malnutrition, in cachexia negative energy balance and muscle loss are not solely a result of reduced food intake. Metabolic derangements also contribute (e.g., elevated resting metabolic rate, insulin resistance, excess catabolic drive, lipolysis, proteolysis) to the activation of weight loss. Both host- and tumor-derived inflammatory mediators and catabolic factors may be involved, with the results that cancer cachexia cannot be fully reversed by conventional nutritional support.

The defining features of cancer cachexia:

- Is multifactorial in nature.
- Is characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass).

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- It cannot be fully reversed by conventional nutritional support.
- Has as a consequence progressive functional impairment.
- Its pathophysiology is characterized by a variable combination of reduced food intake and abnormal metabolism including tumor metabolism and inflammation.

Management of cancer cachexia depends upon identifying elements contributing to patient wasting. The tumor itself imposes a metabolic demand, which may vary between a negligible value and >800 kcal/day [4], in function of tumor burden and metabolic activity. Aberrant chronic inflammation is generated by interaction of the tumor with the host inflammatory response to the tumor. This harmful inflammatory process is similar to the acute response to infection or injury. Inflammation is unabated, causing enhanced tumor symptoms and increased cancer growth. This is the result of direct tumor stimulation by inflammatory products and interference with natural killer cells and other elements of an antitumor immune response. Excess inflammatory mediators generate lipolysis and proteolysis by local action on adipose and muscle tissue; persistent inflammation in the central nervous system has been demonstrated in animal models, and this contributes to sustained anorexia as well as catabolic outputs to peripheral tissues [5]. Cancer patients are, however, also bedeviled by a plethora of problems that contribute to poor food intake. A list of these is listed in Table 23.1, together with a brief listing of possible therapeutic options. The management of these issues should be prioritized, as they may be readily reversed by appropriate treatments (e.g., pain, nausea, reduced bowel motility, mood disorders).

**Table 23.1** An approach to identify potentially correctable cause of cancer cachexia

| Potentially correctable problems | Possible approaches |
|---|---|
| *Psychological factors* | |
| Anxiety | Anxiolytics |
| Depression | Antidepressants |
| Family distress | Social assistance |
| Spiritual distress | Counseling |
| *Eating problems* | |
| Appetite | Referral to a nutrition clinic or a dietician |
| Disturbed taste or smell | |
| *Oral* | |
| Dentures, mouth sores | Dental care |
| Thrush | Antifungal medication |
| Dry mouth | Oral moisteners, change medications |
| *Swallowing difficulties* | Related to cause: chewing difficulty, dry mouth, pain Esophageal dilation |
| *Stomach* | Regurgitation therapy |
| Early satiety | Gastric stimulants |
| Nausea and vomiting | Related to cause |
| *Bowel* | |
| Obstruction | Related to cause |
| Constipation | Laxatives, especially if on opioids |
| Diarrhea | |
| *Malabsorption* | |
| Pancreas | Pancreatic enzymes |
| Fistulas | Related to cause |
| *Fatigue* | Exercise protocol |
| Sleep disturbances | Sleep protocol |
| Physical limitation | Exercise protocol |
| Motivation | |
| Cognitive fatigue | Methylphenidate |
| *Function* | Exercise protocol |
| Home setting | Cause related |
| *Pain* | Appropriate analgesics |
| | Nerve blocks: surgical, percutaneous |
| | Counseling |
| *Metabolic* | As indicated |
| Diabetes | |
| Adrenal insufficiency | |
| Hypogonadism | |
| Thyroid insufficiency | |

## Clinical Work-Up

In concordance with the criteria mentioned above, the clinical work-up focuses on:

- The degree and rate of depletion of body weight, muscle protein, and energy stores in adipose tissue
- Evaluation of muscle mass and degree of functional impairment
- Anorexia and reduced food intake due to all causes
- Catabolic drivers including tumor burden, systemic inflammation, and altered endocrine status

- Psychosocial stress related to food, eating, and altered body image

Cachexia is not just a late-stage phenomenon; patients with some tumors (e.g., pancreas, upper gastrointestinal, and lung cancer) commonly present with weight loss, anorexia, and other nutritional issues. Early identification of cachexia may lead to treatments that reverse or prevent, if only for a while, further deterioration. Therefore, it is strongly recommended that oncology clinics employ protocols for screening as well as further detailed assessment, as indicated, of all patients with advanced cancer, at diagnosis and at periodic intervals over the course of their illness. Elements of this protocol include the evaluation of weight and weight loss, level of dietary intake, biological criteria, and nutritional risk factors associated with the underlying pathologies and treatments.

Patient-reported outcomes are of value in the assessment of various facets of cachexia. There is evidence to support the reliability of self-reported height, weight, and weight history [6]. Patient-/family-generated questionnaires are valuable for the screening process. We use the following battery; however, a variety of similar tools exist that may be used to capture the same information:

- Edmonton Symptom System Assessment (ESAS) [7] helps to identify and measure the severity of common symptoms affecting people with advanced cancer, using a 0–10 scale.
- Patient-Generated Subjective Global Assessment (PG-SGA) [8] is an adaptation for oncology patients of the earlier SGA that was originally validated as a screening tool for malnutrition in hospitalized patients. The PG-SGA is scored and incorporates questions relating to intake, weight, and nutritional risk factors and is a mixture of patient report (for weight history, food intake, functional status, and symptoms affecting food intake) and assessments made by healthcare professionals (comorbid conditions, physical examination, corticosteroid use, and fever).
- Distress Thermometer [9]. This screening tool is used to assess the level of patient distress (on a 0–10 scale) and the specific problems contributing to it by giving them a problem list to indicate their reason(s) for distress. It is an easy way for patients to differentiate between the normal distress and a more significant form of distress that requires help from a healthcare professional. Patients can fill these questionnaires in a few minutes. Initially, instruction from clinic personnel is desirable.

## Assessment of Weight and Weight Loss

Body weight should be determined and recorded in a consistent fashion, with caution taken to remove footwear, and the contents of pockets. The same scale should be used consistently for follow-up weights, and all scales used in the unit should be regularly calibrated. A measurement of patients' height, determined with a stadiometer, must be entered into the patient's record, to facilitate computation of the common anthropometric descriptor, body mass index (BMI) ($kg/m^2$). The percentage of the weight lost is calculated, either relative to premorbid (habitual) weight or over a defined period of time (e.g., 6 months). Edema, ascites, increased organ volume (e.g., hepatomegaly), constipation, and tumor burden, including metastasis, contribute to shifts in body weight in advanced cancer patients [10, 11] and should be taken into account in the assessment of weight and weight change over time.

In the past weight loss and BMI, cut points have been treated rather heterogeneously in the nutrition screening tools, in the literature, in the Common Terminology Criteria for Adverse Events (CTCAE), and in the publications by various health authorities and expert groups. To address this issue, the international group which had earlier provided a consensus framework for cancer cachexia developed a revised set of diagnostic criteria for the classification of cancer-associated weight loss [12]. Using a risk stratification for overall survival, a robust grading system incorporating the independent prognostic significance of both BMI and weight loss was developed (Fig. 23.1).

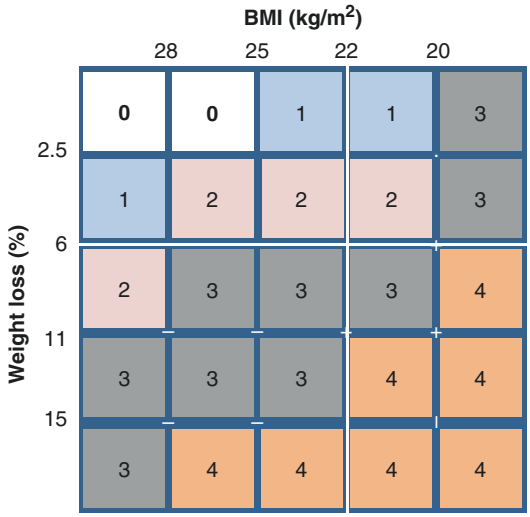


**Fig. 23.1** A 5 × 5 matrix representing five weight loss categories within each of five BMI categories was graded 0, 1, 2, 3, or 4 based on median survival. All combinations of BMI and weight loss within the same grade have the same survival probability

This grading scheme is superior to conventional grading systems applied to weight loss in patients with cancer (i.e., CTCAE, cachexia scores, and screening tools for malnutrition) which typically employ simple weight loss cutoffs (e.g., 10%). Using a single cutoff inappropriately subgroups patients with disparate degrees of risk. For example, in Fig. 23.1, patients with weight loss <10% include significantly different subsets of patients including Grade 0 (survival 21.5 months) and Grade 4 (survival 4.7 months).

This system should be considered by oncologists evaluating the risk benefit/analysis of chemotherapy in advanced cancer patients.

## Evaluation of Muscle Mass and Degree of Functional Impairment

Wasting of lean tissues especially skeletal muscle is an important component of cancer-associated weight loss. Muscle wasting can coexist with the depletion of adipose tissue but may also coexist with obesity, and this independent behavior of lean and adipose tissues makes body composition analyses essential. Precise and specific measures of skeletal muscle mass and loss using computed tomography have greatly enabled our understanding of the clinical importance of muscle loss [13]. Cancer patients with significant erosion of skeletal muscle (even if they have large body weights) have an elevated risk of being partially or entirely bedridden and a substantially reduced survival [13]. Sarcopenic patients are also prone to severe toxicity during chemotherapy [14–16], necessitating reductions in the dose of drugs or treatment delays.

Defined sex-specific reference values and standardized body composition measurements are essential to perform assessment of skeletal muscle depletion. There remains a paucity of reference values related to cancer-specific outcomes. A generally accepted rule is an absolute muscularity below the fifth percentile for normal healthy adults. Assessment of muscularity remains far from routine, although a variety of clinically expedient approaches are available. The following approaches are suggested [3]; sex-specific cut points consistent with sarcopenia are given for each measure:

- Mid-upper arm muscle area by anthropometry: men <32 $cm^2$, women <18 $cm^2$
- Appendicular skeletal muscle index determined by dual-energy X-ray absorptiometry: men <7.26 $kg/m^2$, women <5.45 $kg/m^2$
- Lumbar skeletal muscle index [12] determined by CT imaging: men <55 $cm^2/m^2$, women <39 $cm^2/m^2$
- Whole body fat-free mass index without bone determined by bioelectrical impedance: men 14.6 $kg/m^2$, women 11.4 $kg/m^2$

It should be noted that these values were determined in Caucasians and that sex-specific cut points for sarcopenia are emerging for other populations [17].

## Function Tests

Simple tests, with minimal patient burden, can be employed. We use a 6-min walk, sit-to-stand time, gait speed, and the Community Health Activities Model Program for Seniors (CHAMPS) tests. Physician assessment of patient capacity to perform a 6-min walk is necessary prior to testing.

Articles which outline their use and precautions include:

- Jones and Eves. Cardiorespiratory exercise testing in clinical oncology research (LANCET Oncology 2008 9 (8): 757–65)
- ATS Statement on 6-min walk test (American Journal of Respiratory Critical Care Medicine (2002) 166:111–117)
- Carli F et al. Analgesia and functional outcome after total knee arthroplasty (British Journal of Anaesthesiology 2010 106: 196–200)

## Assessment of Dietary Intake

Prospectively collected dietary records are the gold standard for evaluation of total energy and macronutrient intake. A 3-day collection period seems to be the compromise generally taken between the length of the assessment and the frailty or vulnerability of patients with advanced cancer; 24-h dietary recall and food frequency questionnaires are sometimes used as alternates. Dietary records require the specialized expertise of a registered dietitian and are not commonly used in clinical practice. Nutrition screening tools generally replace dietary records with questions pertaining to the type, number, and frequency of meals or verbal descriptors such as "very little of anything," "only liquids," or "little solid food" [7]. Questions related to the patient's ability to purchase, shop for, prepare food, and eat independently are often included, especially in nutrition assessment tools for the elderly. Dozens of symptoms have the potential to exert a negative impact on food intake (e.g., nausea, vomiting, constipation, early satiety, chemosensory dysfunction, pain, fatigue, difficulty swallowing, mouth sores, dental problems) and should be evaluated.

## Biological Criteria

The most clinically useful laboratory measures relate to the acute-phase response, a series of reactions initiated in response to infection, physical trauma, or malignancy. The acute phase response is characterized by leukocytosis, sometimes fever, alterations in the metabolism of many organs as well as changes in the plasma concentrations of acute-phase proteins [17, 18]. The positive acute-phase proteins (fibrinogen, α1-acid glycoprotein serum amyloid A, and C-reactive protein) increase, and negative acute-phase proteins albumin and transferrin decrease during an inflammatory disorder. The laboratory values vary according to different authors: albumin (cut points variously <30 to <35 g/L), transthyretin (prealbumin) (<110 or <180 mg/L), and C-reactive protein (>5 or >10 mg/L). The Glasgow prognostic score, grading for reduced albumin and increased CRP or both, is established as a powerful prognostic tool in multiple cancers for both tumor progress, survival [19], and symptom burden [20]. Where CRP testing is still not available, neutrophil to lymphocyte ratios offer similar prognostic information on tumor prognosis [21]. The value of both of these indices is supported by meta-analyses in multiple disease sites. While the production of proinflammatory cytokines is understood to be central to the host inflammatory response to malignant disease, serum cytokine levels have proven too inconsistent to be useful biological criteria. Thyroid function and the possible presence of hypogonadism (testosterone screen) may provide additional information on possible causes of weight and muscle loss.

## Assessment of Nutritional Risk Factors Associated with the Underlying Pathology(ies) and Treatments

This category is quite heterogeneous and includes any factors likely to drive weight loss or poor food intake. Some examples in this category include old age, poor social support, poor cognition, limited mobility, advanced disease stage, extensive tumor burden and metastases, presence of fever, and comorbid conditions associated with additional nutritional risk (i.e., compromised organ function, major stress, infection). Depression is a significant independent factor

explaining nutritional risks. A variety of medications may contribute to poor food intake or altered metabolism (i.e., high-dose corticosteroid).

## General Therapeutic Platform

The management of cancer cachexia is a moving target; new approaches are expected in the near future. While awaiting clinical research advances, much can be done today. Elements include:

1. Evaluate which elements of cachexia are present. If the patient has a high C-reactive protein or unexplained high neutrophil/low lymphocyte count, they are likely to be experiencing inflammation—related catabolic drive. A low albumin is usually a late feature. All identified secondary issues related to food intake should be addressed. A variety of treatment approaches may be required.
2. Team approach—adoption of this concept is critical. In addition to the nurse/physician dyad, core members of the team should include a dietitian and a physiotherapist; availability of an occupational therapist, social worker, and a clinical psychologist is also desirable.
3. Our clinics have varying resources. Based on the initial work-up, you may establish decision points for the involvement of the registered dietitians based on PG-SGA quantitative scores or physiotherapists based on fatigue/activity scores.
4. Exercise patients within their safe capacity. It is becoming increasingly clear that many categories of cancer patients can benefit from planned physical activity. Physiotherapists and occupational therapists can evaluate and motivate your fatigued, inactive patients to exercise and carry out daily tasks. Fatigue, the most prevalent, devastating symptom encountered by cancer patients, has no established drug therapy; however, directed exercise can relieve fatigue.
5. Involve the patient and family as members of the therapy team. Almost all cancer therapies call for patients to be passive receptors of care—somebody is doing something to them. Diet and exercise are *their* therapies. We advise but they run the enterprise. We stress that involving caregivers is not simply an empty rhetorical phrase. They are often more distressed than the patient as they observe a loved one wasting away. Their anxiety can be transferred to the patient leading to conflicts over food intake and preparation. Ideally dietary advice is initially offered to both patient and caregivers. Both patients and caregivers can benefit from an understanding of the biologic factors beyond their control that limit food intake and enjoyment. This knowledge may help ease their anxiety and enhance the partnership. Follow-up protocols are particularly key when patients have poor social support.
6. Stress must be placed on early detection and management. Meticulous attention to the early onset of weight or muscle loss, inflammation, or other contributing causes can forestall the development of severe wasting.
7. Work from protocols. It is of importance to develop standard practices in the care unit with regard to cachexia and anorexia.
   - What is your screening platform?
   - What is your nutrition platform?
   - How do you identify and manage constipation?
   - What is your policy on appetite stimulants?
   - What is your exercise policy?

## Maintaining Volitional Food Intake

Nutrition interventions aim to maintain or improve food intake. Recent evidence-based clinical practice guidelines for nutrition in clinical oncology are available [22] and are a valuable reference. Nutrition counseling is the first-line approach. Such intervention by an accredited healthcare professional aims to support patients with a thorough understanding of their nutritional needs and of the specific eating habits that they can undertake to meet those needs. A dietician

can help patients achieve desirable levels of energy and protein as part of a balanced diet and within the context of their dietary customs. In addition to counseling, oral nutritional supplements are sometimes required. Oral nutritional supplements are nutritionally complete nutrient mixtures intended to supplement volitional food intake. Research findings indicate that the combination of nutrition counselling with oral nutrition supplements typically supports a net increase of intake of ~400 kcal/day. Estimates of daily energy expenditure for cancer patients vary between 24 and 28 kcal/kg body weight per day. If intake remains inadequate despite counseling and supplementation, appetite stimulants and artificial nutrition by the enteral or parenteral route may be indicated [22].

## Therapeutic Application of Specific Micronutrients

1. Protein intake should be >1 g/kg/day and if possible up to 1.5 g/kg/day with emphasis on high-quality protein from animal, fish, dairy, or plant sources [22]. No specific enhanced amino acid supplements are proven; however, there is current research interest in leucine, branch chain amino acids, and glutamine.
2. Omega-3 fatty acids are lipids of proven benefit in maintaining cardiac health. In a wide range of animal studies, they demonstrate antitumor effects, maintain muscle mass in tumor-bearing mice, and protect against chemotherapy injury. A pedigree such as the above makes them attractive agents in oncology practice, particularly as they are safe components of human diets. Patients with advanced cancer undergoing chemotherapy and at risk of weight loss or who are malnourished are recommended to use supplementation with long-chain omega-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass, and body weight [22]. Omega-3 fatty acids act as broadly based anti-inflammatory agents that reduce both inflammatory prostanoid and cytokine production; they may particularly benefit the high C-reactive protein group, but studies are lacking. The usual dose is eicosapentanoic acid (EPA) 2.0–2.5 g daily. Use with caution in those with low platelet counts or bleeding disorders.
3. Vitamins and minerals should be supplied in amounts approximately equal to the recommended daily allowances taken from recommendations of WHO/FAO and national and international nutrition societies [22]. The use of single high-dose micronutrients in the absence of specific deficiencies is to be avoided. Vitamin deficiencies, notably C, D, and Bs, are common in patients following prolonged hospitalization. Although there is only modest research on this topic, it may reasonably be assumed that a number of malnourished outpatients may also develop deficiencies. It is our practice to prescribe multivitamin therapy in physiologic doses, plus Vitamin D, based on clinical assessment. While the multivitamin dose is low, some oncologists may prefer that they be withheld during chemo/radiotherapy because of antioxidant properties.
4. Complementary therapy supplements. While it is estimated that half of all cancer patients consume complementary or alternative medical products, none are proven; take care as some may have unknown adverse effects and drug interactions.

## Appetite Stimulation

Agents capable of stimulating ingestive behavior in patients with cancer are an active area of investigation. Limited efficacy and side effects are the primary limitations to the currently available choices.

### Corticosteroids

These agents have powerful orexigenic action [23]. Their mode of action is not clear, but presumably it relates to their anti-inflammatory properties. Unfortunately, this benefit is

purchased at the cost of increasing muscle catabolism, insulin resistance, and risk of infection. Consequently, aside from other long-term adverse effects, they are not suitable for continual therapy in mobile patients with reasonable muscle function, other than for restricted periods of time (1–3 weeks) [22]. They are useful in patients whose maintenance of physical function is no longer a high priority. Prednisone and its congeners are the corticosteroids of choice, as dexamethasone, a fluorinated corticoid, is particularly active in stimulating muscle breakdown.

## Megestrol Acetate

At least 30 randomized studies support the use of megestrol and other progestational agents for appetite enhancement [24]. These molecules are structurally similar to corticosteroids and probably increase appetite through their anti-inflammatory actions. These agents may also have catabolic effects on skeletal muscle. Moreover, they may increase the risk of thromboembolism, although this risk seems to be modest at usually employed dose levels in patients without a prior history of thrombotic disease and low-risk factors.

Weight gain during therapy with progestational agents is composed of fat, and this can be a welcome finding in patients with severe weight loss. Concern for muscle function leads many clinicians to limit megestrol use to intermittent schedules, reserving longer term therapy for patients no longer fighting to maintain strength and mobility.

## Cannabinoids

Cannabis has a well-defined orexigenic effect in many patients. In some part, this benefit stems from the unique ability of cannabinoids to enhance the hedonic appeal of food. This may relate to the central action of cannabinoids on cerebral and hypothalamic centers mediating the sense of pleasure in eating [25]. Cannabinoid receptors are widespread, so they may also enhance appetite through unknown peripheral mechanisms. Their use is limited by real or feared adverse effects and by societal views on marijuana. A virgin user, particularly if elderly, may regard the psychoactive effects as fearful and unpleasant, a view perhaps not shared by younger, experienced patients. At usual doses, psychoactive properties are commonly not expressed while a side benefit, improved sleep, may be noticed.

Cannabinoids are possibly underutilized. They may be helpful in people who are not at risk for cognitive changes (e.g., people with dementia or at risk for becoming demented) or interactive adverse drug effects. What is the best route of administration? A number of oral cannabinoids are available, albeit marketed as antinauseants for chemotherapy patients. It is not clear whether smoked marijuana or tetrahydrocannabinol aerosols (marketed to relieve muscle spasms in multiple sclerosis and patients with other neurologic symptoms) are superior.

## Gastric Stimulants and Laxatives

While not direct appetite stimulants, these agents may reduce gastric atony and constipation, thus making the gastrointestinal tract more receptive to nutrition. In patients complaining of early satiety, after diagnosing and treating constipation, prokinetic agents may be considered. Metoclopramide is widely employed as a gastric stimulant, and tolerability is usually good [22]. The safety profile of metoclopramide, however, includes somnolence, depression, hallucinations, extrapyramidal symptoms, and potentially irreversible dyskinesias.

Without doubt, constipation, which can cause a wide range of symptoms including anorexia, is often overlooked, even in patients not on opioids. A history of a daily stool does not rule out constipation; how much stool is passed and what are its characteristics? A daily stool may be extruded from a column of feces backed up to the ileum. Increasingly, physicians are ordering abdominal films in patients at risk, to determine the presence and severity of constipation, which will guide the patient's laxative protocol.

### Anabolic Steroids

There may be a role for physiologic replacement doses of testosterone in hypogonadal male patients [26]. Hypogonadism is common in advanced cancer patients, who are generally elderly, and clinically practical approaches to treatment are available in the gerontology literature. Notably, many chemotherapy drugs and opioids can reduce testosterone production. Screening for this condition as part of the metabolic profile of the cachexia patient is recommended.

### Enteral and Parenteral Feeding

Patients with defined limitations to oral intake may benefit from artificial feeding [22, 27, 28]. Clinical practice guidelines are positive for malnourished cancer patients facing surgery, encountering severe chemotherapy/radiation therapy, or undergoing bone marrow transplantation. Patients unable to ingest adequate nutrients for extended periods of time are candidates for artificial nutrition. If a decision has been made to feed a patient, enteral nutrition is the approach of choice unless there is severe intestinal insufficiency due to radiation enteritis, chronic bowel obstruction, short bowel syndrome, peritoneal carcinosis, or chylothorax. While there are open questions about the specific indications for starting artificial nutrition, clinical practice, contraindications, complications, and monitoring of enteral and parenteral nutrition do not differ between cancer patients and patients with benign diseases.

2016 ESPEN Oncology Nutrition Guidelines [22] states, "*Ethical considerations for artificial nutrition relate to its use during the last weeks and days of life in advanced malignancies. The risks and detriments as well as the possible futility of artificial nutrition must be weighed against possible physiologic and or psychological benefits, for a given patient and family. As a general rule, the risks of PN are regarded to outweigh its benefits for patients with a prognosis of less than 2 months.*" These views are espoused in other international clinical practice guidelines on parenteral nutrition. Clearly, this advice concerns patients with far-advanced illness. Some authors developed prognostic indices to assist in the decision-making process for parenteral nutrition in advanced cancer [28], and further refinements of survival prediction for this context would be welcomed. Lastly, it should be noted that clinical practice regarding artificial nutrition differs due to religious, cultural, and ethnic background of patients as well as social, emotional, and existential aspects of each individual. In some cultures, active feeding in any form is regarded as essential.

## The Future

### Progress in Drug Therapy

To advance treatment, we strongly hold that clinics with research capacity for randomized clinical trials of cachexia and anorexia therapy should ensure that the opportunity to participate in these trials is available to patients in their setting. The introduction of new agents will stem directly from our growing understanding of the pathophysiology of cachexia. Intriguing ideas centered on controlling inflammation and unbalanced autonomic activity are coming to the fore. Agents of special interest in the authors' opinion are listed below; this is not an all-inclusive list and may reflect author bias.

#### Anti-inflammatory Agents

- Cytokine inhibitors directed toward Il-6; Il-1β
- NSAIDS alone and in combination with other agents

#### Effectors of Muscle Anabolism

- Selective androgen receptor modifiers (SARMS), a class of specific ligands for the skeletal muscle androgen receptor. These nonsteroidal compounds enhance muscle synthesis without androgenic effects.
- Anti-myostatin compounds. Monoclonal antibodies or peptibodies neutralizing myostatin activity.

### Autonomic Nerve Modulators

- $B_2$ antagonists and agonists.
- A seeming paradox. The antagonists (beta blockers) can regulate wasteful increased resting energy expenditure and excess sympathetic lipolytic output, while some agonists (e.g., clenbuterol, formoterol) have direct effects enhancing muscle synthesis. How can they both be potential helpful drugs? The answer is not clear and may depend upon the primacy of an increased REE in a given patient or on selective activity of certain second messenger systems in muscle.

### Hypothalamic Neurotransmitters

- Melanocortin receptor 4 (MCR4) inhibitors acting centrally may influence all elements of cachexia. While demonstrated in mice, human data are awaited.
- Ghrelin is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract which functions as a neuropeptide in the central nervous system. The physiological actions of ghrelin include stimulation of appetite, food reward, gastrointestinal motility, pancreatic secretion, lipogenesis, and anabolism. Recent Phase III clinical trials indicate a robust anabolic response to small molecular weight orally active ghrelin analogs in patients with non-small-cell lung cancer [29].

## Cachexia Therapy Integrated with Cancer Treatment

Within the conventional organization of cancer care, there may exist clinical services that have aspects of the management of cachexia in their charge, but there is no set standard. For example, cachexia may fall in the purview of symptom control or palliative care but may equally well be attended to by clinical nutrition services insofar as access to dietitians and medical nutritionists is available in cancer centers and hospitals. While we earlier stressed the importance of multidisciplinary involvement in cachexia management, we do not believe that many examples of purposefully organized cachexia care teams, in practice, exist. There are a few recently published models for cachexia care integrated within a supportive multidisciplinary team approach [30–33]. The benefits of this care have been reported from prospectively conducted nonrandomized studies [30–33]. We foresee that clinical services operated in true partnership between palliative care physicians and the oncology community will emerge, as endorsed currently by many cancer agencies, e.g., American Society of Clinical Oncology [34]. A critically important underlying concept is that the driving forces of pain and symptoms, including cachexia, are the same driving forces advancing tumor growth and metastases. Our past separate approaches to symptom research and antitumor research are not logical. This concept may be particularly important for trials on immune modulators as these compounds theoretically may also alter immune mediators that stimulate cachexia and other cancer symptoms. It is notable in this context that the most recent trials of cachexia therapeutics [29] have been shifted forward in the disease trajectory and are delivered concurrently with first-line chemotherapy rather than in the end-of-life phase [23–25]. We strongly favor the development of integrated structures to provide cachexia therapy and overall pain and symptom management integrated with anticancer therapy. This is in accordance with the current view that patients with advanced cancer should receive dedicated, early palliative care concurrently with standard oncology treatment [34] based on evidence that it improves quality of life, reduces depression, and improves satisfaction with care.

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# 24

# Xerostomia and Dental Problems in the Head and Neck Radiation Patient

A. Vissink, F. K. L. Spijkervet, and Michael T. Brennan

## Introduction

Saliva is the "aqua vita" of the oral cavity. It is protective, and its alimentary qualities are critical to the function of the oral and oropharyngeal tissues and organs [1, 2]. Moreover, saliva is a sensitive indicator of oral and systemic abnormalities and diseases [3]. Yet, this important secretion has been eschewed, neglected, and perceived as ignoble by dentists, physicians, and other healthcare professionals. An example of saliva's perceived insignificance is illustrated by the adage that items viewed as having little value are said to be worth "less than a bucket of warm spit" [1].

But even a half bucket of warm spit may not be sufficient to prevent a subject perceiving his or her mouth as dry. In other words, the important question has to be settled: how much saliva is enough saliva? This question leads to another question: enough for what? Is it how much is enough to prevent oral dryness or is it how much is enough to engage in activities that accrue as a result of normal salivary function? Ofttimes, only a minuscule amount of saliva is necessary to thwart the appearance of dry mouth—just enough to coat the mucous surfaces of the oral cavity. Probably, this coating is due to the actions of the minor salivary glands and, following a swallow, to the residual saliva. Given that the volume secreted by the minor glands is about 8% of the unstimulated flow rate, these are indeed small amounts [1, 2, 4, 5].

Alimentary functions of *stimulated* whole saliva are severely compromised by low flow rates: the ability to taste, to chew, to form a bolus, and to swallow. The unpleasant feeling of oral dryness and its related symptoms are experienced the most by patients in whom salivary secretion is suddenly decreased to negligible amounts. This includes patients who are subjected to one of the most common therapies applied within head and neck oncology, viz., head and neck radiotherapy. These patients do not slowly adapt to a changed oral environment but are suddenly exposed to a rather extreme oral environment: a mouth that suddenly has become dry with major changes to the oral mucosa and a high risk on developing oral infections and dental caries (Fig. 24.1). With the introduction of intensity-modulated radiotherapy (IMRT), this risk has diminished, but it still exists [6–8].

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I. Olver (ed.), *The MASCC Textbook of Cancer Supportive Care and Survivorship*,
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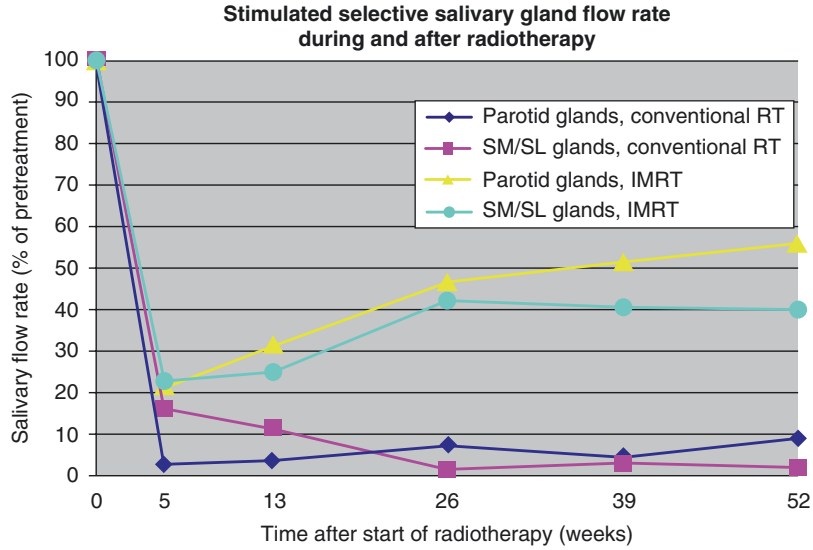


**Fig. 24.1** Flow rate of 2% citric acid-stimulated parotid (single gland) and bilateral submandibular-sublingual (SM/SL) saliva as a function of time after start of radiotherapy (RT) [Conventional RT: both parotid, submandibular, and sublingual glands located in the treatment portal, 2 Gy per day, 5 days per week, total dose 60–70 Gy. Parotid-sparing 3-dimensional (3D)/intensity-modulated RT (IMRT), bilateral (the majority), and unilateral RT (scattered radiation to contralateral gland). For parotid IMRT data, 1.8–2.0 Gy per fraction, prescribed dose to primary target 64 Gy (range 57.6–72 Gy) and for SM/SL IMRT data, 2 Gy per day, 70 Gy to gross disease planning target volume]. Initial flow rates are set to 100% (reprinted with permission from from Vissink A, Mitchell JB, Baum BJ, Limesand KH, Jensen SB, Fox PC et al. Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: successes and barriers. *Int J Radiat Oncol Biol Phys*. 2010;78:983–891

## Head and Neck Radiotherapy and Salivary Glands

Head and neck radiotherapy in addition to its antitumor effects, inevitably induces severe adverse effects to normal oral tissues surrounding the tumor tissue [6–8]. Usually the tumor does not reside within the salivary glands, and the salivary glands are among the normal tissues that have to be passed to reach the tumor in, e.g., the oral cavity or pharynx. Thus, in the radiation treatment for head and neck cancer, the major and minor salivary glands are often included within the radiation portal due to the site and extension of primary tumors and the path of lymphatic spread, which is in close proximity to the salivary glands [6–9].

Tumor cells are actively dividing, and consequently their DNA is highly sensitive to radiation damage, rendering cells incapable of proper cell division and resulting in cell death or senescence of cells that attempt to divide. In contrast, salivary glands are highly specialized organs comprised of well-differentiated cells that have a relatively low mitotic index. Differentiated salivary acinar cells have a mean life-span of more than 3 months and are thought to be replaced by a slowly cycling stem cell population [10–12]. Based on the slow turnover rate of their cells, the salivary glands are expected to be relatively radio-resistant. However, changes in the amount and composition of saliva that occur early after irradiation suggest that the salivary gland is actually an acutely responding tissue [13–16].

As shown in Fig. 24.1, exposure of salivary glands located within the treatment portal subjected to a conventional radiotherapy schedule results in a dramatic loss of gland function within the first week of treatment with a continuous decrease in salivary flow throughout the course of therapy to barely measurable flow rates. Following high-dose radiotherapy (the critical dose limit for parotid and submandibular salivary gland tissue is just below 40 Gy [17, 18], and

most radiation regimens exceed this limit), a second phase of functional deterioration in secretion may be noted up to several months after completion of radiotherapy and is concomitant with progressive, irreversible changes of the salivary gland tissue with no significant recovery in gland function [13, 19, 20].

Serous acinar cells have been hypothesized to develop and replenish via replication of stem/progenitor cells in ductal segments, and when the cells of a functional subunit of the gland (secretory acini and connecting duct branch system) are damaged by radiation, it is unlikely that normalization of function can occur. The severity of glandular damage and potential for recovery are dependent on the irradiated gland volume, the cumulative radiation dose, and the ability of surviving stem cells to repopulate [11, 21, 22]. Recently, it was also shown in humans that the radiation dose to the region of the salivary gland containing the stem/progenitor cells predicts the function of the salivary glands post-radiotherapy [23]. While with IMRT reducing the cumulative dose to the salivary glands, which indeed resulted in less reduction of the salivary flow (Fig. 24.1), a more focused sparing of certain areas within the salivary gland by a slight change in the conformation of the radiation portal might result in even better sparing of salivary gland function (Fig. 24.2).

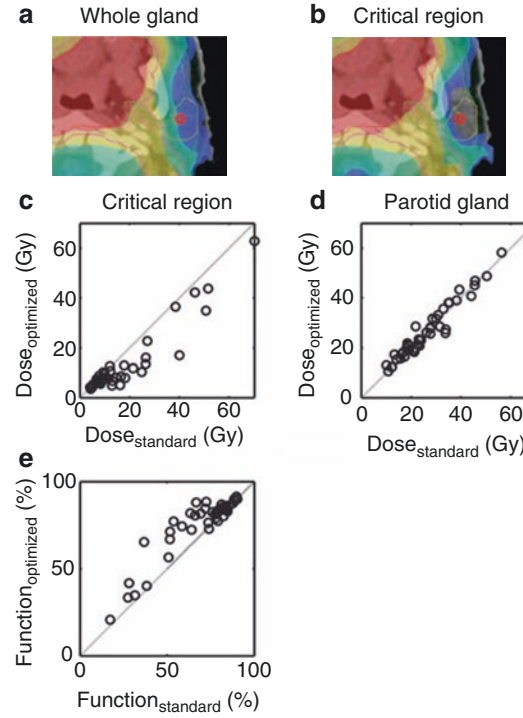


**Fig. 24.2** Sparing the critical region of the human parotid gland after IMRT (**a**, **b**). Minimizing the dose to the critical region (red circle) of the human parotid gland was predicted to result in a redistribution of dose within the parotid glands (**c–e**). This optimization was performed on data from 22 patients with head and neck cancer and was predicted to result in a reduction of dose to the critical region (**c**, **e**), with minimal or no change to the mean dose to the whole parotid gland (**d**). (Reprinted with permission from van Luijk P, Pringle S, Deasy JO, Moiseenko VV, Faber H, Hovan A, Baanstra M et al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. Sci Transl Med. 2015;7:305ra147)

## Symptoms Associated with Mouth Dryness

Xerostomia is rarely an isolated symptom. Xerostomia often appears in consort with hyposalivation, but a complaint of xerostomia does not always correlate well with salivary function [24]. These conditional attributes induce functional impairment of the oral cavity. A reduction in the flow of saliva frequently causes difficulties with speaking, taste, and mastication. Patients with decreased salivary function may have difficulty chewing and swallowing dry foods. They are frequently thirsty and often need to sip water to facilitate deglutition and may keep water at their bedside at night. Edentulous patients may have difficulty wearing dentures. A complaint of tingling and burning sensations of the oral mucosa, especially on the tongue, may be present. The tongue may even stick to the roof of the mouth. Moreover, the oral mucosa may feel particularly sensitive to spicy foods [1]. In head and neck radiation patients, mucosal problems are mostly due to the process of mucositis in combination with the changes in saliva. After cessation of the radiotherapy, the symptoms related to mouth dryness persist, including mucosal sensitivity [7, 8].

## The Clinical Picture of Dry Mouth

Clinical signs associated with oral dryness may be observed in the soft and the hard tissues of the mouth and in the salivary glands. The oral mucosa may appear dry, atrophic, pale, or hyperemic, and there may be abundant evidence of dental caries, especially at the cervical margins of the teeth (Fig. 24.3). The lips may be chapped or fissured, and there may be scaling and fissuring at the corners of the mouth (angular cheilosis; Fig. 24.4). The dorsum of the tongue may be dry and furrowed (Fig. 24.4) or, alternatively, may appear red and hyperemic as a result of the presence of a secondary fungal infection (erythematous candidiasis; Figs. 24.5 and 24.6). The buccal mucosa may look pale and dry (Fig. 24.7); tongue blades used to retract the cheeks may stick to the mucosa. As with the tongue, it may appear erythematous due to a yeast (Candida) infection. These changes in the oral mucosa are, in general, typical for xerostomia of any origin [1].

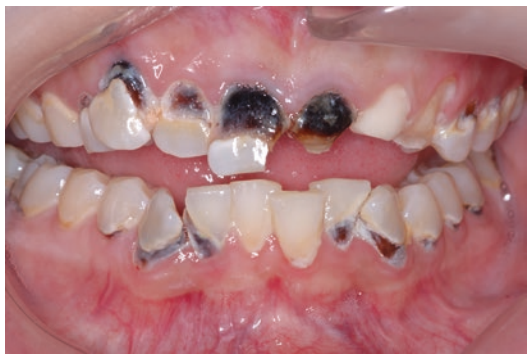

**Fig. 24.3** Oral dryness is associated with abundant, rapidly progressing dental caries. Caries related to oral dryness develops typically at the cervical margins of the teeth, whereas normally dental decay usually develops at the interdental contact and occlusal areas

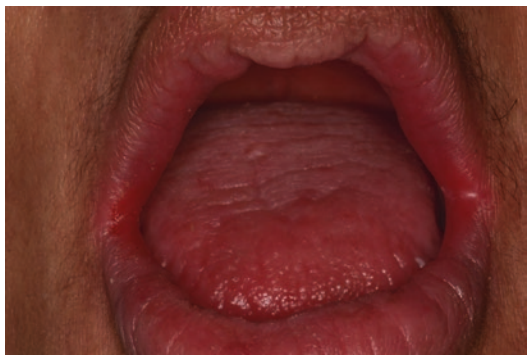

**Fig. 24.4** Angular cheilosis and a dry surface of the tongue

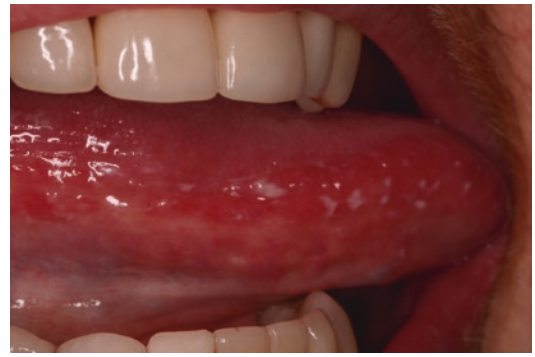

**Fig. 24.5** Candidiasis of the lateral border of the tongue with some yeast colonies but predominantly erythematous

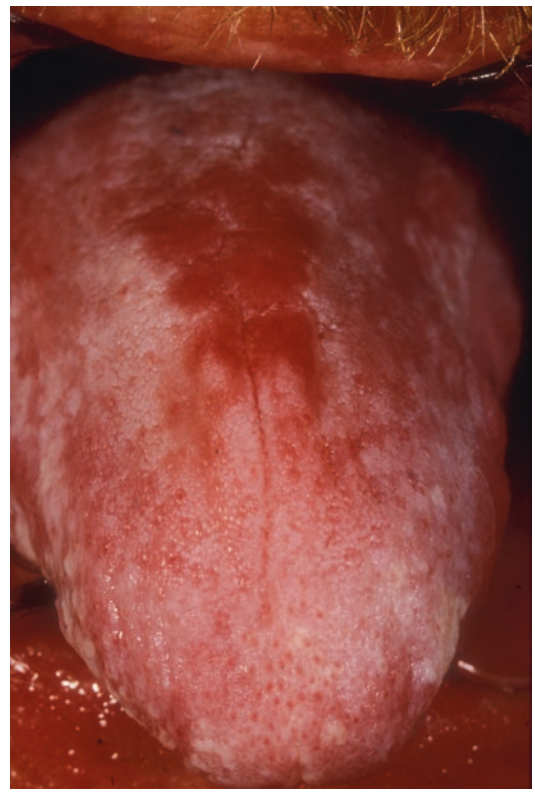

**Fig. 24.6** Erythematous candidiasis of the dorsum of the tongue

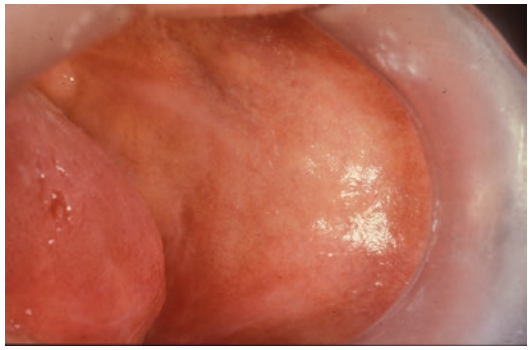

**Fig. 24.7** Pale and dry buccal mucosa

The principal causative factor that underlies the subjective feelings and the clinical findings associated with dry mouth is hyposalivation. Reductions in the flow of saliva, as well as qualitative changes in it, predispose a patient, either directly or indirectly, to a variety of problems. The severity of hyposalivation cannot be predicted with certainty from the patients' complaints. Patients may complain of xerostomia while they still objectively have a reasonable salivary flow, and completely dry patients may not experience xerostomia. In general, however, the greater the reduction in the volume of saliva, the more severe are the symptoms. After curative radiotherapy, a continuous severe reduction of salivary flow rate persists (Fig. 24.1). The consequences in the radiated are: patients are awakened at night because of intense oral dryness; many suffer throughout the day with polyuria and polydipsia; oral functions like speech, chewing, and swallowing are thwarted because of insufficient wetting and lubrication of the mucosal surfaces; and swallowing and chewing are impeded because the decrease in the volume of saliva makes it difficult to form a bolus [1]. Moreover, when lesser amounts of saliva are present, retention of the denture is often poor, and more friction is produced during mastication.

## Xerostomia and the Teeth

There is abundant evidence that hyposalivation commonly causes a marked increase in the incidence of dental caries; in many cases it is severe and rampant (Fig. 24.3). There is conflicting evidence regarding its effect on periodontal diseases, but most authors agree that gingivitis is more prevalent (due to accumulation of dental plaque) in dry mouth patients than in healthy subjects, but periodontal disease is not [25]. Probably the teeth will be lost in cases with an insufficient level of oral hygiene due to the rapidly progressing hyposalivation-related dental caries before periodontal disease has developed. It has to be mentioned, however, that a worse periodontal condition at dental screening makes patients prone to developing osteoradionecrosis [26].

The shift in the oral microflora toward increased amounts of acidogenic, cariogenic bacteria (e.g., *Streptococcus mutans*, *Lactobacillus* species, *Actinomyces viscosus*, and *Streptococcus mitis*) [27] and the reduced salivary flow and oral clearance are accompanied by changes in the composition of saliva. Included among these changes is a reduction in the buffer capacity and pH of saliva and a decline in the presence of the caries-preventive immunoproteins. These changes can result in a rapid increase in the prevalence of hyposalivation-related dental decay. Without special care, dental caries may progress extremely rapidly. A perfect dentition can be totally destroyed within 6 months [1]. Finally, oral candidiasis, when present, may rapidly spread to the pharynx and esophagus.

In addition, these hyposalivatory changes alter the patient's eating habits. Spicy food is a problem, so patients shift their diet to one that is blander. Patients have difficulty with mastication, so they shift to a diet that is soft, sticky, and usually loaded with carbohydrates. Sometimes, the diet may be liquid. These modified, softer diets are adhered to by many dry-mouth patients but are particularly characteristic of the diets consumed by patients who suffer from irradiation-induced xerostomia.

## Dry Mouth, Hyposalivation, and Dental Caries

As mentioned, dental caries is common in patients with dry mouth and hyposalivation, especially in

head- and neck-radiated patients with a sudden onset of hyposalivation and with insufficient anti-caries regimens to prevent tooth decay. Three types of lesions can be observed [13, 28–31]. All of them may be seen in the same mouth. Yet surprisingly, perhaps because of the rapid progress of the decay, there is little, if any, pain associated with them. The histological features of early hyposalivation-related dental carious lesions are similar to those observed in normal incipient lesions [1, 28, 29]. Erosive types of lesions can also be found [29]. A very remarkable thing about these lesions is that they occur in areas of the mouth that are normally relatively immune to dental caries.

The *first* type of lesion usually begins on the labial surface at the cervical area of the incisors and canines (Fig. 24.8). Initially, this lesion extends superficially around the entire cervical area of the tooth, and then progresses inwardly, often resulting in complete amputation of the crown. Amputation is less frequent in the area of the molars. However, the caries tends to spread over all the surfaces of the molar teeth, changes their translucency and color, and induces an increase in their friability. Occasionally, the destruction occurs as a rapid wearing away of the incisal and occlusal surfaces of the teeth, with or without cervical lesions.

The *second* type of lesion is a generalized superficial defect that first affects the buccal and later the lingual or palatal surfaces of the tooth crowns (Fig. 24.9). The proximal surfaces are less affected. When present, this lesion often begins as a diffuse, punctate defect and then progresses to a generalized, irregular erosion of the tooth surfaces. In this type of lesion, decay that is localized to the incisal or occlusal edges may often be observed. The result is a destruction of the coronal enamel and dentin, especially on the buccal and palatal surfaces.

The *third* type is less frequently observed (Fig. 24.10). It consists of a heavy brown-black discoloration of the entire tooth crown, accompa-

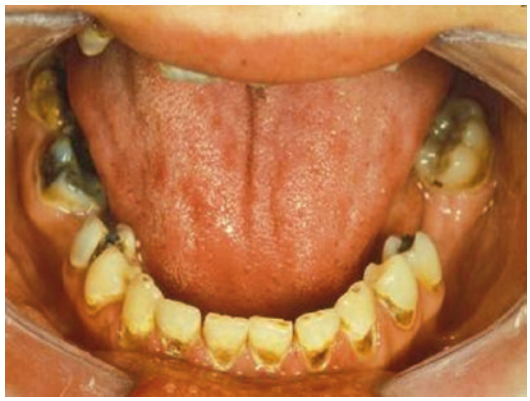

**Fig. 24.8** Hyposalivation-related dental caries type 1: lesions of the cervical area (reprinted with permission from Stegenga B, Vissink A, de Bont LGM, Spijkervet FK eds. *MKA chirurgie. Handboek voor Mondziekten, Kaak- en Aangezichtschirurgie*. Van Gorcum: Assen, the Netherlands; 2013)

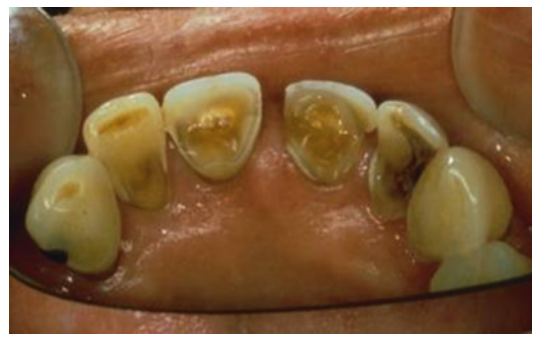

**Fig. 24.9** Hyposalivation-related dental caries type 2: superficial defects of the crown of the tooth (reprinted with permission from Stegenga B, Vissink A, de Bont LGM, Spijkervet FK eds. MKA chirurgie. Handboek voor Mondziekten, en Kaak- en Aangezichtschirurgie. Van Gorcum: Assen, the Netherlands; 2013)

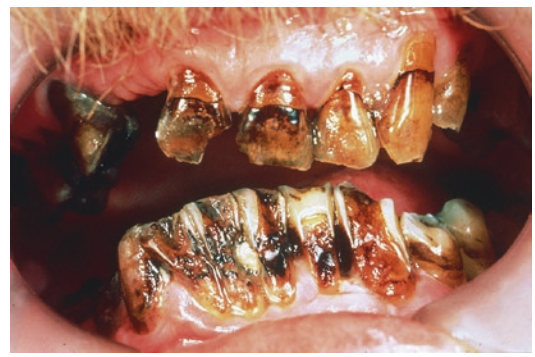

**Fig. 24.10** Hyposalivation-related dental caries type 3: brown-black discoloration of the tooth crown (reprinted with permission from Stegenga B, Vissink A, de Bont LGM, Spijkervet FK eds. MKA chirurgie. Handboek voor Mondziekten, en Kaak- en Aangezichtschirurgie. Van Gorcum: Assen, the Netherlands; 2013)

nied by wearing away of the incisal and occlusal surfaces.

## Treatment

The treatment of xerostomia and salivary gland hypofunction related to head and neck cancer therapy should be based on answers to the following determinations [1, 32]:

1. If stimulation of the flow of saliva is feasible to relieve oral dryness, this approach may readily diminish the oral desiccation.
2. If the saliva cannot be adequately stimulated, it has to be determined whether one can combat the arid feeling by "coating" the surfaces of the oral mucosa.
3. Assess what else can be done to preserve and protect the teeth and the oral soft tissues and provide relief to the patient.

The findings obtained from these assessments should be carefully evaluated. Some patients will respond to a single treatment modality, while other patients will require a combination of treatments. Unfortunately, some patients may not adequately achieve a response to the management of oral dryness, although much can be done to mollify the patient and guard the oral cavity against injury and disease.

## Management of Dry Mouth

Frequent sips of water during the day can be the easiest and most effective technique to improve symptoms of dry mouth in some patients. A slice of lemon or lime can be added to a glass of water to produce a mild acidic flavor that will enhance the output from the major salivary glands [33, 34]. Patients should be counseled, however, that aqueous solutions do not produce long-lasting relief from oral dryness. Water wets the mucosa, but its moisture is not retained since the mucous membranes of xerostomic patients are inadequately coated by a protective glycoprotein layer [35].

### Masticatory, Gustatory, and Mild Acid Stimulation

Dry mucosal surfaces, difficulty wearing dentures, retained interproximal plaque, and difficulty with speaking, tasting, and swallowing may all benefit from the stimulation of salivary secretions. Stimulation will only work if there are residual viable salivary gland cells that are amenable to stimulation. Head and neck cancer patients, who have undergone extensive radiotherapy to their craniofacial regions, in particular, to their major salivary glands, are likely to have lost many functional acinar cells and often will not benefit sufficiently from salivary stimulatory methods.

Masticatory stimulation techniques are easy to implement and have few side effects. The combination of chewing and taste, as provided by gums, lozenges, or mints, can be very effective in relieving symptoms for patients who have remaining salivary function. These compounds are acceptable to most patients and are generally harmless (assuming that they are all sugar free). Also, acid-containing lozenges, for example, containing malic acid, can be very helpful. Dentate patients with dry mouth must be told not to use products that contain sugars, honey, maple syrups, or sorghum as sweeteners, due to the increased risk for dental caries, or use products that contain acids.

### Pharmacologic Aids

Two secretagogues, pilocarpine [36, 37] and cevimeline [38, 39] have been approved by the United States Food and Drug Administration (FDA) for the treatment of dry mouth. Both of these drugs are muscarinic agonists that, in irradiated head and neck cancer patients who have residual functional salivary gland tissue, induce a transient increase in salivary output and decrease their feeling of oral dryness [40]. Pilocarpine is a nonselective muscarinic agonist. Cevimeline has a high affinity for M1 and M3 muscarinic receptor subtypes. Since M2 and M4 receptors are located on cardiac and lung tissues, it is likely that cevimeline's M1 and M3 specificity will

induce fewer cardiac and/or pulmonary side effects. Cevimeline, given at 45 mg t.i.d. doses, was generally well tolerated over a period of 52 weeks in subjects with xerostomia secondary to radiotherapy for cancer in the head and neck region [41].

Common side effects of both medications include sweating, flushing, urinary urgency, and gastrointestinal discomfort. These side effects are frequent but are rarely severe or serious. Parasympathomimetics are contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, or acute iritis and should be used with caution in patients with significant cardiovascular disease, Parkinson's disease, asthma, or chronic obstructive pulmonary disease. The best-tolerated doses for pilocarpine are 5–7.5 mg, given three or four times daily [42]. The duration of action is approximately 2–3 h. Cevimeline is currently recommended at a dosage of 30 mg t.i.d [38, 39]; the duration of secretagogue activity is longer than pilocarpine (3–4 h), but the onset is somewhat slower. In contrast to the USA, Canada, and Japan, cevimeline is not yet licensed in Europe.

## Acupuncture and Electrostimulation

Acupuncture, with the application of needles in the perioral and other regions, has been proposed as a therapy for salivary gland hypofunction and xerostomia. There is some evidence that this procedure alleviates the feeling of oral dryness, but well-controlled trials are needed to fully evaluate this treatment modality [40, 43, 44]. Electrical stimulation has also been examined as a therapy for salivary hypofunction, but it too has inadequate clinical investigation [40, 45, 46].

## What to Do when Stimulants Fail?

Water, although less effective than the patients' natural saliva, is by far the most important fluid supplement for dry-mouth individuals. Patients should be encouraged to sip water and swish it around their mouth throughout the day. This will help to moisten the oral cavity, hydrate the mucosa, and clear debris from the mouth. Patients should be counseled, however, that aqueous solutions do not produce long-lasting relief from oral dryness as water wets the mucosa, but its moisture is not retained [35]. Furthermore, careful water intake *with meals* is very important, since this approach enhances taste perception, enhances the formation of a bolus, and improves mastication and swallowing (particularly for hard and fibrous foods). In postradiation patients, this is even more important since these patients often use diets with high sugar contents due to taste changes. It can also help prevent choking and possible pulmonary aspiration. Frequent use of sugar-free carbonated drinks is not recommended in dentate patients, as the acidic content of many of these beverages is high and may increase tooth demineralization. In edentulous patients, such drinks may irritate the oral mucous membranes and cause them to be sensitive. Finally, an increase in environmental humidity is important as the use of room humidifiers, particularly at night, may lessen discomfort markedly [1].

There are numerous oral rinses, mouthwashes, and gels available for dry-mouth patients [24, 47–51]. Patients should be cautioned to avoid products containing alcohol, sugar, or strong flavorings that may irritate the sensitive, dry oral mucosa. Moisturizing creams can also be very helpful. The frequent use of products containing aloe vera or vitamin E should be encouraged [1].

A variety of commercially available salivary substitutes have demonstrated some efficacy in dry-mouth patients [40, 51, 52]. However, saliva replacements (saliva substitutes or "artificial salivas") are not well accepted long term by many patients, particularly when they have not been precisely instructed how to use them [52, 53]. As a guide to choosing the best substitute for a patient, the following recommendations for the treatment of hyposalivation can be used [1, 47]:

- *Severe hyposalivation*. A saliva substitute with gel-like properties could be used during the night and when daily activities are at a low level. During the day, a saliva substitute with properties resembling the viscoelasticity of

natural saliva such as substitutes that have xanthan gum and mucin (particularly bovine submandibular mucin) as a base should be applied.

- *Moderate hyposalivation*. If gustatory or pharmacological stimulation of the residual salivary secretion does not ameliorate the dry mouth feeling, saliva substitutes with a rather low viscoelasticity, such as substitutes which have carboxymethylcellulose, hydroxypropylmethylcellulose, mucin (porcine gastric mucin), or low concentrations of xanthan gum as a base are indicated. During the night or other periods of severe oral dryness, the application of a gel is helpful.
- *Slight hyposalivation*. The salivary glands of these patients usually contain viable, responsive acinar cells. Gustatory or pharmacological stimulation of the residual secretion is the treatment of choice. Little amelioration is to be expected from the use of saliva substitutes.

Despite the limitations mentioned, the nonstimulatory techniques described in this section should be tried in nonresponsive patients. In addition, they may also be adjunctly helpful in those patients who experience persistent dry mouth and respond to stimulation techniques [1].

## The Role of the Dentist and/or Dental Hygienist

Management of the patient with xerostomia and salivary gland hypofunction due to head and neck radiotherapy starts with the dentist and dental hygienist, who should be part of the oncology team. Treatment should involve a multidisciplinary team of healthcare providers. Communication among them is critical, since patients with salivary hypofunction usually have concomitant oral and medical problems and consume many drugs. Patients should be seen and evaluated frequently [54–56]. A thorough, step-by-step, management strategy should be devised and implemented (Table 24.1) using safe and efficacious techniques [1, 45].

**Table 24.1** Management strategies for xerostomia and salivary hypofunction

| Management strategies | Examples |
|---|---|
| Preventive therapies | Supplemental fluoride, remineralizing solutions, optimal oral hygiene, noncariogenic diet |
| Symptomatic (palliative) treatments | Water, oral rinses, gels, mouthwashes, saliva substitutes, increased humidification, minimize caffeine and alcohol |
| Local or topical salivary stimulation | Sugar-free gums and mints |
| Drug-induced stimulation | Parasympathomimetic secretagogues: cevimeline and pilocarpine |

### Dental Visits

Patients with salivary gland hypofunction require frequent dental visits (usually every 3–4 months) and must work closely with their dentist and dental hygienist to maintain optimal dental health [1]. Sequenced visits might conform to the following order: dentist-dental hygienist-dentist-dental hygienist. Dentate individuals who frequently develop new and/or recurrent carious lesions should have intraoral photographs taken every 6–18 months [57]. Patients who wear prostheses should have their prosthesis-bearing mucosal regions evaluated frequently (every 3–4 months) to help identify the early onset of oral mucosal lesions and infections.

### Oral Hygiene

Patients with salivary gland disorders must maintain meticulous oral hygiene. The enamel slabs placed in the mouth of a severe dry-mouth patient, whose oral hygiene is poor, can be completely destroyed by a combined carious/erosive attack within 6 weeks. On the other hand, slabs placed in the mouth of a normal patient with good oral hygiene hardly show any decalcification in the same period of time [30,58,]. Proper oral hygiene includes toothbrushing, flossing, the use of interproximal plaque removing devices, and the use of mouth rinses. Interdental brushes

and mechanical toothbrushes are helpful for those with gingival recession and oral motor or behavioral complications. Regular brushing of the tongue with a toothbrush or a tongue scraper is also recommended. The team of oral health professionals must play an important role in providing guidance (clinical instructions, written instructions) to the dry-mouth patient, so that he or she is given every opportunity to prevent the onset of the common side effects of salivary hypofunction [1].

## Topical Fluorides and Remineralizing Solutions

The use of topical fluorides in a patient with salivary gland hypofunction is absolutely critical to the control of dental caries [56, 59]. There are many different fluoride therapies available, from low concentration, over-the-counter fluoride rinses, to more potent highly concentrated prescription fluorides (e.g., 1.0% sodium fluoride). These are applied by brush or in a custom carrier (Fig. 24.11). The dosage chosen and the frequency of application (from daily to once a week) should be based on the severity of the salivary hypofunction and the rate of caries development [29, 30, 56, 58, 60]. Particularly in patients with severe oral dryness, non-acidic fluoride gels and/or solutions should be used. Patients treated with acidic sodium fluoride gels often complain of sensitivity and pain in the gingiva and oral mucosa. In addition, a more rapid destruction of the teeth may occur, since there is little saliva to encourage the remineralization of the enamel dissolved by the acidic fluoride gel. Furthermore, a 5000 ppm fluoridated toothpaste, used twice daily, has been recommended for high caries-risk patients with salivary dysfunction [59].

When salivary function is compromised, the normal process of tooth remineralization is interrupted. This enhances demineralization and the consequent loss of tooth structure. Remineralizing solutions may be used to alleviate some of these changes [49].

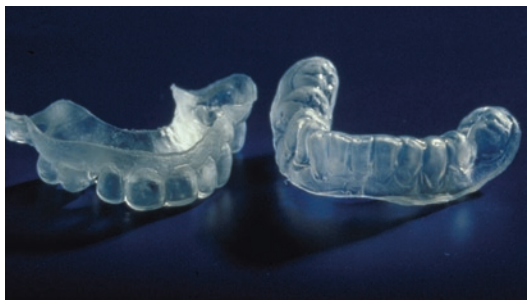

**Fig. 24.11** Custom carrier to apply a neutral fluoride gel (reprinted with permission from Sreebny LM, Vissink A (eds). Dry mouth. The malevolent symptom: a clinical guide, Ames: Wiley-Blackwell 2010)

## Diet Modifications

Patients should be counseled to follow a diet that avoids cariogenic foods (especially fermentable carbohydrates) and beverages. The implementation of meticulous oral hygiene procedures after each meal is critical to help reduce the risk of developing new or recurrent carious lesions. Chronic use of alcohol and caffeine can increase oral dryness and should be minimized [1]. Non-fermentable dietary sweeteners such as xylitol, sorbitol, aspartame, or saccharine are recommended [61]. So, too, is sucralose, a chlorinated, noncariogenic sweetener. Polyols, such as xylitol, are considered to be anticariogenic since they decrease acid fermentation by *S. mutans* [62].

## Oral Candida Therapy

Patients with dry mouth often experience an increase in oral infections, particularly mucosal candidiasis (Fig. 24.12) [1, 50, 63, 64]. This condition often assumes an erythematous form (without the easily recognized pseudomembranous plaques). The mucosa is red, and the patients complain of a burning sensation of the tongue or other oral soft tissues (Fig. 24.13). A high index of suspicion for fungal disease should be maintained, and appropriate antifungal therapies should be instituted as necessary (Table 24.2). Patients with salivary gland dysfunction may

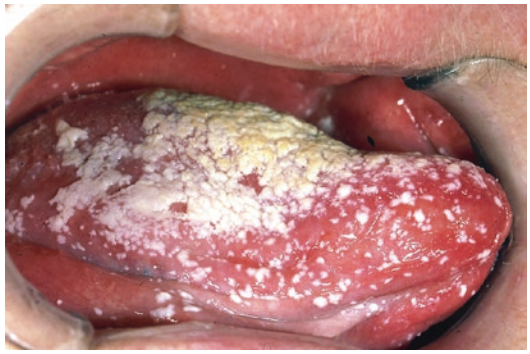

**Fig. 24.12** Candidiasis of the tongue (reprinted with permission from Sreebny LM, Vissink A (eds). Dry mouth. The malevolent symptom: a clinical guide, Ames: Wiley-Blackwell 2010)

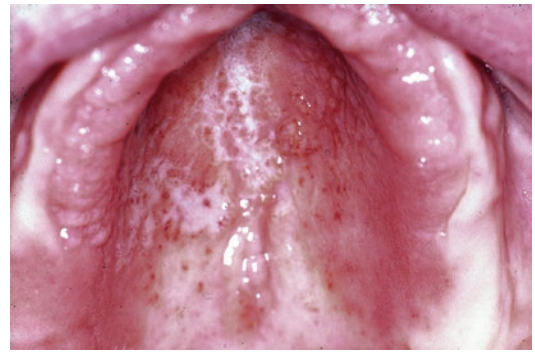

**Fig. 24.13** Erythematous candidiasis of the palate (reprinted with permission from Sreebny LM, Vissink A (eds). Dry mouth. The malevolent symptom: a clinical guide, Ames: Wiley-Blackwell 2010)

**Table 24.2** Antifungal drugs for the management of oral candidiasis

| **Name** | **Nystatin** | **Clotrimazole** | **Ketoconazole** |
|---|---|---|---|
| *Topical agents* | | | |
| Dosage | • Oral suspension (100,000 U/mL): 400,000–600,000 units 4–5 times daily (swish and swallow)<br>• Troche (200,000 U): 200,000–400,000 units 4–5 times/day<br>• 100,000 U/g cream and ointment: apply to the affected area 4–5 times/day<br>• Powder (50 million U): sprinkle on the tissue contact area of denture | • 10 mg troche: dissolve slowly over 15–30 min five times/daily<br>• 1% cream: apply to the affected area bid for 7 days<br>• Cream can be applied to the tissue contact areas of the denture | • 2% Cream: rub gently into the affected area 1–2 times daily<br>Amphotericin B<br>• 10 mg lozenge: dissolve slowly over 15–30 min in the mouth four times/daily |
| **Name** | **Fluconazole** | **Itraconazole** | **Ketoconazole** |
| *Systemic agents* | | | |
| | • Tablets: 200 mg on day 1, then 100 mg daily for 7–14 days<br>• Powder for oral suspension (10 mg/mL); dosing is the same as for tablets | • Tablets: 200 mg daily for 1–2 weeks; if refractory to fluconazole, 100 mg q12h<br>• Solution (10 mg/mL), 100–200 mg/10 mL once a day for 1–2 weeks; if refractory to fluconazole, 100 mg q12h | • 200–400 mg/day as single dose for 7–14 days |

In denture-wearing individuals, the denture should be disinfected overnight in a chlorhexidine mouth rinse to prevent reinfection of the oral cavity by *Candida* species residing in the denture material

require prolonged treatment to eradicate these infections [65].

## Future

Besides radiation techniques such as IRMT, stem cell sparing-driven IMRT, or proton radiotherapy, there are a number of other approaches in development to reduce or restore radiation damage to salivary glands [6]. The most promising are salivary gland transfer, gene therapy, and stem cell therapy.

### Salivary Gland Transfer

Radiation-induced salivary gland hypofunction and xerostomia can be reduced in select patients by surgical transfer of one submandibular gland

to the submental space not included in the radiation portal [66, 67]. Surgical transfer of one submandibular gland to the submental space has been shown to be superior to the administration of oral pilocarpine in the management of radiation-induced xerostomia [68, 69]. A pilot study of two-stage autologous transplantation of one submandibular gland to the forearm during radiotherapy and reimplantation of the gland to the floor of the mouth 2–3 months after radiotherapy has also indicated the potential to reduce radiation-induced salivary gland hypofunction and xerostomia [70]. A complicating factor is the relation of the submandibular salivary gland to be transplanted with the cancer affected lymphnodes, when that submandibular gland is in the area of the neck dissection.

## Gene Therapy

Ductal cells are less affected by radiotherapy than acinar cells. The therapeutic rationale of gene therapy for functional recovery of irradiation-induced damaged salivary gland tissue is based on insertion of a pathway for water transport in the surviving duct cell membranes to elicit water secretion [71]. The water channel protein, human aquaporin-1 (hAQP1), can facilitate rapid movement of water in response to an osmotic gradient and is expressed all around a cell's plasma membrane. Moreover, expression of hAQP1 protein in cell types in which it is not normally found can lead to dramatic increases in osmotically obliged water movement [71, 72]. In vivo animal studies utilizing a recombinant serotype 5 adenoviral vector encoding hAQP1 and AdhAQP1, which is delivered to salivary glands via intraductal cannulation, revealed that in irradiated rats, salivary flow rates returned to near normal [71]. Similarly, after an initial decrease of saliva secretion to less than 20% of baseline in miniature pigs postirradiation, administration of AdhAQP1 resulted in a transient (~2–4 weeks) dose-dependent increase in parotid salivary flow rate to about 80% of pre-radiation levels [73].

Based on the promising results from the animal experiments, a phase I study was performed in which the efficacy and safety of gene transfer in 11 humans with parotid gland hypofunction were tested [74, 75]. All patients tolerated vector (AdHAQP1) delivery and study procedures well. No serious adverse events or dose-limiting toxicities occurred. An objective positive response was observed in six participants; none of these participants had received the highest dose. Five of them also experienced subjective improvement in xerostomia. Four of five non-responders did not perceive amelioration or worsening of their oral dryness. It is yet unknown how long the increase in salivary flow rate will last in humans.

## Stem Cell Therapy

Lack of replacement of differentiated functional cells in salivary glands after radiotherapy is due to destruction of progenitor/stem cells in the gland tissue; hence, it is the remaining, viable stem cells that determine the capacity for regeneration [11, 21]. These stem cells are proposed to be localized in the parotid gland region excretory ducts, an area which when irradiated results in the loss of saliva secretion [23]. Recently, it has been proposed that differentiated acinar cells may also be able to divide in response to damage through a process known as "auto-duplication" [76]. Stem cell transfer could be able to restore tissue homeostasis after irradiation by increasing the regenerative potential of salivary glands [22]. Furthermore, the salivary duct compartment could serve as a natural engraftment place for the transplanted cells as this compartment remains relatively intact after irradiation. Along this line, a population of c-Kit+ cells with capability to regenerate and completely restore function to radiation-induced damaged salivary glands of rodents has been cultured. In vitro, salispheres can be grown from these c-Kit+ stem cells, and cells from these salispheres were shown to express also many other stem cell markers (e.g., Sca-1, c-Kit, Musashi-1, CD49f, and CD133 [77, 78]) and were able to differentiate into all salivary gland lineages [79]. Moreover, these cells were able to self-renew in vitro and in vivo [77, 79, 80]. After stem cell enrichment by flow cyto-

metric selection using c-Kit as a single marker, c-Kit+ cells were able to regenerate and completely restore submandibular gland function. As few as 100 c-Kit+ cells obtained from irradiated primary recipients were shown to completely restore salivary gland function and morphology in irradiated secondary recipients 3 months after transplantation [79]. Also, salispheres cultured from human parotid and submandibular glands have been shown to contain c-Kit+ cells with self-renewal and differentiation capacities in vitro [79, 81, 82]. Clinical trials to assess whether salivary gland stem cell transplantation is feasible in humans are in progress.

**Conclusion**

Xerostomia is often a lifelong problem in head and neck irradiated patients. Therefore, these patients need additional supportive oral care by the dental team. Because of the special needs during and after head and neck radiation, the dental team should be an integral part of the head and neck team as well as take part in the regular follow-up. Currently, xerostomia due to cancer therapy cannot be prevented; however, with additional oral supportive care, the complaints can be reduced or minimized. Finally, techniques are in progress to either further reduce the inevitable radiation damage to salivary gland tissue and to recover lost salivary gland function when it has occurred.

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# Dysphagia, Reflux, and Hiccups

25

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## Introduction

Dysphagia, reflux, and hiccups are common gastrointestinal symptoms in patients with cancer. Broadly speaking, they share a common theme, disruption of the function of the upper gastroesophageal tract, although their etiology is diverse and the mechanisms not fully understood. Persistent symptoms can have a significant impact on nutritional status, as well as general quality of life. In fact, for patients living with advanced cancer, poor nutritional intake and performance status have been described as part of the common terminal pathway, carrying with them significant implications in prognosis [1]. Of all three symptoms, dysphagia is perhaps the best studied. Reflux is well studied in the general population, while intractable hiccups are poorly studied. In this chapter, we will review the prevalence of these symptoms, pathophysiology, and treatment options.

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## Prevalence of Dysphagia, Hiccups, and Reflux

Dysphagia is perhaps most reliably reported, while significant dyspepsia and hiccups are more likely to be under reported. In a survey of 219 medical oncology patients focusing on symptoms with potential impact on nutritional status, dysphagia was noted in 17%, heartburn 14%, and indigestion 21% [2]. In a survey of 1000 patients with advanced cancer attending a palliative program, Walsh et al. found dysphagia reported in 18% of patients, dyspepsia in 19%, and hiccups in 9% [3]. The corresponding estimates were 22, 56, and 15% in a survey of 406 terminally ill cancer patients [4].

For specific subgroups of patients, the expected incidence can be much higher. For example, in patients with esophageal cancer, dysphagia is the presenting symptom in over 90% of patients. For these patients, if a curative intent is possible, depending on the primary treatment modality, local control and permanent relief of dysphagia can be expected in 30–60%. In patients managed with a palliative intent, permanent relief of dysphagia remains challenging, often requiring repeated interventions and aggressive supportive care measures to maintain some degree of swallowing function [5]. In patients undergoing curative combination chemoradiotherapy for head and neck cancer, acute dysphagia as a side effect of treatment is expected in all patients and



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in some requiring the use of prophylactic feeding tube placement [6]. In advanced lung cancer patients undergoing curative chemoradiotherapy, esophagitis and dysphagia are expected to occur in 14–49% and are one of the dose-limiting toxicities [7].

## Dysphagia

### Swallowing Mechanism

#### Swallowing Mechanism

Swallowing involves the complex coordination of multiple muscle groups. This can be divided into three phases. The oral phase involves mastication and propulsion of the bolus to the posterior mouth. The pharyngeal phase further sends the food bolus into the oropharynx by movements of the tongue and soft palate. The esophageal phase sees the food bolus traveling through the esophagus with closure of the airway by the epiglottis, preventing aspiration of food, and closure of the palatopharynx by the soft palate, preventing regurgitation of food into the nasopharynx [8]. The neurophysiology of swallowing has not yet been fully elucidated, although it is known that a swallowing network exists in the brain stem including the nucleus tractus solitarius and nucleus ambiguous. These areas receive cortical input via the reticular formation. Imaging studies indicate that cortical involvement is multifocal and bilateral [9]. Efferent fibers of cranial nerves V, VII, IX, X, and XII are involved in sequentially co-coordinating the muscles involved in swallowing. Peristalsis of the smooth muscle of the thoracic esophagus is stimulated by the autonomic nervous system via the vagus nerve [10].

#### Types of Dysphagia

Malignant dysphagia is defined as direct cancer involvement of the esophagus; it occurs most commonly due to primary esophageal cancer but can also occur as a result of extrinsic compression by malignant mediastinal lymphadenopathies or direct tumor extension, most commonly from lung cancer.

Treatment-related dysphagia secondary to injury to the basal epithelial layer esophagus, also referred to as esophagitis, can occur in the acute phases of treatment, either with radiation therapy involving the esophagus or certain types of chemotherapy, and is typically reversible. Alternations in saliva and short-term pharyngoesophageal edema can contribute to acute dysphagia as well.

Treatment-induced swallowing disorders can manifest months to years later as a result of extensive fibrosis and vascular and neural damage of the pharyngeal and esophageal regions [11]. Posttreatment, injury to the esophagus resulting in scar tissue or stricture formation is typically chronic and irreversible. Neurological compromise of the swallowing pathway, located in the brain stem, and cranial nerve injuries can occur in patients with primary or metastatic tumors or from cancer treatments. Other causes of dysphagia include infection (e.g., candidiasis) and reflux esophagitis.

#### Clinical Assessment and Investigation

For patients presenting with dysphagia, a careful history and physical examination would often reveal the potential cause and guide the appropriate choice of investigations. It is, however, important to note that not all patients with difficulty swallowing will describe it as such. Patients with a lower esophageal obstruction may be adamant they have no difficulty swallowing, but rather food getting stuck lower down in their chest or vomiting and pain after eating. Cough waking a patient up at night or during eating may suggest aspiration. Intractable vomiting may be the only complaint in patients who have developed a fistula, as the body struggles to protect its airway. Quantification of the severity of dysphagia is important for symptom monitoring. Several dysphagia scales have been described although all share very similar characteristics. For example, Mellow and Pinkas described a five-point scale (0–4) where 0 describes the ability to eat all solids and 4 complete dysphagia [12].

Barium swallow or computed tomography can provide radiological information to establish the etiology of the dysphagia such as esophageal primary, extrinsic compression, benign stricture, fistula, or features of complications such as aspiration pneumonia. Endoscopy provides details such as malignant mucosal involvement vs. extrinsic compression, presence of fistula, esophageal candidiasis, reflux esophagitis, and the opportunity to obtain histology for pathological confirmation. Additional investigations such as endoscopic ultrasound and positron-emission tomography are often required as part of the diagnostic work-up of primary esophageal cancer.

Video fluoroscopy is particularly useful in patients where dysphagia is expected to be a late sequel of treatment, allowing anatomy, swallowing function, and aspiration risk to be objectively quantified. It is particularly valuable for estimating the potential value of different behavioral strategies toward managing dysphagia.

## Treatment

After assessment to establish the etiology of dysphagia, management can be broadly divided into four complementary domains: supportive care measures, behavioral and compensatory interventions (to facilitate the physiology of swallowing), mechanical interventions (to restore the esophageal lumen), and where appropriate antineoplastic therapies.

### Supportive Interventions

Supportive care measures are important and appropriate irrespective of etiology. Dysphagia is frequently accompanied by odynophagia or painful swallowing that must be addressed concurrently. The use of systemic analgesics (e.g., opiates) and the choice of the liquid transdermal route of administration may be useful. Counseling by a dietitian in the use of pureed or liquid diets, nutrition supplement preparation, and the minimal amount of fluid intake required to maintain weight and hydration is important. For patients who are dehydrated, intravenous or subcutaneous hydration may be needed, while other more durable solutions are identified. Treatment of suspected esophageal candidiasis should be considered especially in patients receiving chemotherapy or on prolonged steroid therapy. For patients where the clinical course of the dysphagia is expected to be protracted, enteral feeding via percutaneous gastrostomy tube or total parenteral nutrition may need to be considered.

### Behavioral and Compensatory Interventions

Behavioral and compensatory treatments aim to modify the swallowing action as it is being executed to effectively direct a food bolus toward the esophagus, thus preventing airway entry or residue from remaining in the oropharynx. These can be divided into postural techniques (e.g., chin tuck, head rotation) or the use of specific maneuvers such as the Mendelsohn maneuver, supraglottic swallow, and super-supraglottic swallow [13]. By design, they are only effective if they accompany each swallow.

Chin tuck involves tilting the head downward toward the chest as much as possible without being extended forward. It changes the anatomic relationship between structures involved in swallowing and narrows the width of the airway entrance before swallowing. Head rotation involves rotating the head to the left or right (the weakened side) during swallowing. This results in changes in pharyngeal pressures directing the food bolus to the opposite side. The Mendelsohn maneuver requires the user to maintain hyolaryngeal elevation during swallowing for at least 2 s. This has the physiologic effect of increasing the duration of upper esophageal sphincter opening and improves airway protection. Supraglottic swallow requires the user to hold his or her breath before, during, and after swallowing, where the super-supraglottic requires the additional volitional cough at the completion of the swallow. Physiological studies suggest improved airway protection at least when performed by normal subjects. While there is some evidence in support

of the efficacy of these interventions in patients with neurological disorders or late effects of cancer treatments (i.e., head and neck cancer patients), the evidence is weak and requires further study [14].

The use of prophylactic swallowing exercises in patients with head and neck cancer has reported positive results. In a randomized controlled trial of a schedule of swallowing exercises versus best supportive care by a speech pathologist in 26 patients with locally advanced head and neck cancer, patients who performed swallowing exercises had significantly better swallowing scores at 3 and 6 months compared to the standard of care group [15]. Fatigue is the main barrier for compliance.

## Mechanical Interventions

Narrowing of the esophageal lumen can arise due to malignant involvement with direct infiltration or extrinsic compression. Benign strictures most commonly occur in cancer patients following surgery or radiotherapy. Dilatation can provide transient relief of dysphagia and allow passage of an endoscope through an area of narrowing prior to stenting or brachytherapy. Esophageal stents can be the treatment of choice especially for patients with malignant dysphagia with a life expectancy of a few months.

The placement of a stent across the region of esophageal narrowing provides a means to open the affected lumen rapidly, relieving the obstruction and dysphagia. A stent may also cover an area of tracheoesophageal fistula. While the first esophageal stents were rigid plastic stents, these have been superseded by self-expanding metal stents (SEMS). The most commonly used stents are SEMS, either covered or partially covered with an outer layer, composed of a semipermeable membrane. Covered stents have the advantage of preventing tumor growth into the lumen but may be more prone to stent migration [16]. The location of the obstruction is important in the choice of stent. In particular, the placement of a stent over the gastroesophageal junction can result in significant reflux, often necessitating the use of medication such as proton pump inhibitors (PPI). Approximately 30% of patients with a stent in place might develop recurrent dysphagia. The most common cause of recurrent dysphagia following stent placement is tumor overgrowth, stent migration, and food bolus obstruction. Additional stent insertion could be effective. A systematic review of nine studies on patients undergoing neoadjuvant chemotherapy for esophageal cancer showed that the use of stents significantly decreased dysphagia. However, major adverse events were common including stent migration (32%) and chest discomfort (51%) [17]. A large European cohort study involving over 2900 patients found self-expanding metal stent placement as a bridge to surgery was associated with negative impact on treatment outcomes including in-hospital morbidity and mortality and overall survival [18]. Stents are an excellent choice for patients with shorter life expectancy but are less ideal for those where cure is possible.

## Specific Considerations for Acute Treatment-Induced Esophagitis

The combination of chemotherapy and radiation is often used in the definitive management of thoracic malignancies such as lung and esophageal cancer. Radiation-induced esophagitis is often dose limiting. The dose delivered to the esophagus, expressed as various dosimetric parameters (e.g., volume of esophagus receiving greater or equal to 40Gy; V40), has been found to correlate with moderately severe esophagitis (≥Gd 3) [19, 20]. Other prognostic factors such as early PET response [21], degree of swelling [22], and miRNA [23] have been described. Technological advances including the use of intensity-modulated radiotherapy and avoidance of the contralateral esophageal lumen [24] hold promise to reduce treatment-related toxicities.

The combination of systemic therapy with radiation is expected to increase the toxicity risk. Its effect is not only additive but synergistic due to the radiation-sensitizing effect. Combining new classes of drugs with radiotherapy (e.g., targeted therapies) [25, 26] needs to be examined systematically and with caution as unacceptable

toxicities have been described. The presence of neutropenia can compound the esophagitis risk [27]. Bacterial [28] and candidal [29] infections can escalate symptoms.

Prevention of esophagitis through meticulous planning and avoidance, if technically feasible, is ideal. Glutamine supplement has been shown in randomized trials to reduce the severity of esophagitis although the strategy has not been widely incorporated into clinical practice [30]. Oral epigallocatechin-3-gallate, a green tea extract, has shown promise in a phase I study [31] but requires further investigation. Supportive interventions as described earlier remain the mainstay of care in the presence of symptoms.

### Specific Considerations for Dysphagia Management for Incurable Esophageal Cancer

For patients with potentially curable esophageal cancer, definitive therapy provides the best management of dysphagia. For others, treatment aimed at palliation can range from dilatation, laser therapy, stent insertion, brachytherapy, photodynamic therapy, external beam radiotherapy, and palliative chemotherapy. These treatments can be used sequentially or occasionally in combination. The choice of treatment approach is typically guided by feasibility, toxicity estimates, life expectancy, and of course expected efficacy.

Stent therapy has already been discussed in the previous section. Brachytherapy involves the placement of a treatment catheter within the lumen of the esophagus, through an upper endoscopic procedure. Modern brachytherapy usually utilizes a high-dose-rate source (HDR brachytherapy) enabling treatment in a single dose or in 2–5 divided doses (fractionated) [32]. A recent Cochrane Review based on randomized trials supported the use of brachytherapy for patients with potential survival benefit and better quality of life, while stents can provide more rapid symptom relief and are particularly useful for patients with shorter life expectancies [33].

Palliative external beam radiotherapy is most typically given over 1–2 weeks of daily treatments, although many different dose fractionation schemes are in use. In addition to the effect on restoring the esophageal lumen, it can reduce the risk of extrinsic compression or direct invasion into adjacent airways or vasculature. This is most suitable for patients with longer life expectancies (e.g., >3 months). Dysphagia relief is expected to occur in 50–70% of patients with a duration of relief in the order of 3–6 months [34]. It has not been directly compared with stenting or brachytherapy. In the TROG 03.01 trial, the addition of chemotherapy to external beam radiotherapy did not improve dysphagia relief or survival but was associated with increased moderate to severe toxicities (TROG 03.01 http://www.trog.com.au). The addition of external beam radiotherapy (30 Gy in ten fractions) to brachytherapy (16 Gy in two fractions) showed variable results with no disease-free or overall survival benefit in one [35] but benefit in another [36].

Dilatation and laser therapy have limited efficacy compared with stents and are used to complement more definitive therapies. Photodynamic therapy utilizes light of a particular wavelength to activate photosensitizing chemicals (e.g., porphyrin based), which causes local tissue destruction. It is associated with skin photosensitivity for up to 6 weeks after delivery of the photosensitizer, fever, chest discomfort, and pleural effusion. This is seldom used as first-line therapy and may be useful in patients where other treatment options have failed. Chemotherapy typically consists of a cisplatin or 5 FU-based regimen. It is most commonly recommended when systemic disease dominates the clinical picture given its systemic toxicity profile.

## Reflux

### Mechanism and Assessment

The Global Consensus Group on gastroesophageal reflux disease defined GERD as a condition that develops when the reflux of the stomach contents causes troublesome symptoms and/or complications (Montreal definition). While many symptom descriptors such as heartburn,

dyspepsia, indigestion, and reflux are used interchangeably, two syndromes using the nomenclature of "typical reflux syndrome" and "reflux chest pain syndrome" have been described. Typical reflux syndrome is characterized by heartburn (defined as a burning sensation in the retrosternal area) and/or regurgitation (the perception of flow of refluxed gastric content into the mouth or hypopharynx). The reflux chest pain syndrome consists of chest pain mimicking cardiac pain [37].

### Pathophysiology

Gastroesophageal reflux disease and its symptoms, by definition, are attributed to the reflux of stomach contents into the esophagus. This can be objectively confirmed by pH studies. Patients with symptoms suggestive of gastroesophageal reflux disease can have a range of endoscopic findings, from normal, to Barrett's esophagus (a hallmark of chronic reflux) and esophagitis (mucosal breaks). The presence of *Helicobacter pylori* infection may be etiologic as well as compounding the symptoms. Esophageal and gastric dysmotility can cause functional dyspepsia [38]. Patients with irritable bowel syndrome have been associated with an increased risk of reflux symptoms.

In patients with cancer, malignant involvement of the stomach or esophagus can directly disrupt the anatomy and motility resulting in reflux. Similarly, surgical treatment for cancer such as gastroesophagectomy or esophageal stent placement [39] can result in reflux. Acute and chronic esophagitis can result from chemotherapy, radiotherapy [7, 40], or infective etiologies. Medications such as dexamethasone, anti-inflammatories, and aspirin may result in gastritis and esophagitis, all with the potential of causing reflux symptoms.

### Clinical Assessment and Investigation

For the majority of cancer patients with reflux symptoms, a careful history will guide further evaluations. Similar to GERD in the general population, endoscopic confirmation of esophagitis and pH studies are not always necessary and may not be cost-effective. In a patient with a history suggestive of the above cancer-related etiologies, empirical treatment with a PPI may be appropriate. For patients with persistent symptoms despite appropriate use of a PPI (proton pump inhibitor), esophagogastroduodenoscopy, 24-h esophageal and gastric pH metry, and *H. pylori* testing may be appropriate for selected cancer patients [41].

## Treatment

### General Considerations

Dietary modifications including small frequent, low-fat meals, avoidance of spicy foods, alcohol, and smoking should be considered. Elevation of the head of the bed is particularly important for patients with stents or gastroesophageal resection.

### Medical Therapy

Optimal empirical use of a PPI is frequently recommended (e.g., once daily dosing). While H2 receptor antagonist (H2RA) (e.g., famotidine) and prokinetic agents (e.g., domperidone) have all been shown to be effective, the effect is strongest with PPI [42]. Failure of this strategy is not uncommon, occurring in about two-thirds of patients in the general population. The use of double-dose PPI has been shown to provide incremental benefit in reducing acid secretions. Switching PPI has been suggested in refractory patients, although there is no evidence to support its efficacy. The addition of an H2RA at bedtime has been shown to enhance the effect of PPI [41]. In patients who are intolerant of PPIs, H2RA and prokinetic agents should be considered. Anecdotal evidence exists for symptom response with the use of subcutaneous or intravenous omeprazole in the far advanced cancer patient where oral dosing was suboptimal [27, 43].

While radioprotective agents, such as glutamine [44] and amifostine [45], have been shown to reduce esophagitis in patients undergoing high-dose chemoradiation, their use remains investigational.

## Hiccups or Singultus

Hiccup (more commonly spelled "hiccough" in the UK) is created by spasmodic involuntary contraction of the diaphragm and intercostal muscles which is followed by closure of the glottis causing the characteristic hiccup sound. Singultus, the medical term for hiccups, meaning to gasp or sigh, is sometimes used for more intractable hiccups [46]. Hiccups typically occur in a pattern of 4–60 per minute and do not seem to serve a physiologic function [47].

Persistent hiccups (lasting more than 48 h) and intractable hiccups (lasting more than 2 months) can result in psychological effects, sleep disturbance, increased caloric requirements, aspiration, and even pneumomediastinum or dehiscence of surgical wounds in the postoperative setting. In patients with advanced terminal illness, they can be particularly distressing to both patients and families.

## Mechanism and Assessment

### Pathophysiology

The mechanism of hiccup is not fully understood. The hiccup reflex arc consists of afferent and efferent arms and a central hiccup center most probably located in the upper cervical cord (C3–C5) or brain stem. The afferent arm primarily involves the vagus, phrenic, and sympathetic nerves (T6–T12); however other afferent mechanisms have been reported, including stimulation of the trigeminal nerve. The efferent limb of the reflex arc is mediated principally by the phrenic nerve, causing diaphragmatic contraction, often unilateral with the left diaphragm involved more frequently than the right. The external intercostal (T1–T11) and scalenus anticus nerves, as well as the accessory respiratory muscles, are involved. Finally, the recurrent laryngeal nerve stimulates closure of the glottis after contraction of the diaphragm [47].

### Etiologies

Hiccups may be caused by a large number of stimuli with more than 100 being reported in the literature. Benign hiccup bouts often follow gastric distension (such as with large meals or ingestion of carbonated beverages), which is believed to stimulate vagal afferent activity. Gastroesophageal reflux may be one of the most common causes of hiccups occurring in approximately 10% of patients, while other common causes include alcohol, sudden change in temperature, gastric insufflation with gastroscopy, and stress and tympanic irritation. Hiccups have been associated with metabolic disturbance (e.g., uremia) and anesthesia (e.g., inhaled, epidural). Other rarer associations include central nervous system pathology (e.g., stroke) and myocardial infarction [46–48].

In patients with cancer, intractable hiccups may occur as a result of direct cancer involvement, medications, and anticancer therapies. Tumor invasion anywhere along the hiccup pathway, including the esophagus, stomach including malignant gastric outlet obstruction, small-bowel obstruction, volvulus, diaphragm, vagus or phrenic nerve, malignant pleural effusion, and empyema, have all been associated with hiccups. Tumor involvement of the central nervous system along the hiccup reflex arc including the medulla oblongata and cervical spinal cord has been described [49, 50]. Medications commonly used for supportive care, such as antibiotics, benzodiazepines, perphenazine, opioids, and dexamethasone [51]), have been described as potentially causative. Certain chemotherapy drugs such as cisplatin, carboplatin, cyclophosphamide, docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, vindesine, and vinorelbine have been linked to hiccups. In particular, the incidence of hiccups with cisplatin with an unexplained male predominance in the order of 23% has been described [52].

*Medications causing persistent and intractable hiccups* [53]

Dexamethasone
Diazepam
Opioids
Antibiotics
Perphenazine
Short-acting barbiturates
Chemotherapy agents (e.g., cisplatin, carboplatin, cyclophosphamide, docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, vindesine, vinorelbine)

### Clinical Assessment and Investigation

History and physical examination should include neurological assessment and external auditory canal, head and neck, and thorax and abdomen examination looking for features suggestive of a causative etiology.

Imaging of the brain stem and upper cervical spine, head and neck, and thorax and abdomen (including chest X-ray, CT, or MRI) depending on physical findings may reveal or confirm a likely cause. Endoscopy of the upper GI tract may be indicated. In selected cases, complementary investigations could include complete blood count, electrolytes, and renal function.

## Treatments

Removal of any possible contributing factors, especially nonessential causative medications, is an important strategy. Beyond that, a large number of nonpharmacological ("folk remedies") and pharmacological interventions have been described to treat hiccups, as well as a smaller number of more invasive interventions. As intractable hiccups are relatively uncommon, most treatments are supported only by level IV evidence. Hiccups during chemotherapy could be secondary to dexamethasone. Replacing dexamethasone with methylprednisolone has been advocated [51]. Appropriate treatment of esophageal candidiasis has resulted in the relief of epigastric distress and intractable hiccups [29]. Many unproven "folk remedies" exist for hiccups including Valsalva maneuver and biting a lemon [46, 47, 54], sharing a common theme aimed at stimulating either the phrenic or vagus nerves.

### Pharmacology

Chlorpromazine is the only medication with US Food and Drug Administration (FDA) approval for hiccups. It is thought to act centrally, via dopamine antagonism, to suppress the hiccup reflex and is considered to be more effective when given intravenously. Adverse effects include hypotension, urinary retention, glaucoma, and delirium [46, 47].

Baclofen is a gamma-aminobutyric acid (GABA) analog thought to activate an inhibitory neurotransmitter and block the hiccup stimulus [55]. Ramirez performed a crossover randomized study involving only four patients. While no difference in hiccup frequency was seen, baclofen was associated with a longer hiccup-free period [56].

Gabapentin maybe efficacious in terminating persistent hiccups by increasing the levels of GABA, mediated by neural Ca channel blockade modulating diaphragmatic excitability [47], with some recent evidence in support of its efficacy. Given the favorable toxicity and interaction profile of gabapentin, it may be the medication of choice in oncology patients who are often taking multiple pharmaceutical agents and in whom adverse effects may not be tolerated well [46, 47].

Chlorpromazine, baclofen, and gabapentin are reasonable pharmacological agents of choice, depending on the anticipated tolerance to potential side effects. Other agents that have been used include metoclopramide, benzodiazepines, carvedilol, and steroids [47]. Where reflux esophagitis may be a contributory factor, treatment with PPI is a sound initial strategy [57]. If single-agent therapy is not successful, combinations have been used including cisapride, omeprazole, and baclofen [58] and gabapentin and baclofen [59].

Anticonvulsants including phenytoin, valproic acid, and carbamazepine have been used. Individual case reports describing effect with sertraline, nifedipine, nimodipine, carvedilol, amantadine and methylphenidate, intravenous lidocaine, nebulized lidocaine, midazolam, nefopam, and olanzapine have been described [53].

*Medications utilized in the management of intractable hiccups* [53]

Chlorpromazine
Baclofen
Gabapentin
Metoclopramide
Haloperidol
Nifedipine/nimodipine
Carvedilol
Nefopam

Midazolam
Lidocaine
Valproic acid
Phenytoin
Carbamazepine
Olanzapine
Baclofen
Amantadine
Methylphenidate

### Other Strategies

Alternative therapies in the management of hiccups including acupuncture and cupping have been reported. A systematic review of the anesthetic literature found several remedies suggested for the prevention and treatment of anesthesia-associated hiccups in case series [60]. Phrenic nerve blockade, initially achieved by long-acting anesthetic, can be rendered a permanent intervention by phrenic nerve transection in the absence of respiratory compromise [47]. Breathing pacemakers, designed to control diaphragmatic contraction via stimulation of the phrenic nerve, have been reported in a case series for intractable neurogenic hiccups [61]. These more invasive procedures are typically considered only after careful multidisciplinary assessment and reserved for patients with longer-term life expectancies.

## Summary

Dysphagia, reflux, and hiccups are common gastrointestinal symptoms in cancer patients. They can all result from direct tumor involvement or be secondary to adverse effects from cancer treatments, with a negative impact on the optimal function of the gastroesophageal tract and impairment in nutritional status and quality of life. The etiology may be obvious, given what is known about the disease or treatment status of the patient, or may require careful assessment to deduce. The cause would, in turn, guide optimal management, which frequently includes a combination of nutritional support and medical therapies in addition to more specialized modalities depending on the circumstances. Multidisciplinary approaches to the assessment and management of these symptoms are warranted.

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# Nausea and Vomiting

26

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## Introduction

Nausea and vomiting occur as symptoms associated with cancer in many settings. Raised intracranial pressure and liver or renal impairment are examples that can be direct consequences of cancer and its metastases or paraneoplastic effects causing metabolic disturbances, such as hypercalcaemia, which result in these symptoms. Concomitant medication, particularly opiate analgesia, may also cause patients with cancer to experience nausea or vomiting.

It was, however, when cytotoxic chemotherapy was introduced to treat cancer and some drugs were associated with severe emesis, which limited their use, that research into the mechanisms of emesis was boosted. Subsequently, two new classes of antiemetics, the 5-hydroxytryptamine-3 receptor antagonists (5-$HT_3$-RA) and the neurokinin 1 receptor antagonist ($NK_1$-RAs), were developed, and these made a significant impact on both the acute and delayed vomiting associated with chemotherapy [1].

The most common nausea and vomiting that patients experience after chemotherapy occur in the first 24 h and are called acute post-chemotherapy emesis [2]. Delayed emesis commences from about 18 h and can last for at least 5 days [3]. Anticipatory emesis is a conditioned response that occurs prior to subsequent cycles of chemotherapy, after vomiting. Anticipatory emesis can occur with subsequent cycles of chemotherapy as a conditioned response to vomiting in a previous cycle [4].

Patient characteristics and the drugs and their dose and schedule determine the likelihood of emesis post-chemotherapy [5]. Younger patients are more prone to vomiting than older, as are women compared to men. Patients who have had previous vomiting with chemotherapy or motion sickness or vomiting with pregnancy are more likely to vomit post-chemotherapy. Those patients with a prolonged history of heavy alcohol consumption vomit less after chemotherapy.

Drugs are classified as having a high emetic potential if patients have a 90% or greater chance of experiencing emesis and if no antiemetic prophylaxis is given [6, 7]. The best example is cisplatin that when given over an hour at greater than 60 mg/$m^2$ will cause acute and delayed vomiting in almost all patients. The combination

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of anthracyclines and cyclophosphamide is also classified highly emetogenic. Drugs such as oxaliplatin or ifosfamide are classified as of moderate emetic potential (between 30 and 90% chance of emesis). Drugs of low emetic potential (10–30% chance of vomiting) include the taxanes and oral agents such as capecitabine and newer targeted therapies such as the vinca alkaloids, bleomycin, procarbazine and erlotinib (Tables 26.1 and 26.2).

**Table 26.1** Emetic potential of intravenous antineoplastic agents

| Degree of emetogenicity (incidence) | Agent | |
|---|---|---|
| High (>90%) | Anthracycline/cyclophosphamide combinations[a] | |
| | Carmustine | |
| | Cisplatin | |
| | Cyclophosphamide ≥1500 mg/m$^2$ | |
| | Dacarbazine | |
| | Mechlorethamine | |
| | Streptozotocin | |
| Moderate (30–90%) | Alemtuzumab | Idarubicine |
| | Arsenic trioxide | Ifosfamide |
| | Azacitidine | Interferon α, >10,000,000 IU/m$^2$ |
| | Bendamustine | Irinotecan |
| | Carboplatin | Oxaliplatin |
| | Clofarabine | Romidepsine |
| | Cyclophosphamide ≥1500 mg/m$^2$ | Temolozomide[b] |
| | Cytarabine >1000 mg/m$^2$ | Thiotepa[c] |
| | Daunorubicin | Trabectidin |
| | Doxorubicin | Treosulfan |
| | Epirubicin | |
| Low (10–30%) | Aflibercept | Ibritumomab tiuxetan |
| | Aspartic acid | Interferon α, >1,5 < 10,000,000 IU/m$^2$ |
| | Aspartic acid, pegylated | Ipilimumab |
| | Belinostat | Ixabepilon |
| | Blinatumomab | Methotrexate |
| | Bortezomib | Mitomycin |
| | Brentuximab | Mitoxantrone |
| | Cabazitaxel | Nab-paclitaxel |
| | Carfilzomib | Nelarabine |
| | Catumaxumab | Paclitaxel |
| | Cetuximab | Panitumumab |
| | Cytarabine <1000 mg/m$^2$ | Pemetrexed |
| | Dactinomycin | Pentostatin |
| | Decitabine | Pertuzumab |
| | Coxetaxel | Radium-223 |
| | Doxorubicin, liposomal pegylated | Temsirolimus |
| | Eribuline | Topotecan |
| | Etoposide | Trastuzumab emtansine |
| | 5-Fluorouracil | Vinflunine |
| | Gemcitabine | |

**Table 26.1** (continued)

| Degree of emetogenicity (incidence) | Agent | |
|---|---|---|
| Minimal (<10%) | Bevacizumab | Ofatumumab |
| | Bleomycin | Pembrolizumab |
| | Busereline | Pixanthrone |
| | Busulfan | Prlatrexate |
| | 2-Chlorodeoxyadenosine | Ramucirumab |
| | Cladribine | Rituximab |
| | Fludarabine | Siltuximab |
| | Fulvestrant | Trastuzumab |
| | Goserelin | Triptorelin |
| | Interferon α, < 1,500,000 IU/m$^2$ | Vinblastine |
| | Leuprorelin | Vincristine |
| | Nivolumab | Vinorelbine |
| | Obinutuzumab | |

Source: Data from the Multinational Society for Supportive Care in Cancer (MASCC) antiemetic group guidelines are available at www.mascc.org

[a]The combination of anthracycline and cyclophosphamide in patients with breast cancer is classified as highly emetogenic

[b]There is no evidence for the intravenous administration of temozolomide. The evaluation of the emetogenicity is based on the data on oral temozolomide

[c]Emetogenicity was assessed by studies with paediatric patients

**Table 26.2** Emetogenic potential of oral antineoplastic agents

| Degree of emetogenicity (incidence) | Agent | |
|---|---|---|
| High (>90%) | Hexamethylmelamine | |
| | Procarbazine | |
| Moderate (30–90%) | Bosutinib | Imatinib |
| | Ceritinib | Lomustine |
| | Crizotinib | Temozolomide |
| | Cyclophosphamide | Vinorelbine |
| Low (10–30%) | Afatinib | Lenalidomide |
| | Alltrans retinoic acid | Mercaptopurine |
| | Axatinib | Nilotinib |
| | Capecitabine | Olaparib |
| | Dabrafenib | Pazopanib |
| | Dasatinib | Ponatinib |
| | Everolimus | Regorafenib |
| | Estramustine | Sunitinib |
| | Etoposide | Tegafur uracil |
| | Fludarabine | Thalidomide |
| | Ibrutinib | Treosulfan |
| | Idelalisib | Vendetanib |
| | Lapatinib | Vorinostat |

(continued)

**Table 26.2** (continued)

| Degree of emetogenicity (incidence) | Agent | |
|---|---|---|
| Minimal (<10%) | Abarelix | Hydroxyurea |
| | Abirateron | Melphalan |
| | Anagrelid | Lenvatinib |
| | Anastrozol | Letrozol |
| | Busulfan | Methotrexate |
| | Cabozantinib | Nindetanib |
| | Chlorambucil | Pomalidomid |
| | Degarelix | Ruxolitinib |
| | Enzalutamid | Sorafenib |
| | Erlotinib | Tamoxifen |
| | Exemestane | 6-Thioguanine |
| | Flutamid | Vemurafenib |
| | Gefitinib | Vismodegib |

Considerable uncertainty prevails for the emetogenic risk of oral agents
Source: Data from the MASCC antiemetic group guidelines are available at www.mascc.org

Most drugs are not given as single agents. The emetic potential of drug combinations can be judged by the drug with the highest emetic potential. Combinations of drugs of moderate emetic potential have not always been assessed for their overall emetic potential, but the commonly used combination of cyclophosphamide and an anthracycline would induce emesis in 90% or more of patients not given prophylactic antiemetics and so should be considered as having high emetic potential.

In patient surveys ranking side effects, nausea and vomiting are still amongst the most distressing side effects of chemotherapy and have been so in surveys dating back to the early 1980s [8, 9]. One of the reasons for this is not just the discomfort of the side effect itself but its impact on the quality of life and association with other symptoms such as fatigue, anorexia and insomnia [10]. Despite this, doctors and nurses underestimate nausea and vomiting, particularly in the delayed phase, as compared with the patients' experiences, and often do not use aggressive enough prophylaxis [11].

## Nausea

In studies that have been used to demonstrate the antiemetic efficacy of the major antiemetic drugs, the 5-$HT_3$-RAs and the $NK_1$-RAs, nausea is not as well controlled as vomiting and is still reported as a distressing side effect. One reason is that what is reported as nausea may be associated with a cluster of symptoms with different biological origins [12]. "When we had interviewed patients about nausea, the associated symptoms were vomiting, dry retching, loss of appetite, dizziness and indigestion (described as ranging from queasiness to intense abdominal churning). Most patients described psychological symptoms as either difficulty in concentrating, restlessness or anxiety and negative emotions that could also trigger nausea" (Jaklin Eliott, personal communication). It may be that many of the symptoms in the cluster require treatment to alleviate nausea. Certainly non-pharmacological treatments including acupressure and hypnosis have been tried.

In addition, drugs that have shown some efficacy include ginger (and olanzapine, discussed later). In a small study, gabapentin was reported by Guttuso and colleagues as reducing delayed post-chemotherapy nausea in patients being treated for breast cancer with a combination of doxorubicin and cyclophosphamide [13]. Ginger (*Zingiber officinale*), a spice used for centuries for nausea associated with pregnancy, has been shown to reduce the nausea of patients receiving chemotherapy who had nausea in a previous cycle, when it was added to a 5-$HT_3$-RA [14].

## The Initial Drugs Used to Control Chemotherapy-Induced Nausea and Vomiting

When emesis was first encountered with chemotherapy, the antiemetics used to treat a range of other conditions associated with nausea were used for treatment and prophylaxis but had limited efficacy, particularly against cytotoxics with high emetic potential such as cisplatin. Common antiemetics were the dopamine antagonists, domperidone, the substituted benzamides such as metoclopramide or alizapride, phenothiazines, particularly prochlorperazine or metopimazine and butyrophenones, particularly haloperidol or droperidol. Higher doses of metoclopramide were more successful against cisplatin-induced emesis probably because such doses impacted on the serotonin receptors rather than the dopamine receptors [15]. Prochlorperazine was similarly more effective at higher doses but also exhibited more toxicity particularly postural hypotension and extrapyramidal effects [16].

Other drugs investigated at that time included the cannabinoids, tetrahydrocannabinol and the synthetic nabilone and dronabinol, based on reports from marijuana smokers of relief from chemotherapy-induced emesis. Some antiemetic efficacy was found, but many patients did not tolerate the dysphoric side effects [17]. Anticholinergics such as scopolamine patches, which were useful for motion sickness, had little antiemetic efficacy with cisplatin, but antihistamines given in addition to dopamine antagonists reduced their extrapyramidal side effects and added some antiemetic efficacy.

Dexamethasone and methylprednisolone were amongst the earliest agents to be used for chemotherapy-induced emesis, including showing efficacy in decreasing cisplatin-induced emesis [18]. Prior to the introduction of $NK_1$-RAs, dexamethasone was arguably the best available agent for delayed emesis [19]. The Italian Group for Antiemetic Research evaluated the role of dexamethasone alone or combined with ondansetron on days 2–5 in 618 patients who had no emesis and either no or mild nausea in the first 24 h post-chemotherapy of moderate emetic potential. Dexamethasone was statistically significantly superior to placebo in controlling delayed vomiting or moderate to severe nausea (87 vs. 77%), and the combination of dexamethasone and ondansetron was not significantly superior to dexamethasone alone (92 vs. 87%) [20].

Dexamethasone is now used as part of triple therapy with 5-$HT_3$-RAs and $NK_1$-RAs, and doses range between 8 mg to prevent moderate emesis and 20 mg for chemotherapy of high emetic potential (if not combined with an $NK_1$-RA), but the optimal dose for delayed emesis is unknown [21].

Benzodiazepines such as lorazepam were used as adjuvants to other antiemetics. Lorazepam has anxiolytic effects and is associated with retrograde amnesia, which improved the control of post-chemotherapy emesis and lessened the potential for anticipatory emesis [22]. In the last years, olanzapine, a thienobenzodiazepine, which can act on multiple receptors including dopamine (D1, D2, D3, D4), and the serotonin receptors (5HT2a, 5HT2c, 5HT3, 5HT6) as well as adrenergic, muscarinic and histamine receptors have shown activity in studies with 5-$HT_3$-RAs and dexamethasone, in both acute and delayed emesis [23, 24].

## 5HT3 Receptor Antagonists

The first major breakthrough in the control of chemotherapy-induced emesis came with the introduction of the 5-$HT_3$-RA. These resulted from the discovery that chemotherapy caused the release of 5-hydroxytryptamine from the enterochromaffin cells in the small intestine, which stimulated the vagal afferents that connect to the dorsal brainstem, the nucleus tractus solitarius and the area postrema (which is in contact with blood and cerebrospinal fluid), and then efferent fibres go to the central pattern generator more ventrally in the brainstem, and the vomiting reflex is initiated [25].

Ondansetron was the first of the 5-$HT_3$-RAs. When combined with dexamethasone prior to chemotherapy of high emetic potential, it achieved control of acute post-chemotherapy

emesis in over 80% of patients with a rate of around 65%, if used as a single agent [26]. It was well tolerated, the side effects being mild headache, constipation and transient elevation in liver transaminases. Ondansetron, however, had much less efficacy against cisplatin-induced delayed emesis [19]. Other 5-$HT_3$-RAs have been marketed since, but a meta-analysis of randomised studies did not demonstrate major differences in the therapeutic effect between ondansetron, granisetron, tropisetron and dolasetron [27]. Currently, the 5-$HT_3$-RAs are given by single daily dosing rather than the initial multiple day schedules, and oral formulations have been shown to be as effective as intravenous dosing [28, 29].

A second-generation 5-$HT_3$-RA, palonosetron, has a longer mean elimination half-life of approximately 40 h as compared to 4–9 h, and a 30-fold higher binding affinity for the receptor than the first-generation 5-$HT_3$-RAs, but is as well tolerated [30]. Single-agent comparisons with intravenous ondansetron and dolasetron suggested non-inferiority in the control of acute emesis and superiority in the control of delayed emesis associated mainly with chemotherapy of high emetogenic emetic potential [31–33]. A third trial showed non-inferiority for acute, delayed and overall emesis in the prophylaxis of chemotherapy of high emetic potential when palonosetron was compared to ondansetron [34].

Palonosetron and dexamethasone were subsequently compared to granisetron and dexamethasone in 1114 patients receiving chemotherapy of high emetic potential (including the AC combination). The complete response rate for acute emesis was 75.3% in the palonosetron arm vs. 73.3% in the granisetron arm of the study [33]. Palonosetron can be safely given over multiple days, and its efficacy is sustained over multiple cycles [35–37].

## The NK1-Receptor Antagonists

The major issue persisting after the introduction of the 5-$HT_3$-RAs was the challenge of controlling delayed post-chemotherapy emesis. Substance P is a neurotransmitter with a strong affinity for the neurokinin$_1$ ($NK_1$) receptor and is concentrated in areas of the brain associated with nausea and vomiting such as the nucleus tractus solitarius and the area postrema [38]. The $NK_1$-RAs prevent the binding to this receptor.

## Aprepitant/Fosaprepitant

The first of the $NK_1$-RAs on the market was aprepitant, as a nanoparticle oral formulation [39]. Of many potential drug interactions with aprepitant, because it is both a substrate and inhibitor of CYP 3A4, when aprepitant is given with oral dexamethasone, it increases the area under the curve (AUC) of dexamethasone twofold, necessitating halving the dose when given with aprepitant [40]. There have been no clinically important interactions found with 5-$HT_3$-RAs or cytotoxic drugs; in the AUC of ethinyl estradiol and phenytoin and decreases in the international normalised ratio (INR) with warfarin that occur when given with aprepitant should be recognised [41–45].

Given that the combination of a 5-$HT_3$-RA and dexamethasone had become the standard antiemetic regimen to prevent emesis from chemotherapy of high emetic potential, the two major trials tested added it to this combination. Aprepitant (125 mg) was given with ondansetron (32 mg) and dexamethasone (20 mg) on day 1 where it could have impact on the acute phase of the emesis and then days 2 and 3 (80 mg) with dexamethasone (8 mg) from days 2 to 4. The dexamethasone dose was halved because of the pharmacokinetic interaction.

The two trials evaluated 1099 patients and showed significant improvement when aprepitant was added, with overall rates of no emesis and no rescue being 52.7 vs. 43.3% on one study and 72.7 vs. 52.3% on the other ($p < 0.001$). The greatest difference was in the delayed phase of emesis, with complete response rates of 67.7 vs. 45.8% and 74.4 vs. 55.8%, respectively [46, 47]. Fewer patients experienced nausea in the overall and delayed phases. The efficacy of the triple therapy is maintained over six cycles [48].

Aprepitant was well tolerated, the main side effects being asthenia, anorexia and hiccoughs, and the quality of life was improved.

In a subsequent trial with a more intense control arm of 5 days of ondansetron and dexamethasone, the aprepitant arm was still superior in all phases of emesis the overall complete response being 72 vs. 61% ($p = 0.003$) [49].

The aprepitant triple therapy was superior with non-cisplatin combinations such as breast cancer patients receiving cyclophosphamide and anthracyclines, with the control of vomiting without rescue over 5 days being 51 vs. 42% [50]. Similarly, in a study with chemotherapy of moderate emetic potential, those not receiving AC recorded no vomiting overall as 83.2 vs. 71.3% in favour of aprepitant [51]. In a small study, when palonosetron was the 5HT3 RA in triple therapy with chemotherapy of moderate emetic potential, an 83% response rate was recorded [52].

The original trials were done with fosaprepitant dimeglumine (L-758298), an intravenous water-soluble prodrug of aprepitant, whose antiemetic properties are attributable to aprepitant, as it is rapidly converted to aprepitant with a plasma half-life of 2.3 min and complete conversion within 30 min. A dose of 115 mg intravenously is bioequivalent to 125 mg of aprepitant orally [53]. The efficacy and safety data are just those of aprepitant with the addition of venous irritation at 25 mg/mL, at doses of 50 or 100 mg infused over 30 s, and therefore fosaprepitant provides a safe and effective intravenous alternative to oral dosing of aprepitant.

## NEPA

The combination of the highly selective $NK_1$-RA netupitant and the 5-$HT_3$ RA palonosetron called NEPA is the first antiemetic combination agent developed. The approval was based on three pivotal trials with approximately 2500 patients receiving highly and moderately emetogenic chemotherapies [54–56]. NEPA was administered as a single oral dose prior to chemotherapy in combination with oral DEX (day 1 only for AC/MEC, days 1–4 HEC). As shown in Table 26.3, NEPA plus DEX was superior to the oral administration of palonosetron plus DEX for all endpoints after cisplatin-based or AC chemotherapy. In the AC study, patients who received NEPA reported significantly less impact on daily functioning due to nausea and vomiting than patients who received palonosetron [57].

In 1000 patients treated with NEPA in more than 4400 cycles of chemotherapy, it was shown that the effect of NEPA persists longer (Table 26.3) [58, 59]. The safety profile of NEPA is consistent with that expected for the $NK_1$-RA and 5-$HT_3$RA classes [60]; the most common treatment-related adverse events were headache, asthenia, fatigue and dyspepsia. Cardiac adverse events and ECG/QTc data raised no cardiac safety concerns for the use of NEPA [61, 62].

The oral DEX dose should be reduced when used in combination with NEPA, because netupitant inhibits, as aprepitant does, cytochrome P450 3A4 (CYP3A4).

## Rolapitant

The new, highly selective oral $NK_1$-RA rolapitant with its long plasma half-life (180 h) was tested also in 3 pivotal trials with approximately 2500 patients. Patients received a variety of MEC regimens, including AC or cisplatin-based chemotherapy. In all trials, rolapitant was evaluated in combination with IV/oral granisetron and oral DEX and was compared with granisetron plus DEX. Rolapitant was given prior to chemotherapy, while granisetron (days 1–3 MEC, day 1 HEC) or DEX (day 1 MEC, days 1–4 HEC) was administered on the following days as well.

In all three studies, the rolapitant regimen showed statistically superior complete response (CR) rates compared to the granisetron control group during the delayed phase of vomiting. As shown in Table 26.4, significantly higher or numerically higher response rates were observed for the additional efficacy assessments [63, 64]. Furthermore, rolapitant was well tolerated; its safety profile is consistent with that expected for comparable antiemetic drugs and patients receiv-

**Table 26.3** Overview of cycle 1 efficacy for NEPA (reproduced from Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. Ann Oncol. 2015 Jun;26(6):1081–90 [77], with permission of Oxford University Press)

| | Study 1 (Cisplatin HEC) | | | Study 2 (AC) | | | Study 3 (HEC/AC/non-AC MEC)[a] | |
|---|---|---|---|---|---|---|---|---|
| Patients (%) | *NEPA + DEX (N = 136)* | *Oral PALO + DEX (N = 135)* | *p-value*[b] | NEPA + DEX (*N* = 724) | Oral PALO + DEX (*N* = 725) | *p*-value[c] | NEPA + DEX (*N* = 309) | APR + PALO + DEX (*N* = 103) |
| *Complete response* | | | | | | | | |
| Acute (0–24 h) | *98.5* | *89.7* | ***0.007*** | 88.4 | 85.0 | **0.047** | 92.9 | 94.2 |
| Delayed (25–120 h) | *90.4* | *80.1* | ***0.018*** | 76.9 | 69.5 | **0.001** | 83.2 | 77.7 |
| Overall (0–120 h) | *89.6* | *76.5* | ***0.004*** | 74.3 | 66.6 | **0.001** | 80.6 | 75.7 |
| *No significant nausea* | | | | | | | | |
| Acute | *98.5* | *93.4* | ***0.050*** | 87.3 | 87.9 | 0.747 | 90.6 | 93.2 |
| Delayed | *90.4* | *80.9* | ***0.027*** | 76.9 | 71.3 | **0.014** | 85.1 | 81.6 |
| Overall | *89.6* | *79.4* | ***0.021*** | 74.6 | 69.1 | **0.020** | 84.1 | 80.6 |

*HEC* highly emetogenic chemotherapy, *AC* anthracycline-cyclophosphamide, *NEPA* netupitant/palonosetron, *PALO* palonosetron, *DEX* dexamethasone
Complete response: no emesis/no rescue medication; no significant nausea: max score <25 mm of 100 mm visual analog scale
[a]NEPA and APR groups were not formally compared
[b]*P*-value from logistic regression versus oral palonosetron; not adjusted for multiple comparisons
[c]*P*-value from two-sided Cochran-Mantel-Haenszel test including treatment, age class and region as strata

**Table 26.4** Overview of cycle 1 efficacy for rolapitant (reproduced from Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. Ann Oncol. 2015 Jun;26(6):1081–90 [77], with permission of Oxford University Press)

| | Study 1 (AC/non-AC MEC) | | | Study 2 (HEC) | | | Study 3 (HEC) | | |
|---|---|---|---|---|---|---|---|---|---|
| Patients (%) | Rolapitant + GRAN + DEX ($N = 666$) | GRAN + DEX ($N = 666$) | *p*-value | Rolapitant + GRAN + DEX ($N = 264$) | GRAN + DEX ($N = 262$) | *p*-value | Rolapitant + GRAN + DEX ($N = 271$) | GRAN + DEX ($N = 273$) | *p*-value |
| *Complete response* | | | | | | | | | |
| Acute | 83.5 | 80.3 | 0.143 | 83.7 | 73.7 | **0.005** | 83.4 | 79.5 | 0.233 |
| Delayed | 71.3 | 61.6 | **<0.001** | 72.7 | 58.4 | **<0.001** | 70.1 | 61.9 | **0.043** |
| Overall | 68.6 | 57.8 | **<0.001** | 70.1 | 56.5 | **0.001** | 67.5 | 60.4 | 0.084 |
| *No significant nausea* | | | | | | | | | |
| Acute | 82.1 | 84.7 | 0.193 | 86.4 | 79.4 | **0.035** | 90.0 | 85.7 | 0.119 |
| Delayed | 72.7 | 69.4 | 0.194 | 73.5 | 64.9 | **0.034** | 74.5 | 68.9 | 0.137 |
| Overall | 70.6 | 66.5 | 0.118 | 71.6 | 63.0 | **0.037** | 72.7 | 67.8 | 0.203 |

*P*-values from Mantel-Haenszel chi-square test
*AC* anthracycline-cyclophosphamide, *MEC* moderately emetogenic chemotherapy, *HEC* highly emetogenic chemotherapy, *GRAN* granisetron, *DEX* dexamethasone
Complete response: no emesis/no rescue medication; no significant nausea: max score <25 mm of 100 mm visual analog scale

ing chemotherapy. The use of rolapitant may be beneficial in patients where drug-drug interactions should be avoided, because rolapitant – unlike aprepitant and NEPA – does not inhibit nor induce CYP3A4 [65]. Adjustments of concomitantly administered drugs metabolised by CYP3A4 (including DEX) are therefore not required. However, rolapitant is an inhibitor of CYP2D6, BCRP and P-gp; patients should be monitored if given a CYP2D6, BCRP or a P-gp substrate drug with a narrow therapeutic window. The intravenous formulation has been associated with serious anaphylacitc reactions and was suspended from the market.

## Olanzapine

The atypical antipsychotic olanzapine has promising antiemetic properties due to its ability to target many different receptors.

*First-line prophylaxis of CINV*: In 380 patients with highly emetogenic chemotherapy (HEC), a triple antiemetic regimen with 5-$HT_3$-RA, $NK_1$-RA and DEX plus olanzapine was administered in the intervention group and plus placebo in the control group. The primary endpoint was the incidence of nausea in the overall phase. The four-drug regimen including olanzapine was superior to the triple antiemetic regimen in the overall phase with 62.7% of patients having nausea in the olanzapine group and 78.1% in the placebo group ($p = 0.002$). Patients of the olanzapine group reported an increased sedation on day 2 (5% severe) [66].

In 241 chemotherapy-naive patients receiving cisplatin or AC-based chemotherapy, an olanzapine regimen was compared with an aprepitant regimen, both in combination with palonosetron and DEX [67]. Although complete response rates were comparable for both regimens (olanzapine [97% acute, 77% delayed/overall phases] vs. aprepitant [87% acute, 73% delayed/overall phases], the olanzapine regimen resulted in higher no nausea rates during the delayed/overall phases (87% acute, 69% delayed/overall) compared with the aprepitant regimen (87% acute, 38% delayed/overall).

*Breakthrough CINV*: In another Phase III trial, relief of breakthrough CINV was investigated in 276 patients receiving cisplatin- or AC-based chemotherapy randomised to receive olanzapine 10 mg PO 3×/day for 3 days or metoclopramide 10 mg PO 3×/day for 3 days if they failed on initial antiemetic prophylaxis (fosaprepitant/palonosetron/DEX on day 1 and DEX on days 2–4). In 68% and 70% olanzapine patients, no vomiting and no nausea during 0–72 h occurred, respectively, in comparison with 31% and 23% for patients treated with metoclopramide [68]. These data specifically support olanzapine as an effective agent for reducing breakthrough CINV.

The most common adverse events associated with olanzapine include somnolence, postural hypotension, constipation, dizziness, fatigue, dyspepsia and restlessness [69, 70]. These common side effects are mostly tolerable and mild, and, surprisingly, no grade 3 or 4 toxicities were reported in most Phase III trials [57, 68, 71].

## Antiemetic Guidelines

The Multinational Society For Supportive Care In Cancer (MASCC) antiemetic group in conjunction with ESMO (European Society of Medical Oncology) regularly updates its guidelines and last met for a major review of the literature and consensus meeting in June 2015 [72]. Studies reporting at least 10% improvement in outcome were considered as warranting changing a guideline, and a consensus was reached with 66% agreement. The information referred to in this chapter and any updated guidelines and the authors responsible can be accessed at www.mascc.org.

It is crucial to clearly define the optimal prophylactic antiemetic therapy for CINV before chemotherapy begins and to implement it from the start. The emetic potential of the chemotherapy must be established and the agent with the highest potential used to determine the emetogenicity of the entire chemotherapy.

Figure 26.1 depicts the prevention of acute nausea and vomiting following chemotherapy of high emetic potential.

**a** **ACUTE** Nausea and Vomiting: SUMMARY

| EMETIC RISK GROUP | ANTIEMETICS |
|---|---|
| High Non-AC | **5-HT$_3$** + **DEX** + **NK$_1$** |
| High AC | **5-HT$_3$** + **DEX** + **NK$_1$** |
| Carboplatin | **5-HT$_3$** + **DEX** + **NK$_1$** |
| Moderate (other than carboplatin) | **5-HT$_3$** + **DEX** |
| Low | **5-HT$_3$** or **DEX** or **DOP** |
| Minimal | No routine prophylaxis |

**5-HT$_3$** = serotonin$_3$ receptor antagonist

**DEX** = DEXAMETHASONE

**NK$_1$** = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

**DOP** = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT$_3$ receptor antagonist.

**b** **DELAYED** Nausea and Vomiting: SUMMARY

| EMETIC RISK GROUP | ANTIEMETICS |
|---|---|
| High Non-AC | **DEX** or (if APR 125mg for acute: ( **MCP** + **DEX** ) or ( **APR** + **DEX** )) |
| High AC | None or (if APR 125mg for acute: **DEX** or **APR** ) |
| Carboplatin | None or (if APR 125mg for acute: **APR** ) |
| Oxaliplatin, or anthracycline, or cyclophosphamide | **DEX** can be considered |
| Moderate (other) | No routine prophylaxis |
| Low and Minimal | No routine prophylaxis |

**DEX** = DEXAMETHASONE

**MCP** = METOCLOPRAMIDE

**APR** = APREPITANT

**Fig. 26.1** Prevention of acute nausea and vomiting following chemotherapy of high emetic potential

## Cisplatin-Based Chemotherapy

For the prevention of CINV in non-AC highly emetogenic chemotherapy, a three-drug antiemetic regimen is recommended, including single doses of a 5-HT$_3$-RA, dexamethasone and an NK$_1$- RA (aprepitant, fosaprepitant, netupitant or rolapitant).

### AC-Based Chemotherapy

In summary, a single dose of a 5-$HT_3$ RA, dexamethasone and an $NK_1$-RA (aprepitant, fosaprepitant, netupitant or rolapitant), given before chemotherapy, is recommended.

In case in $NK_1$ receptor antagonist is not available, palonosetron is the preferred 5-$HT_3$ RA.

## Prevention of Delayed Nausea and Vomiting Following Chemotherapy of High Emetic Potential

### Cisplatin-Based Chemotherapy

In this setting several options are recommended:

- Dexamethasone on days 2–4
- If aprepitant 125 mg was used on day 1, then dexamethasone 8 mg × 1 (days 2–4) + aprepitant 80 mg × 1 (days 2–3) or dexamethasone 8 mg × 2 (days 2–4) + metoclopramide 20 mg × 4 (days 2–4). Caveat: dosage of metoclopramide, EMA now recommend a maximum of 0.5 mg/kg total daily dose.

### AC-Based Chemotherapy

If aprepitant was used for the prevention of acute emesis, then on days 2 and 3, aprepitant or dexamethasone is recommended. If the $NK_1$ RA of choice was fosaprepitant, netupitant (NEPA) or rolapitant, no further prophylaxis is necessary.

## Prevention of Acute Nausea and Vomiting Following Chemotherapy of Moderate Emetic Potential

MASCC/ESMO has recently made a distinction for patients receiving select MEC agents, such as carboplatin.

## Moderate Emetogenic Chemotherapy Other than Carboplatin

Standard prophylaxis requires a 5-$HT_3$ RA and dexamethasone.

# Carboplatin-Based Chemotherapy

MASCC/ESMO separated carboplatin due to its emetogenic potential in the upper range of MEC. Therefore MASCC/ESMO endorses a prophylactic regimen of $NK_1$ RA, 5-$HT_3$ RA and dexamethasone.

## Prevention of Delayed Nausea and Vomiting Following Chemotherapy of Moderate Emetic Potential

In patients who receive chemotherapy of moderate emetic potential known to be associated with a significant incidence of delayed nausea and vomiting (anthracyclines, oxaliplatin or cyclophosphamide), dexamethasone can be considered. Otherwise no routine prophylaxis of delayed emesis is necessary. This is also true for carboplatin-based chemotherapy.

## Prevention of Acute and Delayed Nausea and Vomiting Following Chemotherapy of Low Emetic Potential

Limited evidence from clinical trials support the choice of antiemetic therapy. In summary, a single antiemetic agent, such as dexamethasone, a 5-HT3 RA or a dopamine RA may be considered for prophylaxis in patients receiving chemotherapy of low emetic risk.

### Prevention of Acute and Delayed Nausea and Vomiting Following Chemotherapy of Low Emetic Potential

In patients receiving chemotherapy of minimal emetogenic potential, no antiemetic prophylaxis is necessary.

### Prevention of Nausea and Vomiting Induced by Multiple-Day Cisplatin

The recommended treatment for these patients is a 5-HT3 RA plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for the prevention of delayed nausea and vomiting.

## Niche Areas in the Control of Nausea and Vomiting

### Anticipatory Nausea and Vomiting

The best strategy to counter anticipatory nausea and vomiting is to achieve better control of post-chemotherapy nausea and vomiting. If it does occur, behavioural therapies such as desensitisation, hypnosis or relaxation are the most promising treatments. Benzodiazepines such as lorazepam that is associated with amnesic effects can be used but with limited success that reduces over multiple cycles.

### High-Dose Chemotherapy

For patients receiving high-dose chemotherapy for stem cell transplantation, a combination of 5-HT3 RA with dexamethasone and aprepitant is recommended.

Two placebo-controlled clinical trials examined antiemetic treatment in this setting ($n = 543$) [73, 74]. In the first study, 179 patients received HDC regimens before autologous or allogeneic SCT. The absolute difference in rates of patients experiencing no emesis was 51% when comparing NK1RA regimens with control regimens. In the second study, 361 patients with multiple myeloma received high-dose melphalan prior to autologous transplantation [74]. Thirteen percent more patients treated with aprepitant had no vomiting during the overall phase than patients in the control arm, which was significant.

### Radiation-Induced Emesis

This is a complex area because the emetic potential will depend on the total dose, dose per fraction and number of fractions, field size and site of the radiation, which is often administered over several weeks. The patients' general health, age, gender and concomitant treatment also influence the likelihood of emesis.

As many as 50–80% of patients undergoing radiotherapy will experience nausea and/or vomiting, depending on the site of irradiation. Fractionated radiotherapy may involve up to 40 fractions over a 6–8-week period, and prolonged symptoms of nausea and vomiting could adversely affect the quality of life. Furthermore, uncontrolled nausea and vomiting may result in patients delaying or refusing further radiotherapy.

The MASCC/ESMO guidelines attempt to ascribe a risk category and recommend prophylactic treatment accordingly (Table 26.5) [75]. Also, there are subgroups of patients receiving radiotherapy such as the elderly where prescribing antiemetics may be problematic due to comorbid conditions and polypharmacy [76].

**Table 26.5** Radiotherapy-induced emesis

| Emetic risk level | Area of treatment | Antiemetic recommendation | MASCC evidence (level of evidence/ grade of recommendation) | ESMO evidence (level of evidence/ grade of recommendation) |
|---|---|---|---|---|
| High | Total body irradiation | Prophylaxis with 5-$HT_3$-RA + DEX | High/high (for the addition of DEX: moderate/high) | II /B (for the addition of DEX: III/C) |
| Moderate | Upper abdomen, craniospinal | Prophylaxis with 5-$HT_3$-RA + optional DEX | High/high (for the addition of DEX: moderate/high) | II/A (for the addition of DEX: II/B) |
| Low | Cranium | Prophylaxis or rescue with DEX | Low/high | IV/D |
| | Head and neck, thorax region, pelvis | Prophylaxis or rescue with DEX, a dopamine RA, or a 5-$HT_3$-RA | Low/high | IV/D |
| Minimal | Extremities, breast | Rescue with DEX, a dopamine RA, or a 5-$HT_3$-RA | Low/high | IV/D |
| Concomitant CRT | In concomitant radiochemotherapy, the antiemetic prophylaxis is according to the chemotherapy-related antiemetic guidelines of the corresponding risk category, unless the risk of emesis is higher with radiotherapy than chemotherapy | | Low/high | IV/D |

*HBI* half-body irradiation; *UBI* upper body irradiation; *H&N* head and neck; *DEX* dexamethasone
Source: Data from the MASCC antiemetic group guidelines are available at www.mascc.org

## Conclusions

Triple therapy with a 5-$HT_3$-RA, an $NK_1$-RA and dexamethasone has made a major impact on the prevention of chemotherapy-induced acute and delayed emesis. Strong recommendations can be made for administering such treatment prior to receiving chemotherapy containing drugs of high emetic potential and regimens such as AC as well as carboplatin-based chemotherapy. Good control of emesis occurs with drugs of moderate emetic potential, but more research is needed to optimise drugs and dosing. With drugs of low or minimal emetic potential, or those given by prolonged oral dosing regimens, more data are required on the incidence, intensity and patterns of emesis before evidence-based recommendations can be considered. Niche areas such as which antiemetic regimens best prevent emesis with high-dose chemotherapy and with radiotherapy require more research.

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# Mucositis (Oral and Gastrointestinal)

27

Rajesh V. Lalla and Joanne M. Bowen

## Introduction

Alimentary mucositis refers to inflammatory, erosive, and ulcerative lesions of any part of the gastrointestinal tract that occur secondary to cancer therapy. Thus, the term alimentary mucositis encompasses both oral and gastrointestinal (GI) mucositis. Mucositis can be classified according to the type of cancer therapy involved as chemotherapy-induced mucositis, radiation-induced mucositis, or a combination of the two. More recently, mucositis following targeted anticancer therapies has been described, but our understanding of that is only beginning to develop. Oral mucositis occurs in approximately 20–40% of patients receiving conventional chemotherapy for solid tumors [1], over 80% of patients receiving head and neck radiotherapy [2], and about 80% of patients undergoing high-dose chemotherapy prior to hematopoietic stem cell transplantation [3]. GI mucositis is also common, with reports of up to 80% with some regimens [4]. In one study, it was reported that 303 of 599 patients (51%) receiving chemotherapy for solid tumors or lymphoma developed oral and/or GI mucositis [5]. Oral mucositis developed in 22% of 1236 cycles of chemotherapy, GI mucositis in 7% of cycles, and both oral and GI mucositis in 8% of cycles.

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## Morbidity and Economic Impact

Mucositis can be very painful and can significantly affect nutritional intake, mouth care, and quality of life [6]. For patients receiving high-dose chemotherapy prior to hematopoietic cell transplantation, mucositis has been reported to be the single most debilitating complication of transplantation [7]. Infections associated with mucositis lesions can cause life-threatening systemic sepsis during periods of profound immunosuppression [8]. Moderate to severe mucositis has been correlated with systemic infection and transplant-related mortality [9]. In patients receiving chemotherapy for solid tumors or lymphoma, the rate of infection during cycles with mucositis was more than twice that during cycles without mucositis and was directly proportional to the severity of mucositis [5]. Infection-related deaths were also more common during cycles with both oral and GI mucositis. In addition, the average duration of hospitalization was significantly longer during chemotherapy cycles with mucositis. Importantly, a reduction in the next dose of chemotherapy was twice as common



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after cycles with mucositis than after cycles without mucositis [5]. Patients receiving head and neck radiation therapy who develop mucositis are significantly more likely to have severe pain and a weight loss of ≥5% [10]. In one study, approximately 16% of patients receiving radiation therapy for head and neck cancer were hospitalized due to mucositis [11]. Further, 11% of the patients receiving radiation therapy for head and neck cancer had unplanned breaks in radiation therapy due to severe mucositis [11]. Thus, mucositis can be a dose-limiting toxicity of cancer therapy with direct effects on patient survival.

Patients who have significant mucositis require supportive care measures such as pain management, liquid diet supplements, placement of gastrostomy tubes or delivery of total parenteral nutrition, fluid replacement, and prophylaxis/treatment against infections. These can add substantially to the total cost of care. For example, in a 2003 study of patients receiving chemotherapy for solid tumors or lymphoma, the estimated cost of hospitalization was $3893 USD per chemotherapy cycle without mucositis, $6277 USD per cycle with oral mucositis, and $9132 USD per cycle with both oral and GI mucositis [5]. In a 2007 study of patients receiving radiation therapy for head and neck cancer, oral mucositis was associated with an increase in costs ranging from $1700 to $6000 per patient, depending on the grade of oral mucositis [10]. In a 2013 systematic review [12], it was reported that severe diarrhea in patients receiving chemotherapy following surgery for breast cancer cost $2717 per adverse event [13]. Whereas for patients with colorectal cancer hospitalized due to severe diarrhea, the cost was $7754 [14]. Given the clustering of toxicities and associated increase in resource utilization, the economic impact of mucositis on cancer care is significant.

## Pathogenesis and Risk Factors

Although direct damage to epithelial cells plays a role in the pathogenesis of mucositis, multiple additional mechanisms are also believed to be involved [15, 16]. A model has been described [17, 18] that consists of the following five stages:

1. *Initiation of tissue injury*: Radiation and/or chemotherapy induces cellular damage resulting in death of basal epithelial cells. The generation of free oxygen radicals by radiation or chemotherapy is also believed to play a role in the initiation of mucosal injury. These small highly reactive molecules are by-products of oxygen metabolism and can cause significant cellular damage.
2. *Upregulation and message generation*: In addition to causing direct cell death, free radicals activate second messengers that transmit signals from cell surface receptors to the nucleus, leading to increased expression of pro-inflammatory cytokines, tissue injury, and cell death.
3. *Signaling and amplification*: Upregulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha, produced mainly by macrophages, injures mucosal cells and also activates molecular pathways that intensify mucosal injury.
4. *Ulceration and inflammation*: A significant inflammatory cell infiltrate is associated with the mucosal ulcerations, partly in reaction to the metabolic by-products of the colonizing oral microflora. Production of pro-inflammatory cytokines is also further increased due to this secondary infection [19].
5. *Healing*: This phase involves epithelial proliferation as well as cellular and tissue differentiation [20], leading to restoration of the integrity of the epithelium.

The various stages are likely to have significant overlap and are thought to involve multiple cell types and various classes of mediators including reactive oxygen species, pro-inflammatory cytokines, and transcription factors. Some studies have used a bioinformatics approach to identify gene expression changes associated with mucositis development and should lead to an increased understanding of its pathogenesis [21, 22]. These studies have also shown that there is significant overlap in

molecular markers and tissue changes for both oral and GI mucositis, indicating that the pathobiology is conserved throughout the alimentary tract.

The severity and extent of mucositis that develops in any patient are dependent on both treatment-related and host-related risk factors. Treatment-related risk factors include the specific type and dose of cancer therapy (for example, certain chemotherapy drugs such as 5-fluorouracil are particularly mucotoxic, especially at high doses). Host-related risk factors include genetic polymorphisms and systemic disease. Polymorphisms in genes for enzymes involved in drug metabolism have been found to result in an increased risk of mucositis. For example, patients who carry the 677TT genotype for methylenetetrahydrofolate reductase have more severe mucositis in response to methotrexate use [23]. Similarly, patients with a polymorphism resulting in increased production of the pro-inflammatory cytokine tumor necrosis factor (TNF) were reported to have a significantly increased risk of chemotherapy-related toxicity including mucositis in high dose [24] and standard dose settings [25]. Certain systemic diseases associated with increased apoptosis (e.g., Addison's disease) may increase risk of mucositis, while others associated with reduced apoptosis (e.g., psoriasis) may be protective. The effects of general host-related factors such as age and gender on risk for mucositis are not clear [26]. Recently, microbial profiles in the oral cavity and lower digestive tract have also been postulated to modulate risk of mucositis [27, 28], although confirmation in large well-designed studies is required.

## Clinical Signs and Symptoms

Oral mucositis initially presents as erythema of the oral mucosa, with subsequent progression to erosion and ulceration, depending on the intensity of the cancer therapy [29]. The ulcerations may be covered by a white pseudomembrane. Oral mucositis lesions are usually limited to nonkeratinized areas of the mouth such as the lateral and ventral tongue (Fig. 27.1), buccal mucosa, and soft palate. In radiation-induced oral mucositis, lesions are limited to the tissues in the field of radiation. Most patients who have received more than 50 Gy to the oral mucosa will develop severe ulcerative oral mucositis. The time required for healing is proportional to the extent and severity of the lesions. Oral mucositis in patients receiving conventional chemotherapy may resolve between 10 and 18 days after cessation of chemotherapy, while in patients who have received high-dose radiation, several weeks may be needed for healing. The most common symptom of oral mucositis is pain, which impacts on nutrition, oral hygiene, and speech.

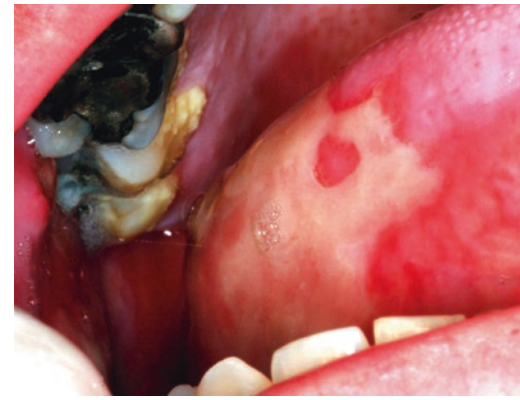

**Fig. 27.1** Radiation-induced oral mucositis on the lateral tongue of a patient who had received 4600 cGy of a total planned dose of 6200 cGy, without concurrent chemotherapy, for treatment of squamous cell carcinoma of the tongue. Reprinted from Lalla RV et al., Dent Clin North Am. 2008 Jan;52(1):61–77, viii, with permission of Elsevier

GI mucositis may present as abdominal pain, bloating, nausea, or diarrhea. It usually starts within 3–7 days of chemotherapy and resolves by about day 14 [30]. This can be prolonged in high-dose chemotherapy or pelvic radiotherapy patients and can impact on nutrition. Due to the difficulty in accessing the lower GI tract for visual inspection, the tissue changes associated with symptoms have been largely determined with the use of rodent models [31]. These include mucosal atrophy, mucus hypersecretion followed by goblet cell depletion, and increased apoptosis in the crypt compartment. A small study using video capsule endoscopy in patients undergoing

high-dose chemotherapy and stem cell transplantation has confirmed that frank ulceration and bleeding occur in the small intestine at the time of peak gastrointestinal symptoms [32].

## Diagnosis and Complicating Factors

Diagnosis of mucositis is based on a recent history of cancer therapy and the presence of clinical signs (for oral mucositis) or symptoms (for GI mucositis). However, lesions of oral mucositis may be resembled or secondarily infected by other conditions including fungal infection (most commonly candidiasis), viral infection (most commonly HSV), and graft vs host disease (in transplant recipients). An alternative diagnosis or secondary infection should especially be suspected when lesions occur in unusual sites or last for longer than expected. Symptoms similar to those of GI mucositis may be caused by infection, peptic ulcer disease, inflammatory bowel disease, and motility disorders. Transient lactose intolerance can occur post chemotherapy such that dairy foods can worsen the symptoms.

## Measurement

A number of different scales are available to record the severity of oral mucositis. The World Health Organization (WHO) scale is a simple, easy to use scale that is suitable for daily use in clinical practice. This scale combines both subjective and objective measures of oral mucositis (Table 27.1). The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grades oral mucositis based on the degree of pain and resulting impact on diet [33]. The Oral Mucositis Assessment Scale (OMAS), suitable for research purposes, measures erythema and ulceration at nine different sites in the oral cavity. This scale has been validated in a multicenter trial with high interobserver reproducibility and strong correlation of objective mucositis scores with patient symptoms [34]. The most frequent approach to measuring GI mucositis is to grade diarrhea as a clinical end point [35]. Other symptoms and signs graded include constipation, esophagitis, and proctitis, with the choice generally regimen-specific. There is a need for the development of a new scale for GI mucositis that could better delineate the problem.

**Table 27.1** World Health Organization (WHO) scale for oral mucositis

| |
|---|
| Grade 0 = No oral mucositis |
| Grade 1 = Erythema and soreness |
| Grade 2 = Ulcers, able to eat solids |
| Grade 3 = Ulcers, requires liquid diet (due to mucositis) |
| Grade 4 = Ulcers, alimentation not possible (due to mucositis) |

## Management

The Mucositis Study Group of MASCC/ISOO has published evidence-based clinical practice guidelines for the management of oral and gastrointestinal mucositis [36]. The guidelines include recommendations (based on stronger evidence) and suggestions (based on weaker evidence) [37]. These guidelines are listed in Table 27.2 and are referred to in the sections below as applicable.

### General Preventive Measures

The maintenance of good oral hygiene can result in reduced incidence and severity of oral mucositis [38–40]. The MASCC/ISOO mucositis guidelines suggest the use of a standardized oral care protocol for the prevention of oral mucositis across all cancer treatment modalities. Such protocols typically include brushing with a soft toothbrush, flossing, and the use of non-medicated rinses (e.g., saline, sodium bicarbonate rinse). No guideline was possible related to the individual use of mixed medication mouthrinses (including magic/miracle mouthwash) or related to use of calcium phosphate mouthrinses [41].

**Table 27.2** Summary of MASCC/ISOO evidence-based clinical practice guidelines for the management of patients with oral and gastrointestinal mucositis

| **Oral mucositis** |
|---|
| Recommendations **in favor** of an intervention (i.e., strong evidence supports effectiveness in the treatment setting listed) |
| 1. The panel *recommends* that 30 min of oral cryotherapy be used to *prevent* oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (level of evidence II) |
| 2. The panel *recommends* that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to *prevent* oral mucositis (at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days posttransplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (level of evidence II) |
| 3. The panel *recommends* that low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm2) be used to *prevent* oral mucositis in patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation (level of evidence II) |
| 4. The panel *recommends* that patient-controlled analgesia with morphine be used to *treat* pain due to oral mucositis in patients undergoing hematopoietic stem cell transplantation (level of evidence II) |
| 5. 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 (level of evidence I). |
| **Oral mucositis** |
| Suggestions **in favor** of an intervention (i.e., weaker evidence supports effectiveness in the treatment setting listed) |
| 1. The panel *suggests* that oral care protocols be used to *prevent* oral mucositis in all age groups and across all cancer treatment modalities (level of evidence III) |
| 2. The panel *suggests* that oral cryotherapy be used to *prevent* oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for hematopoietic stem cell transplantation (level of evidence III) |
| 3. The panel *suggests* that low-level laser therapy (wavelength around 632.8 nm) be used to *prevent* oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer (level of evidence III) |
| 4. The panel *suggests* that transdermal fentanyl may be effective to *treat* pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy, with or without total body irradiation (level of evidence III) |
| 5. The panel *suggests* that 0.2% morphine mouthwash may be effective to *treat* pain due to oral mucositis in patients receiving chemoradiation for head and neck cancer (level of evidence III) |
| 6. The panel *suggests* that 0.5% doxepin mouthwash may be effective to *treat* pain due to oral mucositis (level of evidence IV) |
| 7. The panel *suggests* that systemic zinc supplements administered orally may be of benefit to *prevent* oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (level of evidence III) |
| **Oral mucositis** |
| Recommendations **against** an intervention (i.e., strong evidence indicates lack of effectiveness in the treatment setting listed) |
| 1. The panel *recommends* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and cancer (level of evidence II) |
| 2. The panel *recommends* that iseganan antimicrobial mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for hematopoietic stem cell transplantation (level of evidence II) or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (level of evidence II) |
| 3. The panel *recommends* that sucralfate mouthwash *not* be used to *prevent* oral mucositis in patients receiving chemotherapy for cancer (level of evidence I) or in patients receiving radiation therapy (level of evidence I) or concomitant chemoradiation (level of evidence II) for head and neck cancer |
| 4. The panel *recommends* that sucralfate mouthwash *not* be used to *treat* oral mucositis in patients receiving chemotherapy for cancer (level of evidence I) or in patients receiving radiation therapy (level of evidence II) for head and neck cancer |

(continued)

**Table 27.2** (continued)

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| 5. The panel *recommends* that intravenous glutamine *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for hematopoietic stem cell transplantation (level of evidence II) |
| **Oral mucositis** |
| Suggestions **against** an intervention (i.e., weaker evidence indicates lack of effectiveness in the treatment setting listed) |
| 1. The panel *suggests* that chlorhexidine mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (level of evidence III) |
| 2. The panel *suggests* that granulocyte macrophage colony-stimulating factor (GM-CSF) mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (level of evidence II) |
| 3. The panel *suggests* that misoprostol mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (level of evidence III) |
| 4. The panel *suggests* that systemic pentoxifylline, administered orally, *not* be used to *prevent* oral mucositis in patients undergoing bone marrow transplantation (level of evidence III) |
| 5. The panel *suggests* that systemic pilocarpine, administered orally, *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (level of evidence III) or in patients receiving high-dose chemotherapy, with or without total body irradiation, for hematopoietic stem cell transplantation (level of evidence II) |
| **Gastrointestinal mucositis (other than the oral cavity)** |
| Recommendations **in favor** of an intervention (i.e., strong evidence supports effectiveness in the treatment setting listed) |
| 1. The panel *recommends* that intravenous amifostine be used, at a dose of ≥340 mg/m$^2$, to *prevent* radiation proctitis in patients receiving radiation therapy (level of evidence II) |
| 2. The panel *recommends* that octreotide, at a dose of ≥100 μg subcutaneously twice daily, be used to *treat* diarrhea induced by standard- or high-dose chemotherapy associated with hematopoietic stem cell transplant, if loperamide is ineffective (level of evidence II) |
| **Gastrointestinal mucositis (other than the oral cavity)** |
| Suggestions **in favor** of an intervention (i.e., weaker evidence supports effectiveness in the treatment setting listed) |
| 1. The panel *suggests* that intravenous amifostine be used to *prevent* esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small cell lung carcinoma (level of evidence III) |
| 2. The panel *suggests* that sucralfate enemas be used to *treat* chronic radiation-induced proctitis in patients with rectal bleeding (level of evidence III) |
| 3. The panel *suggests* that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to *prevent* radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (level of evidence II) |
| 4. The panel *suggests* that probiotics containing lactobacillus species be used to *prevent* diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (level of evidence III) |
| 5. The panel *suggests* that hyperbaric oxygen be used to *treat* radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (level of evidence IV) |
| **Gastrointestinal mucositis (other than the oral cavity)** |
| Recommendations **against** an intervention (i.e., strong evidence indicates lack of effectiveness in the treatment setting listed) |
| 1. The panel *recommends* that systemic sucralfate, administered orally, *not* be used to *treat* gastrointestinal mucositis in patients receiving radiation therapy for a solid tumor (level of evidence I) |
| 2. The panel *recommends* that 5-acetylsalicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, *not* be used to *prevent* acute radiation-induced diarrhea in patients receiving radiation therapy for a pelvic malignancy (level of evidence I) |
| 3. The panel *recommends* that misoprostol suppositories *not* be used to *prevent* acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (level of evidence I) |
| **Gastrointestinal mucositis (other than the oral cavity)** |
| Suggestions **against** an intervention (i.e., weaker evidence indicates lack of effectiveness in the treatment setting listed) |
| None |

To minimize the likelihood of developing GI mucositis, maintenance of adequate hydration is recommended, and the presence of transient lactose intolerance and bacterial pathogens should be considered [42].

## Pain Control

Pain is the most distressing symptom experienced by patients due to mucositis. Many centers use topical mouthrinses containing an anesthetic such as 2% viscous lidocaine for short-term relief. The lidocaine may be mixed with equal volumes of diphenhydramine and a soothing covering agent such as Maalox (Novartis Consumer Health, Inc., Fremont, MI). The MASCC/ISOO guidelines suggest that 0.2% morphine mouthrinse and 0.5% doxepin mouthrinse may be effective to treat pain due to oral mucositis [43]. A number of other topical mucosal bioadherent agents are also available that are postulated to reduce pain by forming a protective coating over ulcerated mucosa. Of these, sucralfate is the most widely studied. Based on strong evidence of lack of efficacy, the MASCC/ISOO guidelines recommend against the use of sucralfate mouthwash for the prevention or treatment of oral mucositis in patients receiving chemotherapy, RT, or concomitant chemoradiation [43]. In addition to the use of topical agents, most patients with severe mucositis require systemic analgesics, often including opioids, for satisfactory pain relief. The MASCC/ISOO guidelines recommend patient-controlled analgesia with morphine for patients undergoing hematopoietic cell transplantation and suggest that transdermal fentanyl may be effective for oral mucositis pain in patients receiving conventional or high-dose chemotherapy [43]. Likewise, the pain of GI mucositis should be treated symptomatically, with the added benefit that the opioids can improve diarrhea. Previous MASCC/ISOO guidelines also recommended the use of either ranitidine or omeprazole for the prevention of epigastric pain following chemotherapy [42].

## Nutritional Support

Nutritional intake can be severely compromised by mucositis. Furthermore, taste changes can also occur secondary to chemotherapy and/or radiation therapy [44, 45]. The patient's nutritional intake and weight should be monitored regularly over the course of cancer therapy. A soft diet and liquid diet supplements are often more easily tolerated than a normal diet. A gastrostomy tube is sometimes placed prophylactically, especially in patients receiving head and neck radiotherapy. In patients undergoing hematopoietic cell transplantation, total parenteral nutrition is usually given via an indwelling catheter such as a Hickman line.

## Specific Interventions for Oral Mucositis

### Cryotherapy

The use of cryotherapy, in patients receiving bolus doses of chemotherapeutic agents with short half-lives, reduces the severity of oral mucositis. Ice chips are placed in the mouth, beginning 5 min before administration of chemotherapy and replenished as needed, usually for up to 30 min. This effect is likely to be mediated through local vasoconstriction and reduced blood flow, resulting in decreased delivery of the chemotherapeutic agent to the oral mucosa. The MASCC/ISOO guidelines recommend the use of cryotherapy to reduce oral mucositis in patients receiving bolus doses of 5-fluorouracil and suggest cryotherapy in patients receiving high-dose melphalan as conditioning for hematopoietic cell transplant [46].

### Growth Factors

Recombinant human keratinocyte growth factor-1 (Palifermin, Biovitrum, Stockholm, Sweden) significantly reduced the incidence of WHO grade 3 and 4 oral mucositis in patients with hematologic malignancies (e.g., leukemia, lymphoma, and multiple myeloma) receiving

high-dose chemotherapy and total body irradiation before autologous hematopoietic cell transplantation [47]. Based on this, the MASCC/ISOO guidelines recommend the use of this growth factor in this specific population [48]. Palifermin has been approved by the United States (US) Food and Drug Administration (FDA) for patients with hematologic malignancies receiving myelotoxic therapies requiring hematopoietic cell support. Use of this growth factor has not been approved in patients with solid tumors.

### Laser Therapy

Several clinical trials have reported that intraoral low-level laser therapy reduces the severity of oral mucositis. Animal studies suggest that low-level laser therapy has an anti-inflammatory effect and promotes wound healing [49, 50]. Based on the evidence, the MASCC/ISOO guidelines recommend the use of low-level laser therapy for the prevention of oral mucositis in patients receiving high-dose chemotherapy for hematopoietic cell transplant. In addition, the guidelines suggest the use of low-level laser therapy for the prevention of oral mucositis in patients receiving head and neck radiation therapy without concomitant chemotherapy [51].

### Anti-inflammatory Agents

Benzydamine hydrochloride (MGI Pharma) is a nonsteroidal anti-inflammatory drug that inhibits pro-inflammatory cytokines including TNF-α. In one phase III trial, benzydamine hydrochloride mouthrinse reduced the severity of mucositis in patients with head and neck cancer undergoing radiation therapy of cumulative doses up to 50 Gy radiation therapy [52]. Based on this and the previous studies, the MASCC/ISOO guidelines recommend the use of this agent in patients receiving moderate-dose radiation therapy (up to 50 Gy) without concomitant chemotherapy [53]. However, this agent has not received approval for this use from the US FDA; furthermore, most patients with head and neck cancer receive well over 50 Gy radiation therapy, with concomitant chemotherapy.

### Antioxidants

Amifostine (Ethylol, MedImmune, Gaithersburg, MD) is thought to act as a scavenger for harmful reactive oxygen species. However, due to conflicting evidence, a MASCC/ISOO guideline could not be established regarding the use of this agent in oral mucositis in chemotherapy or radiation therapy patients [54].

## Therapeutic Interventions for GI Mucositis

Loperamide, the non-analgesic opioid, is the mainstay of treatment for radiation or chemotherapy-induced diarrhea. It can be given in a dose of up to 11 2.1 mg tablets per 24 h (i.e., 2.1 mg every 2 h during the day and every 4 h overnight) [42]. However, when this does not work, octreotide, in a dose of at least 100 micrograms subcutaneously, twice a day, is recommended [35]. A lactose-free diet may also help. Evidence for the emerging role of probiotics in prevention of chemotherapy and radiation-induced diarrhea allowed a new suggestion in the most recent guidelines, specifically that a probiotic containing *Lactobacillus* spp. may be beneficial in patients with pelvic malignancy [35].

Sulfasalazine is suggested for the prevention of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis [35]. The use of intravenous amifostine was recommended to prevent radiation proctitis and suggested for the prevention of esophagitis in patients receiving chemoradiation for non-small cell lung cancer [35]. In chronic radiation-induced proctitis with bleeding, the use of sucralfate enemas is suggested [35]. The panel also suggested hyperbaric oxygen therapy to treat radiation-induced proctitis [35].

## Targeted Anticancer Therapies

Some of the newer targeted anticancer agents are associated with oral and gastrointestinal side effects. mTOR inhibitors (e.g., everolimus) can cause painful oral ulcers that resemble aphthous

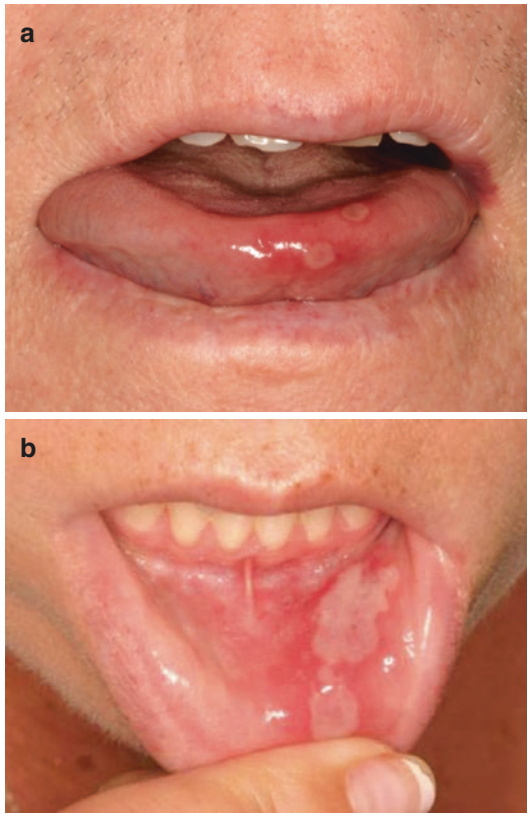


**Fig. 27.2** mTOR inhibitor-associated stomatitis. (**a**) Lesions are usually less than 1 cm, resembling minor recurrent aphthous stomatitis (canker sores). (**b**) Occasionally, lesions may be larger, resembling major recurrent aphthous stomatitis. From Pilotte AP et al. Clin J Onc Nurs 2011,15(5):E83–9, reproduced with permission; From Sonis S et al. Cancer. 2010;116:210–215, reproduced with permission from John Wiley & Sons

ulcers (canker sores). These typically present on nonkeratinized oral mucosa as oval or round ulcerations with a yellowish center and an erythematous border (Fig. 27.2a, b). Due to the different clinical presentation from conventional oral mucositis, this entity is referred to as mTOR inhibitor-associated stomatitis. A recent meta-analysis of phase III trials of everolimus for various solid tumors ($n$ = 1455) reported that the overall rate of stomatitis was 67% [55]. Most events were grade 1 or 2 (symptomatic but able to tolerate a modified diet). Nine percent of patients had grade 3 stomatitis (affecting ability to eat and drink adequately). Most first stomatitis events occurred within 8 weeks of initiating everolimus. The median time to the first episode was about 24 days after the initiation of everolimus. Overall, stomatitis led to dose-reductions or interruptions in 24% of all patients. Dose-reductions were more frequent in patients experiencing grade 3/4 stomatitis (87%) as compared to grade 1/2 stomatitis (17%) [55]. Topical steroids have been found to be effective for the prevention and treatment of these lesions. The prophylactic use of 10 mL (1 mg) dexamethasone mouthrinse (swish and spit) in breast cancer patients receiving everolimus has been recently reported to result in a markedly reduced incidence of stomatitis (21.2%) compared with historical controls (67%) [56]. Other targeted agents may also have oral side effects. Tyrosine kinase inhibitors (e.g., sunitinib, sorafenib) have been associated with oral sensitivity and burning but often without visible oral ulceration [57]. BRAF inhibitors (e.g., vemurafenib, dabrafenib) have been reported to cause hyperkeratotic oral mucosal lesions, accompanied by hyperkeratotic skin lesions [58]. Infrequent oral lichenoid mucositis has been reported with immune checkpoint agents (anti-PD-1, anti-PD-L1) [59].

Diarrhea is among the most frequent adverse events of many targeted therapies. It can occur as early as 3 days after initiation of therapy, be prolonged, and lead to treatment interruption. In patients receiving afatinib, diarrhea can occur in up to 83% and be severe in 18% [60]. The risk of diarrhea is also increased when targeted therapies are used in combination with conventional cancer therapies [61]. In the absence of evidence-based guidelines in this area, GI mucositis secondary to targeted therapies is treated in the same way as chemotherapy-induced GI mucositis [62]. Guidelines based on expert consensus are emerging, although are limited to a small number of agents [63]. However, given that there is some evidence of tachyphylaxis with the targeted agents, and even some suggestion of a similarity to ischemic colitis, withdrawal and reintroduction of treatment has been tried with some success, and the use of prophylactic loperamide is effective in some settings. However, without a clear understanding of the underlying mechanisms causing GI side effects, broadly applicable

preventative strategies are yet to be discovered. More research in this area is clearly required.

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# 28

# Diarrhea, Constipation, and Obstruction in Cancer Management

Lowell B. Anthony and Aman Chauhan

## Introduction

Gastrointestinal symptoms are frequently encountered in cancer patients and are commonly present not only as initial symptoms but also as side effects from cancer treatments. Diarrhea is an expected and manageable side effect from some cytotoxic and targeted agents. While constipation can be severe from analgesics, thalidomide, lenalidomide, and vinca alkaloids, management may vary depending upon anatomical considerations. The latter may include obstruction from adhesions, the underlying malignancy, or a combination of etiologies. The management of these adverse effects is reviewed.

## Diarrhea

Diarrhea induced by cytotoxic chemotherapy (CID) involving 5-fluorouracil (5-FU), capecitabine, irinotecan, and docetaxel can be dose limiting. CID incidence ranges from 30 to 87% depending upon the NCI Common Toxicity Criteria grade (1–4) and whether single or combination regimens are present [1]. Severe diarrhea can be significantly debilitating leading to dehydration, electrolyte abnormalities, secondary infections, and malnutrition. CID may lead to chemotherapy dose reductions resulting in shorter survival in some clinical investigations [2]. Loose stool frequency exceeding three per 24 h is considered by the NCI CTC as diarrhea [3].

## Etiology and Specific Agents

### 5-Fluorouracil

Cytotoxic therapies can damage the intestinal mucosa resulting in a loss of epithelium [4]. Repair of the damaged mucosa is influenced by 5-FU that induces mitotic arrest of the crypt cells [5]. Intestinal secretion exceeds the colonic resorptive capacity resulting in clinically significant diarrhea, electrolyte abnormalities, and dehydration.

Efficacy and toxicity of 5-FU are increased when given as a bolus with or without the biochemical modulator, leucovorin (LV), and used in many regimens and schedules [6]. Diarrhea from weekly 5-FU/LV has been reported with up to 50% of patients requiring IV fluids with elderly patients with myelosuppression and sepsis [7]. With palliative-intent chemotherapy, treatment is

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I. Olver (ed.), *The MASCC Textbook of Cancer Supportive Care and Survivorship*,
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usually withheld for >grade 2 diarrhea. Factors increasing the risk for 5-FU toxicity include an unresected primary tumor, prior CID, bolus 5-FU and LV with oxaliplatin, female gender, and being in the summer months [8–10]. Various pheno- and genotypic markers predicting life-threatening toxicity to 5-FU have been evaluated, but none have been incorporated into routine patient care.

Dihydropyrimidine dehydrogenase (DPD) is the initial catabolic enzyme for 5-FU. Partial DPD deficiency can produce life-threatening side effects to 5-FU therapy [11, 12]. DPD activity is more of a continuum rather than an absolute with complete DPD deficiency rate. Decreased DPD activity is more common in blacks and females [13]. Testing for DPD deficiency prospectively has been evaluated [14, 15]. In a 5-FU monotherapy prospective study, the sensitivity of DPYD*2A genotyping for overall toxicity was 5% with a positive predictive value for grade 3/4 toxicity of 46% [16]. Based on these findings, most cases of DPD deficiency are diagnosed following a severe 5-FU reaction. Management of these patients includes aggressive supportive care with vasopressors, parenteral nutrition, antibiotics, and granulocyte colony stimulating factors.

5-FU is usually dosed according to body surface area (BSA). An alternative dosing method, to improve the therapeutic index, is pharmacokinetically (PK) guided. In one prospective study, 208 metastatic colorectal cancer patients received 1500 mg/m$^2$ 5-FU over 8 h and LV. Patients were randomly assigned to either continue weekly BSA-based fixed dosing or PK-individualized dosing based upon a single 5-FU plasma concentration measurement at steady state [17]. Patients who were randomized to the PK-guided dosing regimen had significantly higher response rates (34 vs. 18%), longer median survival (22 vs. 16 months), and less toxicity, including diarrhea.

While incorporating PK-guided dosing into daily clinical practice seems intriguing, certain barriers remain. As the 5-FU/LV regimen chosen for this trial is not typical, additional data are needed regarding the potential benefits of PK-based dosing patients receiving more common 5-FU regimens either as a single agent or in combination with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Also, drug monitoring is labor-intensive and requires rapid processing. The latter may limit its incorporation into smaller clinical practices.

The combination of oxaliplatin and 5-FU (FLOX, FOLFOX) has become one of the most commonly used adjuvant and first-line regimens in colorectal cancer. The enterotoxicity associated with these regimens is dependent on the schedule of 5-FU administration. The incidence of grades 3 and 4 diarrhea is <20% when 5-FU is administered as a short-term infusion rather than daily or weekly boluses. Being female or aged more than 60 years are additional risk factors in predicting enterotoxicity [9, 18, 19].

Capecitabine, a prodrug, is considered an oral 5-FU equivalent. Following near complete intestinal absorption, capecitabine undergoes hepatic first-pass metabolism and is converted to its active moiety in three sequential enzymatic reactions. Its dose-limiting toxicities include diarrhea, hand-foot syndrome (HFS), and myelosuppression. Capecitabine's initially approved dose for the treatment of metastatic breast cancer was 2500 mg/m$^2$/day for 14 of every 21 days. Later studies combined with post-marketing surveillance suggested that a lower dose (starting at 2000 mg/m$^2$/day for 14 of every 21 days) offered improved tolerability without compromising efficacy. Large regional differences in capecitabine's therapeutic index exist [20]. These differences include population-specific pharmacogenomics, diet, and differences in lifestyle. Because of these issues, optimal capecitabine dosing for North American patients remains to be determined with titration to tolerability an option in all usage.

Combining oxaliplatin with capecitabine (CAPOX, XELOX) has become intensely investigated. XELOX (capecitabine 1000 mg/m$^2$ b.i.d. for 14 days plus oxaliplatin 130 mg/m$^2$ on day 1 every 3 weeks) was compared to FOLFOX (continuous infusion of 5-FU at 2250 mg/m$^2$ over 48 h on days 1, 8, 15, 22, 29, and 36 plus oxaliplatin 85 mg/m$^2$ on days 1, 15, and 29 every 6 weeks) in a phase III trial of patients with metastatic colorectal cancer. A significantly lower rate of grades 3 and 4 diarrhea was observed with XELOX (14 vs. 24%); however, a significantly higher rate of

grade 1 or 2 hyperbilirubinemia (37 vs. 21%) occurred.

Capecitabine combinations with epirubicin and either cisplatin or oxaliplatin have been evaluated in esophageal and gastric cancers. A phase III comparison of regimens containing epirubicin with either cisplatin or oxaliplatin and either 5-FU or capecitabine reported a rate of grade 3/4 diarrhea of 12% EOX (day 1 epirubicin 50 mg/m$^2$, day 1 oxaliplatin 130 mg/m$^2$, and b.i.d. capecitabine 625 mg/m$^2$) [21].

## Irinotecan (CPT-11)

Immediate side effects occurring during or several hours following irinotecan infusion are cholinergically mediated [22]. Late effects from irinotecan result from its metabolite's, SN-38, toxic effect on the intestinal mucosa [23]. This metabolite is formed by hepatic glucuronidation followed by biliary excretion. Deconjugation by intestinal bacteria results in a direct toxic effect on the colonic mucosa [24, 25]. Altered hepatic glucuronidation as present in Gilbert's syndrome patients results in severe irinotecan intestinal toxicity [26]. Antibiotics inhibiting intestinal deconjugation protect against the mucosal injury, and common genetic polymorphisms of the UDP-glucuronyltransferase enzyme influence diarrhea severity [27].

Irinotecan's dose-limiting toxicities are diarrhea and leucopenia. Grades 3/4 CID occurred in 31% of patients with all grades of diarrhea developing in 50–88%. Primary prophylaxis with loperamide lowered the incidence of CID and allowed irinotecan to become the second cytotoxic agent approved in the management of colorectal cancer. Adherence to aggressive use of loperamide is imperative in irinotecan's use. The median onset of late diarrhea is 6–11 days following irinotecan's dosing with the 3-week (350 mg/m$^2$) and weekly (125 mg/m$^2$) schedules, respectively [28, 29]. Comparing two dosing schedules in a randomized trial, irinotecan's antitumor efficacy was similar between the every 3 weeks and the every week schedule, but the incidence of severe CID was significantly less for the 3-week regimen (19 vs. 36%). Cholinergic symptoms were, however, significantly lower with the weekly schedule (31 vs. 61%) [30].

Irinotecan's active metabolite, SN-38, is hepatically glucuronidated by the polymorphic enzyme uridine diphosphoglucuronosyltransferase 1A1 (UGT1A1). Intratumoral UGT1A1 enzymatic activity is reduced in 10% of the North American population who inherit genetic polymorphisms such as the UGT1A1*28 allele (Gilbert's syndrome). Some studies have shown that both homozygotes and heterozygotes to this specific allele have had significantly higher rates of toxicity to irinotecan [30]. Even though genetic testing is available, the clinical relevance of identifying homozygotes remains unclear as the absolute risk of increased treatment-related toxicity in homozygotes is small.

Combination irinotecan regimens such as FOLFIRI (short-term infusional 5-FU/LV) result in less severe GI and bone marrow toxicity than IFL (bolus 5-FU/LV) [31].

## Large and Small Molecule EGFR Inhibitors

Epidermal growth factor receptor (EGFR)-directed monoclonal antibodies (MoAb) such as cetuximab ($IgG_1$ class) and panitumumab ($IgG_2$ class) bind to the extracellular domain of the receptor and competitively inhibit ligand binding. In contrast to the small molecule EGFR inhibitors that act intracellularly, MoAb-related diarrhea is generally not as severe. Single-agent cetuximab treatment in 346 metastatic colorectal cancer patients caused any grade diarrhea in 12.7% [32]. Although the incidence of significant diarrhea in metastatic colorectal cancer patients treated with the combination of cetuximab and irinotecan was reported to be 81.2% ($n$ = 518 of 638) in a Phase III clinical trial, only 28.4% ($n$ = 181) experienced grades 3 or 4 [33]. In a lung cancer phase II trial, 22.7% of patients reported diarrhea (all grades) with 1.5% experiencing grade 3 or 4 [34].

The incidence of any grade diarrhea in the panitumumab phase III registration trial of best

supportive care (BSC) with or without panitumumab was 21 vs. 11%, respectively. Grade 3 diarrhea incidence was 1 vs. 0% (BSC + panitumumab vs. BSC) [35]. These data have been confirmed by other investigators evaluating panitumumab as monotherapy [36].

Combining MoAb that target the vascular endothelial growth factor (VEGF) receptor with EGFR-targeted MoAb and cytotoxic chemotherapy resulted in grade 3/4 diarrhea as being the dose-limiting event (24% double MoAb + FOLFOX vs. 13% VEGF-MoAb + FOLFOX). Dose reductions and delays were observed with the double MoAb therapy and were most likely the cause of the significant decrease in the median survival [2].

Small molecule tyrosine kinase inhibitors (TKIs) such as erlotinib, lapatinib, and gefitinib that target the intracellular epidermal growth factor pathway(s) have diarrhea as a predictable and manageable adverse event in up to 60% of patients [37–40]. All diarrheal grades have been reported in up to 60% with grades 3 and 4 <10% of patients. In general, the diarrhea is easily managed with loperamide followed by dose reduction and/or treatment delay.

Combining targeted agents such as the small molecule TKIs with cytotoxic chemotherapy or radiotherapy may result in overlapping toxicities with diarrhea having been a significant dose-limiting toxicity in several clinical trials [41, 42].

## Multikinase Inhibitors

Agents that target multiple intracellular signaling pathways include sorafenib, sunitinib, and imatinib. These oral agents are indicated for multiple neoplasms as monotherapy. Sorafenib, a VEGF pathway multikinase inhibitor (MKI), causes all-grade diarrhea in 30–45% of patients treated at the approved dose of 400 mg twice daily. Grades 3/4 diarrhea occurred in <5% [43]. In the sorafenib registration trial for renal cell cancer, the incidence of all-grade diarrhea (sorafenib vs. placebo) was 43 vs. 13% and 3/4 2 vs. 1% [44]. In other disease states such as hepatocellular cancer, all-grade diarrhea incidence from sorafenib ranges from 66 to 73% for Child's class B and A, respectively, and 100% in Child's class C, though the patient numbers were small [45].

Another oral MKI is sunitinib, a VEGF and platelet-derived growth factor (PDGF) receptor TKI. Sunitinib is typically dosed at 50 mg daily for 4 weeks followed by a 2-week rest. All-grade diarrhea from sunitinib in various solid tumor patients ranged from 30 to 60% with grade 3 diarrhea incidence range of 3–6% [46–48]. Therapy with imatinib, a Bcr-Abl protein TKI, active in CML and gastrointestinal stromal tumor, causes all-grade diarrhea in approximately 30% of patients [49].

## Immune Checkpoint Inhibitors

Immunotherapy has taken the world of oncology by storm. At present there are about 20 immune checkpoint inhibitors either approved or in drug development pipeline and over 800 registered clinical trials studying these agents. Immune checkpoint inhibitors work by making the host immune system aware of tumor cells by blocking immune evading signaling proteins like PD-1 and PD-L1. The unique mechanism of action confers great advantages over conventional chemotherapy especially with regards to toxicity. But as these drugs are being widely used, we are seeing a host of immune-mediated side effects. Colitis and diarrhea are among the commonest side effects associated with immune checkpoint inhibitors. A phase III study of nivolumab, a PD-1 inhibitor, as first line treatment for metastatic melanoma reported 16% ($n = 33$) incidence of any grade diarrhea among 206 patients with only 2 patients experiencing grade 3/4 diarrhea [50]. The recently published Keynote 24 study, a phase III clinical trial evaluating pembrolizumab as a first-line treatment in PD-L1-positive non-small cell lung cancer, noted 13.3% ($n = 22$) incidence of any grade diarrhea among 154 patients treated with pembrolizumab. Six patients were reported to have grade 3 or 4 diarrhea [51]. Ipilimumab, a CTLA-4 inhibitor, was studied in melanoma patients as a single agent as well as in combination with nivolumab. Out of 311 patients treated with ipilimumab alone, about 33.1% (103)

patients developed any grade diarrhea. Nineteen of these patients had grade 3 or 4 diarrhea. GI toxicity was much worse in the combination arm of ipilimumab plus nivolumab. Out of 313 patients treated with the combination, 44.1% ($n$ = 138) developed any grade diarrhea. Twenty nine of these patients had grade 3 or 4 diarrhea [52]. Toxicities associated with immune checkpoint inhibitors are usually not dose dependent, and grade 2 or greater toxicity warrants withholding the offending agent and administering a short course of steroids. Immune checkpoint inhibitors can be carefully restarted with close monitoring for relapse of side effects. Grade IV toxicity is an indication for permanent cessation of immune checkpoint inhibitors. Colitis refractory to standard steroid treatment has been treated with infliximab in some instances [53]. The long-term burden of gastrointestinal side effects is yet to be evaluated as the use of these agents spreads across various malignancies and newer combinations with other immunomodulatory agents or cytotoxic agents are tried.

### Other Targeted Inhibitors

Sirolimus, temsirolimus, and everolimus are inhibitors of the mammalian target of rapamycin (mTOR). The renal cell cancer everolimus registration trial reported an incidence of grades 1 and 2 diarrhea of 17% (vs. 3% in the placebo group), and grade 3 was only 1% (vs. 0% placebo) [54]. In a phase II everolimus clinical trial in pancreatic neuroendocrine cancer, the incidence of all-grade diarrhea was 39%, and grade 3 or 4 was 4%; in the group that also received octreotide with everolimus, the incidence of all-grade diarrhea was 14% with no grade 3 or 4 events [55].

Bortezomib, a proteasome inhibitor, induced diarrhea in approximately half of the multiple myeloma patients enrolled in the registrational trial. The incidence of grade 3 or 4 diarrhea in this trial was 8% [56]. Vorinostat, a histone deacetylase inhibitor active in cutaneous T-cell lymphoma, induced all-grade diarrhea in 52% of the patients enrolled in the registration trial. Severe diarrhea was rarely observed [57].

### Antibody-Drug Conjugate (ADC)

ADC are a novel class of drugs wherein a cytotoxic payload is linked to a targeted monoclonal antibody. ADC are designed to minimize the effects of chemotherapy on normal host cells. Currently FDA-approved ADC's include adotrastuzumab emtansine (TDM-1) for HER2-positive metastatic breast cancer and brentuximab vedotin, for relapsed Hodgkin lymphoma. Any grade diarrhea was noted in 23.3% ($n$ = 114) patients out of 490 patients treated with TDM-1 for progressive metastatic breast cancer. Only eight patients developed grade 3 or 4 diarrhea [58]. A double-blinded, phase III clinical trial of brentuximab for high-risk Hodgkin lymphoma reported a 20% ($n$ = 33) incidence of any grade diarrhea. Only 3 out of 167 treated patients developed grade 3 or 4 diarrhea [59]. Currently rovalpituzumab, an ADC directed against DLL-3, a NOTCH pathway ligand, is being studied in small-cell lung cancer. Phase I study results presented at ASCO 2016 were impressive in terms of efficacy, but the toxicity data from the Phase I study and currently ongoing Phase II study are awaited (NCT02674568).

## Clinical Assessment

The algorithm for CID evaluation and management is shown in Fig. 28.1a,b. The initial assessment of CID focuses on the history not only to begin formulating a differential diagnosis but also to assess diarrhea severity according to the

**a**

| Severity Grade | Definition |
|---|---|
| **Grade I** | <4 stools/day, More than baseline |
| **Grade II** | 4–6 stools/day |
| **Grade III** | >7 stools/day; incontinence |
| **Grade IV** | Life threatening consequences |

**Fig. 28.1** (**a**) Diarrhea grading. (**b**) Diarrhea management algorithm. (**c**) Octreotide protocol for refractory diarrhea

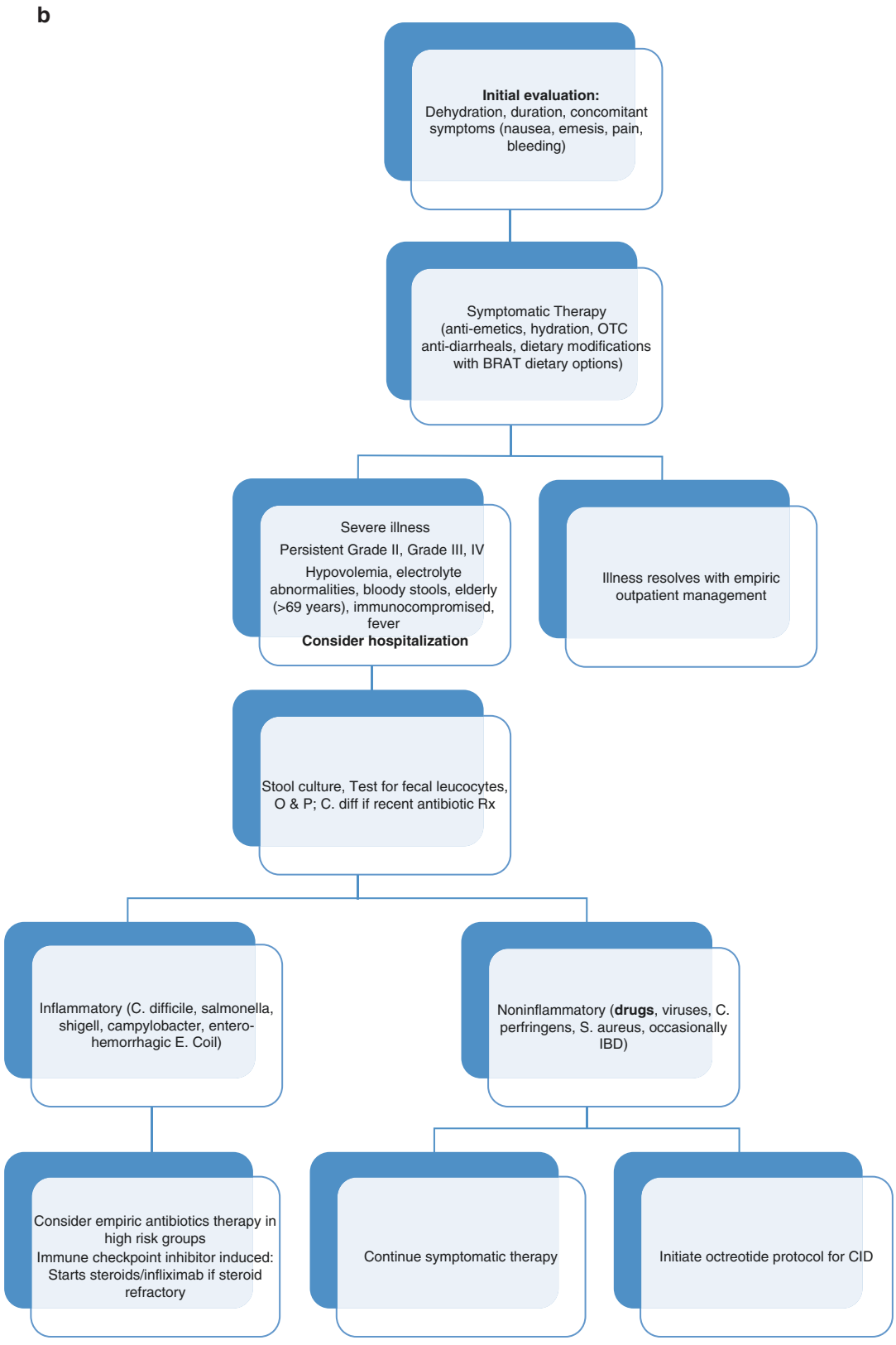


**Fig. 28.1** (continued)

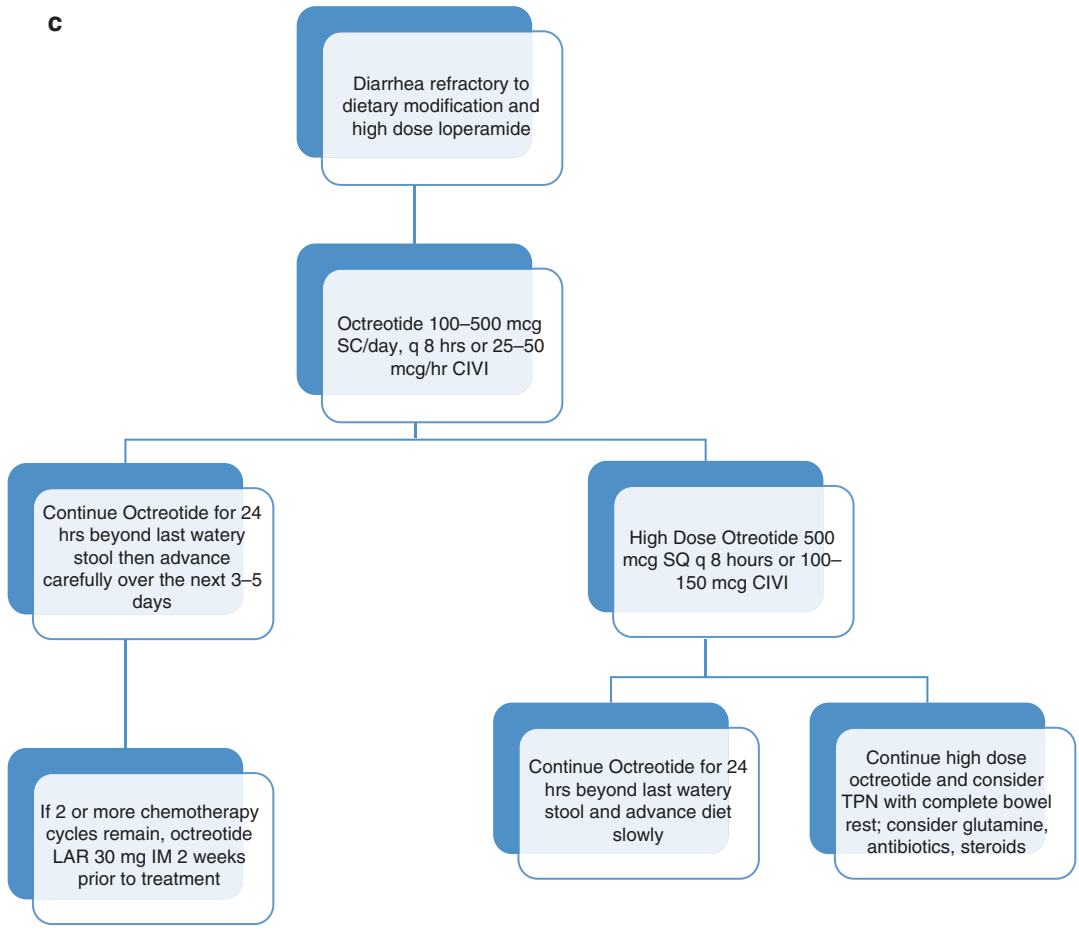


**Fig. 28.1** (continued)

NCI CTC grading system [3]. The quantity, quality, and duration of the diarrhea should be determined. Specific questions directed toward diet, drugs (including OTC and nutritional supplements), recent illnesses, and hospitalizations will provide insight into possible etiologies and exclude osmotic agents. Specific diets need to be considered as a temporary lactase deficiency may develop because the loss of the intestinal brush border is part of the pathophysiology of the cytotoxic agent-induced mucosal damage. Other food groups such as fruits may be taken with good intention but aggravate the underlying condition. The history may also uncover some issues relative to the cancer patient such as concomitant radiation, prior surgical procedures, and intestinal infections (e.g., *Clostridium difficile*, *Helicobacter pylori*). Finally, identifying the presence of pain, fever, dizziness, nausea, emesis, or bleeding should assist in triaging to establish the urgency and classifying the illness as self-limiting or of major complexity.

The physical examination should be focused on the vital signs with special attention to signs of volume depletion as indicated by hypotension, orthostatic blood pressure, pulse rate, skin "tenting," low jugular venous pressure, and nutritional status (temporal muscle wasting, etc.). Laboratory assessment includes a standard complete metabolic profile inclusive of blood glucose, albumin, complete blood count, and stool culture. Radiologic tests such as plain X-rays, ultrasound, and CT/MRI scanning would be determined according to the clinical scenarios. Consultative assistance with gastroenterology, infectious diseases, surgery, and other medical specialties

would be driven by the illness' severity including comorbidities and response to initial empiric intervention(s).

## Treatment

Prior to initiating definitive or empiric treatment, establishing the CID diagnosis is not only dependent upon identifying the specific antineoplastic agent(s) but also on the timing of treatment. In general, with the first occurrence of CID, outpatient management for the first 24 h is appropriate as the diet modification (nonpharmacologic) and OTC antimotility agents (pharmacologic) may be prescribed. Once CID symptoms are refractory to first-line (outpatient) intervention, physician assessment becomes important.

In palliative settings, the antineoplastic treatment may be either delayed or dose(s) reduced. Should hospitalization be required, initiating the octreotide protocol (see Fig. 28.1c) within the first 24 h of admission may shorten the hospital stay. With response to either low- or high-dose octreotide, the patient's hospital stay is usually limited to 2–3 days. For patients not responding within 48–72 h of admission, the differential diagnosis should be broadened and further work-up and nutritional support considered. Patients relapsing after initially improving usually do so by advancing the diet too quickly or discontinuing octreotide. To prevent conditioning and to improve the quality of life, the use of depot octreotide should be considered in patients with more than one additional chemotherapy cycle [60].

The initial drug therapy for CID is the opiates including loperamide (Imodium), diphenoxylate/atropine (Lomotil), and paregoric and deodorized tincture of opium (DTO). Loperamide and diphenoxylate/atropine are FDA-approved for diarrhea management and have a short onset of action. Treatment guidelines recommend loperamide initially as it is obtained OTC and may be more effective [61, 62]. Loperamide is initially administered at 4 mg followed by 2 mg every 4 h or after every loose stool. Higher-dose loperamide is 4 mg initially followed by 2 mg every 2 h or 4 mg every 4 h until CID has resolved for at least 12 h.

Octreotide acetate, a synthetic somatostatin congener, slows intestinal motility, decreases intestinal secretions, and stimulates intestinal absorption of water and electrolytes [63]. Octreotide is effective in the management of CID with dose titration as the optimal dose remains undetermined [64, 65]. The starting octreotide dose is 100–150 μg subcutaneously every 8–12 h [66]. Should symptoms not respond within 24 h, higher doses (500 μg SC every 8 h) may be more effective [67]. Octreotide is generally well tolerated with expected adverse effects being steatorrhea, abdominal cramping, and flatulence. The use of the long-acting formulation (LAR) of octreotide offers choices for patients having additional chemotherapy cycles. Similar to the immediate-acting octreotide, the optimal octreotide LAR dose remains uncertain [60].

## Constipation

Constipation is the slow movement of feces through the intestinal tract resulting in a decreased defecation frequency and is a common (50–87%) symptom in advanced cancer patients [68]. In 462 cancer patients, constipation was the third most common symptom (prevalence of 16% with 5% severe and 11% moderate) reported during cytotoxic chemotherapy [69].

Stool frequency of fewer than three per week and accompanied by pain or strain is considered pathologic. The etiology of constipation in the cancer patient is more likely to be multifactorial as primary, secondary, and iatrogenic causes are likely to be present. Primary causes include decreased fluid intake secondary to the debilitating illness, nausea, malaise, and depression. Low fiber diets may also contribute to these primary causes. Secondary causes may be obstructive lesions from adhesions, strictures, impaction, or masses. Dysmotility from an autonomic neuropathy, physical inactivity, diabetes, and metabolic derangements (hypercalcemia, hypokalemia) or from hypothyroidism or spinal cord impairment is an additional secondary etiology of constipation. Iatrogenic causes are from the expected complications of specific pharmacologic agents such as analgesics, antiemetics (ondansetron), and certain chemotherapy drugs.

Presenting symptoms of constipation include headache, abdominal pain and swelling, malaise, nausea, emesis, anorexia, and hemorrhoids. The pain from constipation may be of such severity that further analgesic therapy is significantly reduced or discontinued. The clinician should consider withdrawal symptoms as a potential additional complication of constipation management.

## Vinca Alkaloids

Even though constipation is present in approximately half of all cancer patients, constipation from chemotherapy is uncommon except for the vinca alkaloids such as vincristine, vinblastine, and vinorelbine. The vincas will induce constipation in approximately 25–30% of patients with grade 3 or 4 symptoms occurring infrequently (2–3%). The vinca alkaloids' gut motility shortly after administration (3–10 days) usually resolves but is not cumulative [70].

Up to one-third of cancer patients will experience constipation [71]. Grades 3 and 4 constipation is uncommon with hospitalization of patients suffering from adynamic ileus occurring infrequently (2–3%) [71, 72].

Vinca-induced constipation is dose-related with the greatest incidence occurring at doses above 2 mg. An example of the severity of vincristine-induced constipation is Hodgkin and non-Hodgkin lymphoma patients ($N$ = 104) treated with 90% of patients receiving doses >2 mg [73]. Severe constipation developed in 10% with improvement occurring within a few weeks after completing therapy.

## Thalidomide

Thalidomide therapy has a clinically significant incidence of constipation that is dose-related. In a clinical trial of patients with refractory myeloma and other diseases, constipation developed in approximately one-third of patients treated with 200 mg daily doses vs. 60% of those receiving 800 mg/day [74]. In a phase II clinical trial of thalidomide in high-grade glioma, constipation occurred in 19% without severe episodes [75]. Thalidomide-induced constipation is dose-dependent and develops within 2–4 days of drug initiation. Its severity is greatest in those patients older than 70 years and those receiving concomitant opioid therapy [76]. For patients developing constipation later in their treatment course, thalidomide-induced hypothyroidism should be considered.

## Therapy

Prevention through prophylaxis and patient education is critical in constipation management. The NCCN palliative care guidelines recommend screening for the presence of constipation during routine symptom assessment and placing it in the context of life expectancy [77]. Increasing fluid intake and physical activity may also improve bowel function. Increasing dietary fiber to 20–25 g/day for several weeks may assist some patients. Laxatives should be administered concomitantly with narcotics and at the initial signs and symptoms of constipation. Initiating laxative therapy with senna, bisacodyl, and docusate is common. Should resistance to these first-line agents develop, then magnesium salts, polyethylene glycol, sorbitol, and lactulose are therapeutic options [78, 79]. In one small study, colchicine was effective in improving bowel function in chronic constipation patients who had failed other therapies [80]. Prokinetic agents such as metoclopramide may be effective in patients without physical obstruction.

Recent advances in the management of analgesic-induced constipation include the 2008 FDA approval of methylnaltrexone, a pure peripherally acting opiate antagonist, for patients with advanced illnesses receiving palliative care. Blocking the opiate μ-receptor in the peripheral nervous system compartment alone, methylnaltrexone does not reverse the analgesic effect of opiates or induce withdrawal. The methylnaltrexone registration trial randomized patients between subcutaneous methylnaltrexone (0.15 mg/kg subcutaneous, every other day) and placebo. The methylnaltrexone-treated group exhibited significant efficacy (48% of methylnaltrexone-treated patients experienced

laxation within 4 h vs. 15% on the placebo arm) without altering central analgesia or inducing withdrawal [81]. Additional data are required to use this agent either prophylactically or reactively for analgesic-induced constipation.

Should medical therapy fail, total colectomy with ileorectal anastomosis can be considered [82]. See Fig. 28.2 for an algorithm for managing constipation.

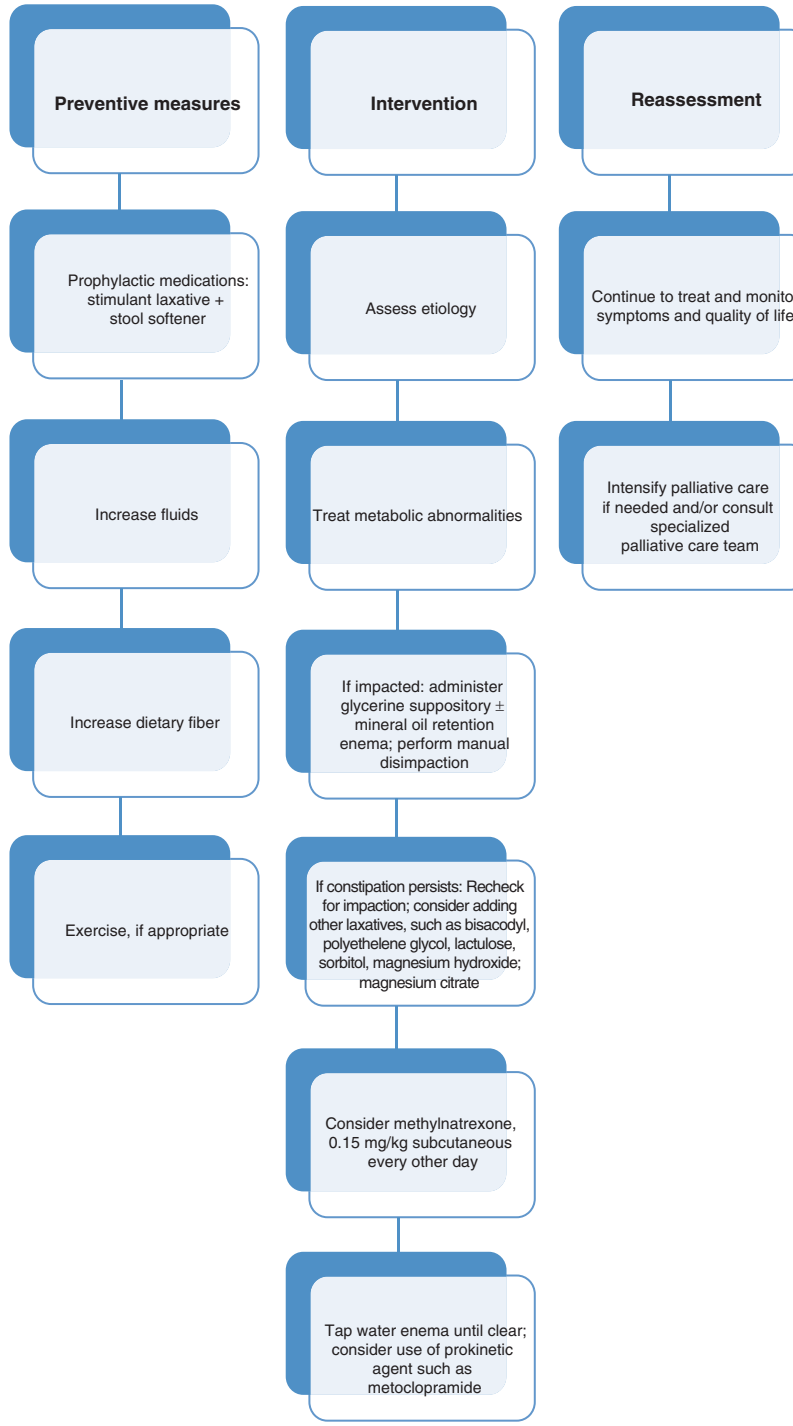


**Fig. 28.2** Constipation management algorithm (data from [77])

## Obstruction

Malignant bowel obstruction (MBO) occurs in approximately 3–15% of patients and usually signifies a short prognosis [83]. The symptoms are generally distressing with the diagnosis made clinically and confirmed with imaging modalities such as plain films or CT scans. Intervention is dependent upon life expectancy. For those patients with months to years to live, appropriate screening should be performed with reversible causes treated appropriately. Total parenteral nutrition may be considered prior to surgical intervention. Even though surgery is the primary treatment for obstruction from malignant disease, it is appropriate in selected patients with advanced disease and poor performance status to offer medical intervention only. This latter patient group generally has only days to weeks to live. Medical intervention includes the use of opioid analgesics, antiemetics, anticholinergics, somatostatin congeners, and steroids. Using these agents in combination may offer improved symptom control [83–85]. The NCCN guidelines suggest an algorithm directed by the patient's expected survival in the context of the initial assessment and establishment of specific goals followed by appropriate intervention(s) followed by reassessment [84] (Fig. 28.3).

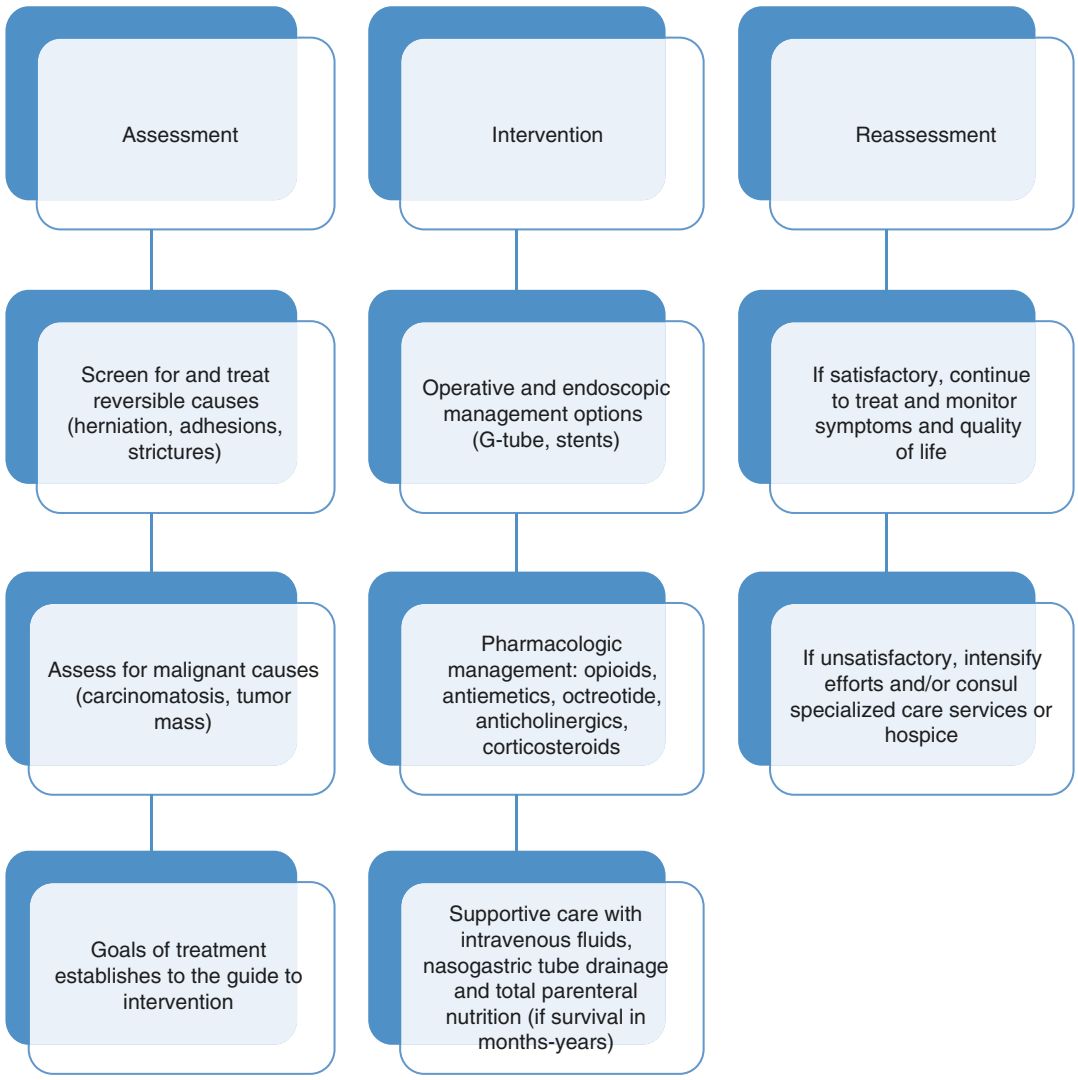


**Fig. 28.3** Malignant bowel obstruction algorithm (data from [77])

### Corticosteroids

By reducing the peritumoral inflammation and edema, intestinal transit improves. Reduction in water and salt secretion also occurs with steroid therapy. Because of the low cost, convenience, and good tolerability, corticosteroids are frequently prescribed in the palliative care setting for MBO [86]. Steroids are also the mainstay of treatment in immune checkpoint inhibitor-related diarrhea and colitis.

### Anticholinergics

The antisecretory effects of the anticholinergics are desirable pharmacologic effects in MBO management. Even though mostly used in combinations, the anticholinergics, such as hyoscine butylbromide, hyoscine hydrobromide, and glycopyrrolate, are frequently used in improving MBO symptoms through muscarinic receptor inhibition producing ganglionic neural transmission impairment.

### Octreotide

Somatostatin congeners, such as octreotide, reduce intestinal secretions and slow motility through their direct and indirect actions [63]. The initial report of using octreotide in MBO was in a 40 patient cohort with only two patients surgically managed [87]. Subsequent prospective randomized trials compared octreotide therapy to hyoscine butylbromide. These trials all reported outcomes favoring octreotide [88–90]. Combining octreotide with other supportive care agents may offer improved outcomes, but its optimal use in the MBO setting remains undefined [84, 91]. The use of the LAR of octreotide for MBO management has been reported in small numbers of patients, but for patients with an anticipated longer survival (>45–60 days), depot octreotide may offer advantages [92, 93].

### Telotristat Ethyl

Telotristat is a first in class tryptophan hydroxylase inhibitor and has been recently studied in a large placebo-controlled phase III clinical trial ($n$ = 135) for the management of carcinoid syndrome. Forty-four percent of study patients treated with telotristat were noted to have >30% reduction in bowel movement frequency. Telotristat use was also associated with a statistically significant reduction in mean urinary 5 HIAA. Based on the results of this trial, an FDA approval for the use of telotristat in somatostatin analog refractory carcinoid syndrome patients is anticipated [94].

## Summary

An algorithm for MBO management is shown in Fig. 28.3. Following MBOs initial assessment and decision to proceed with medical intervention, the decision regarding the best route(s) of drug administration is necessary. As the oral route is generally contraindicated, sublingual, intravenous, subcutaneous, rectal, transdermal, and intramuscular routes are the options depending upon specific drug formulations. Analgesic choices are usually the opioid class that could worsen a partial obstruction and constipation symptoms. Antiemetic choices should exclude the promotility agents such as metoclopramide that may be of benefit in partial bowel obstruction. Octreotide should be considered early in MBO management with initial subcutaneous doses at 150 μg every 8–12 h with dose titration to 300 μg every 8–12 h. Alternatively, continuous intravenous or subcutaneous infusions are options, and with more chronic use, octreotide LAR at 20–30 mg intramuscularly every 30 days is suggested. Combining analgesics, antiemetics, and octreotide with the anticholinergics and corticosteroids would be considered the maximal medical effort in relieving MBO symptoms. Corticosteroids administered up to 60 mg/day of dexamethasone or its equivalent should be discontinued if no improvement is noted in 3–5 days.

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# Ascites

29

Rohit Joshi and Hooi Wen Hong

## Introduction

Ascites is the pathological accumulation of fluid in the abdominal cavity caused by an imbalance of fluid in and out of the blood and lymphatic vessels. Cirrhosis leading on to portal hypertension accounts for nearly 80% of the cases of ascites [1]. However, malignant and infectious causes are also common. Cancer-induced ascites is present in about 10% of all patients [2]. Ascites in patients with cancer is caused by the metastatic spread to the peritoneum in 50% of the cases, lymphatic invasion in 20%, portal venous compression and liver invasion in 15%, and the combined effect of metastatic spread and liver invasion in 15% [3]. Advanced cancer accounts for about 10% of ascites, and the 1-year survival is less than 10% [4]. Palliation of ascites is important for holistic patient management.

Multivariate analyses show significantly shortened survival in patients with liver metastases and elevated serum bilirubin, while ovarian cancer is a significant independent predictor of prolonged survival [5]. The median survival after the diagnosis of malignant ascites was only 20 weeks from the time of diagnosis of ascites. However, tumors of ovarian and lymphatic origin have better mean survivals (32 and 58 weeks, respectively) [6].

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## Anatomy

The peritoneum lines the abdominal and pelvic cavity (parietal peritoneum) and covers the intra-abdominal organs (visceral peritoneum). It consists of mesothelial tissue with squamous epithelium facing the abdominal cavity, which is supported by an inner layer of tissue, called the lamina propria. The squamous epithelium is not a closed layer but contains foramina allowing macromolecules and cells to enter the abdominal cavity. Furthermore, plasma filters into the abdominal cavity via the peritoneal capillaries and drains off via open endings of lymphatic channels in the serosa. In the healthy state, approximately 50–100 mL of fluid fills the peritoneal cavity allowing the organs to slide freely over each other.

## Etiology and Pathogenesis

Chronic liver disease with portal hypertension, congestive cardiac failure, tuberculosis, and malignancy are important causes of ascites. Various causes of ascites are shown in Table 29.1 [7].


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**Table 29.1** Causes of ascites

| | |
|---|---|
| **Hepatic causes** | Portal hypertension<br>Chronic cirrhosis<br>Hepatic venous outflow obstruction |
| **Systemic causes** | |
| *Cardiac* | Congestive cardiac failure<br>Constrictive pericarditis |
| *Renal* | Nephrotic syndrome |
| *Rheumatological* | Systemic lupus erythematosus |
| *Endocrinological* | Thyroid myxedema |
| *Infectious* | Tuberculous peritonitis<br>Spontaneous bacterial peritonitis<br>Parasites<br>Fungal |
| *Malignancies* | Peritoneal carcinomatosis<br>Lymphomas<br>Leukemias |
| **Miscellaneous causes** | Chylous ascites<br>Pancreatic ascites<br>Severe hypoalbuminemia (e.g., malnutrition) |

The most common cancers associated with ascites are adenocarcinomas of the ovary, breast, colon, stomach, and pancreas. The cancer type largely influences the sites of abdominal metastases and the cause of the ascites.

Potential causes of ascites in patients with cancer include peritoneal carcinomatosis, malignant obstruction of draining lymphatics, portal vein thrombosis, elevated portal venous pressure from cirrhosis, congestive heart failure, and peritoneal infections [8, 9]. Studies have shown that malignant effusions arise in part from increased production and activity of vascular endothelial growth factors (VEGFs). VEGFs increase vascular permeability and establish an ideal environment for the accumulation of malignant effusions [10]. The presence of portal hypertension also contributes to the development of ascites in patients who have cirrhosis.

Hypoalbuminemia (common in cancer patients due to poor dietary history and catabolic effects of the malignancy) reduces plasma oncotic pressure and may lead to transudation from the vascular to peritoneal compartment. This also causes loss of fluid from the vascular compartment into the peritoneal cavity.

## Clinical Manifestations

The manifestation of symptoms depends on the amount of fluid, rapidity of fluid accumulation, and the cause of ascites.

Patients often notice an increase in abdominal girth, peripheral swelling, and edema, after at least 2 L of fluid has accumulated in the abdomen. Patients with massive ascites are often malnourished, have muscle wasting, weight loss, and excessive fatigue.

Patients often first seek medical attention because of abdominal discomfort, pain, breathing difficulty, or early satiety. They may also complain of reduced appetite, nausea, vomiting, lower extremity edema, weight gain, and reduced mobility [9].

If present, an umbilical nodule (Sister Mary Joseph nodule) suggests cancer as a possible cause of ascites.

Abdominal pain may be due to a combination of factors including nerve invasion by the tumor, stretching of the liver capsule, or stretching of the abdominal wall.

## Diagnosis

The diagnosis is based upon the clinical setting, imaging tests, and ascitic fluid analysis [11]. Patients with malignancy may have minimal fluid, which is picked up during investigations.

Ascites needs to be differentiated from abdominal distension due to causes like gross obesity, gaseous distention, bowel obstruction, abdominal cysts, or masses. The diagnosis may be obvious in a patient with massive ascites, but when only a small or moderate amount of fluid is present, the accuracy of physical assessment is only about 50%, even by experienced gastroenterologists [12].

Flank dullness that is present in nearly 90% of the patients with nonloculated ascites is the most sensitive physical sign. Shifting dullness on percussion is more specific but less sensitive than flank dullness for the detection of ascites. A fluid thrill or wave may be demonstrable in cases of tense ascites. Occasionally, massive ovarian or

hydatid cysts and pregnancy with hydramnios can masquerade as ascites. The puddle sign (the patient is examined while placed in a knee-elbow position; one flank is percussed while a stethoscope is placed over the most dependent portion of the abdomen and gradually moved toward the flank opposite to the percussion; a sharp increase in the intensity of the sound indicates the level of fluid) reported to detect as little as 120 mL of fluid clinically requires the patient to be in the knee-elbow position during examination. The utility of puddle sign and auscultatory percussion for detecting ascites has been assessed using ultrasound of the abdomen as gold standard. It was observed that auscultatory percussion has a greater sensitivity (66 vs. 45%) but a lower specificity (48 vs. 68%) than the puddle sign [13].

Radiologic studies are useful in detecting small amounts of ascitic fluid as well as helpful in assessing the etiology of ascites. Ultrasonography is the commonest and most convenient investigation for diagnosing ascites [11]. It does not require exposure to radiation or use of contrast and may detect as little as 100 mL of intraperitoneal fluid.

Depending on the clinical setting, computed tomography (CT) or magnetic resonance imaging (MRI) scans are excellent investigations. CT or MRI scans provide much more detailed information about the abdomen and pelvis, which may be difficult to obtain on ultrasonography. In patients with carcinomatosis or inflammatory peritonitis, a contrast enhanced CT or MRI scan may demonstrate enhancement of the peritoneal lining.

Clear ascitic fluid (translucent or yellow) is usually caused by portal hypertension and cirrhosis, infections cause the fluid to turn cloudy (due to the presence of high number of cells), milky fluid indicates chyle (triglyceride concentration greater than serum and greater than 200 mg/dL), and blood-stained fluid (red cell concentration of >10,000 cells/$mm^3$) may suggest cancer (Table 29.2).

The next step in the evaluation of the patient with ascites of unknown etiology is to differentiate those causes arising from portal hypertension (usually cirrhosis) from other causes (including malignancy). This is supported by the serum-to-ascites albumin gradient (SAAG), that is, the difference between serum albumin and ascitic fluid albumin [14]. A SAAG value of less than 1.1 signifies a nonportal hypertension etiology of the ascites. An ascites-to-serum ratio of LDH greater than 1 indicates that the enzyme is actively being produced in the ascitic fluid and suggests malignancy.

**Table 29.2** Tests performed on ascitic fluid

| Routine tests | Other tests |
|---|---|
| Total protein | Gram's stain and culture |
| Albumin | AFB smear and culture |
| Cell count | Malignant cytology |
| | Amylase |
| | Lactate dehydrogenase |
| | Triglycerides |
| | Glucose |
| | Adenosine deaminase |

The detection of tumor cells by cytology remains the gold standard for the detection of malignancy. For patients with peritoneal carcinomatosis due to cellular exfoliation into the ascitic fluid, malignant cells can be detected nearly 100% of the time [15]. The overall sensitivity for cytology smears for the detection of malignancy-related ascites is between 40–75 and 58–75% [16].

A more definitive diagnosis can also be ascertained by performing immunohistochemistry studies on the malignant cells or a cell block.

Ascites in the setting of probable cancer of an unknown primary may require biopsies via laparoscopy or laparotomy, as both are extremely sensitive for picking up peritoneal carcinomatosis. Omental biopsies can also be performed under ultrasound or CT guidance.

Patients with a known malignancy who develop ascites, in the setting of a non-ovarian cancer, have a very poor prognosis [17].

Patients with fever or abdominal pain along with ascites should also be evaluated for infectious causes of ascites [18].

## Treatment

In most instances, the treatment of metastatic cancer with ascites is palliative. Symptoms such as breathlessness, abdominal discomfort, fatigue, or loss of appetite may indicate a need for

initiating treatment. Therapies to manage fluid overload such as diuresis and abdominoparacentesis are relatively simple and can be combined with chemotherapy.

While diuretics are well tolerated, inexpensive, and simple to use [19], their use in the management of malignant ascites is controversial. Diuretics are not a definitive treatment option in malignant ascites as mechanisms affecting renal handling of excess fluid, and sodium may not be very effective in cancer treatment [20]. Also, malignant ascites results from increased fluid production due to the presence of tumor cells in the peritoneum and not from increased portal pressure [21].

A distal tubule diuretic such as spironolactone may be used alone or along with furosemide. Patients should weigh themselves daily to check for weight changes [8]. Excessive diuresis may cause hypotension, volume depletion, renal failure, and electrolyte abnormalities.

## Paracentesis

Large-volume paracentesis is the most commonly used low-risk method for palliation of malignant ascites [22]. It may rapidly improve shortness of breath and early satiety temporarily. Paracentesis provides relief in up to 90% of patients of malignant ascites [23]. Complications of large-volume paracentesis include dehydration, intravascular volume depletion, hypotension, and renal failure. Colloid replacement post large-volume paracentesis remains controversial. Randomized trials of albumin infusion have not been specifically performed for malignancy-related ascites. Repeated paracentesis may lead to bleeding, pain, infection, loss of protein, electrolyte loss, and bowel perforation [8].

## Peritoneovenous Shunting

Peritoneovenous shunting, introduced by LeVeen for alcoholic liver disease, is an option in managing malignant ascites [24]. Patients do not lose protein and thus maintain or improve intravascular oncotic pressures, which allow management of the ascites without hospitalization.

Rapid increase in intravascular volume from the infusion of a large amount of ascitic fluid may result in congestive heart failure, immediately after the placement of the pump. Performing a large-volume paracentesis immediately prior to the procedure can minimize this risk. Patients with peritonitis or those not able to handle large, rapid fluid shifts (patients with significant cardiac or renal dysfunction) would not be candidates for shunt placement.

Peritoneovenous shunting is effective in controlling ascites between 62 and 88% of the time [25]. However, there was no survival or quality of life advantage when peritoneovenous shunting was compared with repeated paracentesis [26].

## Drainage Catheters

Peritoneal ports and indwelling tunneled catheters can be considered for patients intolerant of repeated paracentesis. Patients are therefore able to perform repeated paracentesis by themselves at home. Potential complications include leakage around insertion site, catheter blockage, and infections [27]. Contraindications include multifocal loculated pockets of ascites, peritonitis, or uncorrected coagulopathy.

## Surgery

Peritonectomy is performed to remove various parts of the peritoneum, omentum, and some intra-abdominal organs, as a method of tumor cytoreduction [28]. Studies show modest success with this procedure in increasing survival time and in the prevention or recurrence of the development of malignant ascites; its use in the treatment of ascites, however, has not been well evaluated [29]. Peritonectomy is unlikely to help in patients with advanced, malignant ascites, as patients in this setting often have chemotherapy-refractory disease. Surgery is very helpful for conditions like ovarian and primary peritoneal cancer.

## Intraperitoneal Therapy

Intraperitoneal (IP) therapy is often administered in an attempt to deliver higher doses of chemotherapy locally [30]. The response to IP therapy to treat ascites and abdominal malignancies depends on the primary cancer and prior chemotherapy. IP administration of cisplatin has been studied extensively in the setting of ovarian cancer, and there is a suggestion that IP therapy has better efficacy than intravenous chemotherapy [31].

## Tumor-Targeted Treatment

For women with ovarian cancer, surgical debulking and chemotherapy are the best options available. More than one-half of patients with advanced ovarian cancer will have a complete remission from initial therapy, although only 10–30% will remain disease-free in the long term.

VEGF appears to have an important role in permitting tumors to attach to the peritoneum; some VEGF inhibitors have been reported to provide some palliation. There are some data to suggest that intraperitoneal bevacizumab is a relatively safe and effective way to palliate the symptoms of refractory malignant ascites [10]. There have also been reports of complete remission of ovarian cancer-induced intractable malignant ascites with intraperitoneal bevacizumab. Immunological analyses showed an initial increase in the proportion and function of CD8(+) effector T cells and a reduction of circulating T(reg) cells. Intraperitoneal administration induces an immune activation and appears promising in the treatment of malignant ascites [32]. Aflibercept, potent dual inhibitor of VEGF and placental growth factor administered intravenously, has also demonstrated efficacy of VEGF blockade in reduction of refractory malignant ascites. It is however associated with fatal gastrointestinal events [33].

Gemcitabine infusions may benefit patients with ascites from pancreatic cancer.

There are reports with good results of intraperitoneal administration of imatinib mesylate for ascites due to chronic myeloid leukemia [34] and rituximab for ascites due to lymphoma [35].

Patients with peritoneal mesothelioma and diffuse peritoneal adenomucinosis (pseudomyxoma peritonei) and selected patients with isolated peritoneal carcinomatosis from appendiceal or colorectal adenocarcinoma may benefit from aggressive cytoreductive therapy combined with intraperitoneal hyperthermic chemotherapy [36–38].

Catumaxomab is a trifunctional bispecific antibody directed against epithelial cell adhesion molecule (EpCAM) and T-cell antigen CD3 expressed on the majority of epithelial carcinomas. Patients with malignant ascites due to epithelial cancer treated with catumaxomab intraperitoneally resulted in a clinically relevant prolongation of puncture-free survival, defined as the time to the next therapeutic puncture or the time to death, whichever occurred first. Catumaxomab demonstrated a significant clinical benefit in patients with malignant ascites independent of the primary tumor (ovarian or non-ovarian) or other prognostic factors. Modest prolongation of survival was most notable in the gastric cancer population [39, 40]. In chemotherapy-refractory ovarian cancer patients, catumaxomab was the only medication that demonstrated improvement in puncture-free interval, time to first therapeutic puncture, and quality of life [41–43].

## Newer Treatments

Other newer treatments currently under investigations include matrix metalloproteinase inhibitors such as batimastat, interferon alpha, tumor necrosis factor-alpha, Corynebacterium parvum and streptococcal preparation of OK-432 agent, as well as radioimmunotherapy such as monoclonal antibody radiolabeled with 131I. There is limited data available to support usage of these newer agents outside of a clinical trial setting [44].

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# Hepatotoxicity and Hepatic Dysfunction

30

Ahmet Taner Sümbül and Özgür Özyılkan

## Introduction

It is believed that "primum non nocere" should be the main aim for clinicians. Most drugs combined in chemotherapeutic regimens have a narrow therapeutic index which can be narrower in patients with preexisting liver or other chronic systemic diseases. It is known that many of the cytotoxic drugs are metabolized by the liver, resulting in either inactivating drugs or activating prodrugs. Also novel therapies such as immunotherapeutics (antiCTLA4, antiPD1, and anti-PDL1 antibodies) have additional toxic effects to the liver related with autoimmunity. Therefore, every patient should be evaluated about liver effects during the entire treatment, and it is always not to be forgotten that in patients with preexisting liver disease, these drugs may cause more toxicity than usual or be less effective than usual. Generally, the incidence of hepatotoxicity is rare and mostly unpredictable and mostly not dose dependent. It typically occurs weeks to 2 months after initiating the therapy and multiple exposures to the drugs usually increase the risk.

The interaction between chemotherapy and the liver can be divided into three groups:

1. Drug-related direct hepatotoxicity and autoimmunity
2. Aggravating the underlying liver disease such as steatohepatitis and viral hepatitis
3. Affecting the metabolism and excretion of the drugs due to underlying liver disease (Gilbert disease)

Prediction of these effects can be achieved by careful assessment of the patient before initiating the therapeutic modality and follow-up.

A detailed patient history and physical examination for underlying liver disease should be the initial step, after which laboratory tests for assessing the liver's synthetic function (serum albumin, bilirubin, prothrombin time), tests for cellular injury (aspartate aminotransferase (AST), alanine aminotransferase (ALT)), tests helpful for assessing duct injury or cholestasis (alkaline phosphatase (ALP), gammaglutamyltransferase (γGT), and direct-reacting bilirubin), and tests showing underlying viral hepatitis (HBsAg, AntiHBs, AntiHCV) should be performed [1, 2] (Table 30.1).

However, neither total serum bilirubin levels nor transaminase levels are ideal parameters for assessing hepatic function or hepatic damage. Dynamic liver function tests (galactose elimination capacity, antipyrine test, bromosulphthalein clearance, etc.) are much more ideal, but using these tests in daily practice is very difficult [3]. It is not a rule, but increased age, female sex,

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**Table. 30.1** Common nonmalignant causes of abnormal serum liver enzymes

| |
|---|
| *Increased alkaline phosphatase* |
| Bone disease (e.g., Paget's disease; hyperparathyroidism—Any cause of increased bone turnover) |
| During fracture repair |
| Increased parathyroid hormone (via effects on bone) |
| Cirrhosis, especially during the course of primary biliary cirrhosis |
| Pregnancy associated (placental) |
| *Increased gammaglutamyl transferase* |
| Chronic alcoholism |
| Drug associated (e.g., phenytoin, barbiturates) |
| Iron overload |
| Fatty liver or obesity associated |
| Diabetes mellitus |
| Myocardial infarction |
| *Increased alkaline phosphatase and gammaglutamyl transferase* |
| Marker of extrahepatic cholestasis (multiple causes) |
| Cholecystitis or cholelithiasis |
| Drug associated |
| *Increased aspartate aminotransferase* |
| Rhabdomyolysis (cardiac or skeletal) |
| Hemolysis (aspartate aminotransferase present in erythrocytes) |
| Alcohol-associated hepatitis |
| Chronic liver disease or cirrhosis |
| *Increased aspartate aminotransferase and alanine aminotransferase* |
| Markers of hepatocellular injury |
| Alcohol-associated hepatitis |
| Hepatitis (i.e., viral, autoimmune, or drug-induced) |
| Drug associated (e.g., isoniazid, statins, and amiodarone) |
| Nonalcoholic steatohepatitis |
| Ischemic or hypoxic liver injury |
| *Increased bilirubin prehepatic (*i.e.*, unconjugated hyperbilirubinemia)* |
| Hemolysis |
| Gilbert's syndrome |
| Crigler-Najjar syndrome (types I and II) |
| Intrahepatic cholestasis (i.e., conjugated hyperbilirubinemia) |
| Drug associated (e.g., capecitabine and mitomycin) |
| Posthepatic (i.e., conjugated hyperbilirubinemia) |
| Biliary obstruction (any cause) |
| *Decreased albumin* |
| Decreased production |
| Malnutrition |
| Malabsorption |
| Liver failure (any cause, usually chronic) |
| Inflammatory states |
| Increased loss |
| Nephrotic syndrome |
| Protein-losing enteropathy |
| Burns |
| Congestive heart failure |
| Redistribution |
| Negative acute-phase protein (i.e., serum level decreases with intercurrent illness) |
| Ascites |
| *Increased international normalized ratio (INR) or prothrombin time* |
| Vitamin K deficiency |
| Warfarin administration |
| Coagulopathy (e.g., disseminated intravascular coagulation) |
| Liver disease or cirrhosis (any cause) |

metabolic syndrome, and concomitant drugs metabolized by the liver, tobacco, and alcohol usage increased the risk [4, 5]. Also there are some familial clusters which have been studied with a risk of 25% developing a drug reaction [6].

Radiologic imaging such as ultrasonography, computerized tomography, and magnetic resonance imaging could be useful in certain groups of patients. But, we should be aware that nearly 3% of the healthy population has abnormal liver function tests despite having a normal functioning liver. They are outside a two standard deviations (SD) compared with the normal distribution for laboratory reference ranges [7]. The other important issue is that liver function tests can fall into the normal range in patients with histopathologically proven liver disease. It has been reported that nearly 16% of patients with chronic hepatitis C infection and 13% with nonalcoholic fatty liver disease with proven histopathological damage have normal liver function tests [8–10].

During the evaluation period, the effects of cancer on liver function should be considered. Primary liver tumors, metastatic liver disease, or tumors next to the liver or biliary tree can affect liver function either by invading the normal liver tissue or by obstructing the bile tract. Also thrombosis of big vessels of the liver such as the portal vein or hepatic vein might occur because of a hypercoagulable state or compression or by direct infiltration of the vein.

## Underlying Liver Disease

At the initial evaluation of oncologic patients, considering the underlying liver disease is an important issue. Both chemotherapy and other therapeutic modalities may cause exacerbation of underlying liver disease, and also these patients may be more susceptible to drug-induced hepatotoxicity. Avoiding these risks can be achieved by a full diagnostic work up before deciding upon the therapeutic management of these patients [11]. This approach will help clinicians to make realistic choices and avoid using or making dose reductions of certain drugs because of their possible side effects.

Chronic infection with hepatitis B, hepatitis C, and nonalcoholic steatohepatitis are the most encountered preexisting liver diseases.

## Hepatitis B Infection

Hepatitis B is a chronic viral infection that may lead to cirrhosis and hepatocellular cancer. In the absence of prophylaxis, chemotherapy can cause hepatitis B reactivation in HbsAg (+) patients. Reactivation may cause serious liver failure that can end in fatal complications [12]. There have been many reports about HBV reactivation during the course of chemotherapy and chemoradiotherapy in different hematologic and solid organ malignancies [13]. The risk of reactivation reported in these series ranged between 20 and 50%. It is known that the risk is highest in patients who have stopped their therapy [14]. Studies focused on HbsAg (+) patients have shown that the risk is highest in men; younger age groups; HbeAg (+) patients; patients with high HBV DNA levels, lymphoma, or hematologic malignancies; and patients using corticosteroids, anthracyclines, and rituximab therapy [15]. These studies have also shown that there was no association between reactivation status and pretreatment serum ALT or bilirubin values. Reactivation of HBV during the course of chemotherapy can manifest itself by the development of jaundice, nonfatal hepatic failure, and death in 22, 4, and 4%, respectively [16] (Table 30.2). The increased risk of HBV reactivation associated with anti-CD20 agents (rituximab, ofatumumab, and obinutuzumab) has resulted in a consensus on the recommendation of routine prophylactic treatment recommendation in patients who are positive for either HBsAg or antiHbc.

**Table. 30.2** Risk factors associated with HBV reactivation in oncology patients

| |
|---|
| Male sex |
| Younger age |
| HbeAg positive or high levels of HBV DNA |
| Corticosteroid, anthracycline, rituximab-containing chemotherapies |
| Hematologic malignancies |

Management of patients with HBV infection has been investigated in these studies, and it has been shown that prophylactic usage of lamivudine is associated with fewer exacerbations and hepatic failure, although other nucleoside and nucleotide analogues such as adefovir dipivoxil, entecavir, telbivudine, and tenofovir have shown similar effects in these patients [17, 18]. It is not recommended to use interferon in this setting because it may cause much more bone marrow suppression and also can cause exacerbation of hepatitis. Patients should use these drugs at the beginning of chemotherapy, and they should be maintained for at least 6 months after the chemotherapy has ended.

## Hepatitis C Infection

Hepatitis C virus (HCV) infection may also cause cirrhosis and related complications. It often stays undiagnosed in asymptomatic carriers but may become clinically relevant during periods of immunosuppression or severe illness. Reactivation of HBV is well documented in patients receiving chemotherapy, but this is less clear for HCV. In the literature, there are a growing number of case reports documenting fulminant hepatitis after chemotherapy in patients with HCV infection [19, 20]. Most of these reports are related to hematologic malignancies; reactivation or exacerbation in patients being treated for solid tumors is rare. Because the clinical course of HCV infection differs from patient to patient and

the mainstay of therapy consists of interferon, there is no current recommendation about the preemptive therapy of HCV (+) patients concurrent with chemotherapy. Often, carefully following transaminase levels and the patient clinically is the mainstay of management.

## Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis is another important condition, which can be a preexisting disease that could be exacerbated by chemotherapy or could develop after chemotherapy. It is associated with fatty accumulation in hepatocytes and necroinflammatory activity [21]. Its prevalence increases in parallel with insulin resistance and obesity. Many case reports and studies demonstrate that chemotherapy is associated with steatosis and steatohepatitis [22]. Most of these reports are from patients with colorectal disease who were treated with neoadjuvant chemotherapy. In most of them, this situation is found to be related to increased postoperative morbidity and mortality [23].

## Chemotherapy-Induced Hepatotoxicity

Many drugs can cause alterations in liver biochemical tests, but most of them are not associated with progressive decline in liver function and can be ignored. If the elevation in serum alanine transferase (ALT) is greater than three times the upper limit of the normal value, it is accepted as drug-induced liver injury (DILI) [24, 25]. Standardized criteria have been developed by the National Cancer Institute and World Health Organization to grade the severity of chemotherapy-induced liver toxicity (Table 30.3). The time of onset and the response to rechallenge are important factors in diagnosing DILI. Most of the DILIs start between 5 and 90 days after starting therapy, and decreases of more than 50% of serum liver transferase concentrations are usually seen within 10 days of cessation. DILI usually resolves in 30 days, but it can be prolonged to 6 months. Rechallenging with the drug after resolution as well as observing the elevation in liver enzymes again is another sign of DILI. Liver biopsy is needed in rare conditions; this is for persistent liver enzyme elevation for more than 6 months and for distinguishing sinusoidal obstruction syndrome (hepatic veno-occlusive syndrome) from hyperacute graft vs. host disease in bone marrow transplants.

Hepatocyte necrosis and related hepatocellular failure are the most commonly seen scenarios of many toxic chemotherapeutics at the late stage. Some of the toxic effects are related to damage to the bile system (especially intrahepatic) or harmful effects on endothelial and stellate cells.

**Table 30.3** National Cancer Institute terminology for hepatotoxicity

| | Grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Alkaline phosphatase bilirubin GGT AST ALT liver failure portal hypertension | >ULN-2.5 × ULN | >2.5–5× ULN | >5–20× ULN | >20× ULN | |
| | >ULN-1.5× ULN | >1.5–3× ULN | >3–10× ULN | >10× ULN | |
| | >ULN-2.5× ULN | >2.5–5× ULN | >5–20× ULN | >20× ULN | |
| | >ULN-3× ULN | >3–5× ULN | >5–20× ULN | >20× ULN | |
| | >ULN-3× ULN | >3–5× ULN | >5–20× ULN | >20× ULN | |
| | | | Asterixis, mild HE | Moderate-severe HE; life-threatening consequences | Death |
| | | Decreased portal vein flow | Reversal retrograde portal vein flow associated with varices/ascites | Life-threatening consequences; urgent operative intervention needed | Death |

**Table. 30.4** Common causes of abnormality in liver biochemical tests in cancer patients

| |
|---|
| Direct toxic effect or interactions of chemotherapeutics |
| Viral hepatitis |
| Infiltration of the liver by tumor |
| Compressing bile ducts or big vessels |
| Radiotherapy-related injury |
| Sepsis or fungal liver disease related |
| Total parenteral nutrition and supportive care related |
| Paraneoplastic (e.g., Stauffer syndrome, associated with renal cell carcinoma) |
| Hemolysis |
| Cardiac failure related (congestive hepatopathy) |
| Graft vs. host disease |

Drug-induced hepatocellular injury is considered in two groups:

1. Predictable: Direct toxic effect of offending drug on liver tissue.
2. Unpredictable: This type of reaction is usually idiosyncratic.

Many of the chemotherapeutic drugs can affect liver function by idiosyncratic reactions [26]. These kinds of reactions are unpredictable and not dose dependent. Also, the latent period between exposure to the drug and the seriousness of the reaction varies between individuals (Table 30.4).

There are several factors affecting chemotherapy-induced liver injury:

- Age
- Gender
- Preexisting liver disease
- Concomitant medications
- Genetic susceptibility
- Hepatic tumor involvement
- Immunocompromised
- Malnutrition

## Selected Cytotoxic Agents and Their Effects

### Alkylating Agents

Nitrogen mustards, ethyleneamines, alkyl sulfonates, nitrosoureas, and triazenes are members of this group. Currently commonly used agents of this family are nitrogen mustards: cyclophosphamide, ifosfamide, melphalan, chlorambucil, and mechlorethamine.

These groups of drugs are uncommonly related to hepatotoxicity. Mechanisms of hepatotoxicity are less clear. Possible offending causes are reduction in glutathione levels and increased oxidative stress.

### Cyclophosphamide

Cyclophosphamide is metabolized by liver by the CYP2C9 and 3A4 enzyme systems and converted to 4-hydroxycyclophosphamide. This form appears in the circulation, and the blood concentration of this form is in equilibrium with aldophosphamide (the other metabolic product). Aldophosphamide can be metabolized by aldehyde dehydrogenase 1, and the end products can be either carboxyethyl phosphoramide mustard or phosphoramide mustard and acrolein by spontaneous cleavage. Phosphoramide mustard is the cytotoxic end molecule, and acrolein is the toxic metabolite especially for the endothelial cells. This molecule is blamed in both hepatic veno-occlusive disease and hemorrhagic cystitis. Despite the metabolism of cyclophosphamide by the liver, at usual doses it is an unusual cause of drug-induced liver injury. Rare case reports report cyclophosphamide associated liver toxicity. In most of them, this effect is attributed to an idiosyncratic reaction rather than direct toxicity [27].

Giving cyclophosphamide with azathioprine in the treatment of vasculitis has been associated with serious liver injury. Four cases are reported in the literature, and three of them were reported as serious liver injury with hepatic necrosis. In two of them, cyclophosphamide had been used in treatment previously without any toxic effect and elevations in liver enzymes started after adding azathioprine to the therapy [28].

Hepatic veno-occlusive disease associated with cyclophosphamide is usually related to higher doses especially in bone marrow transplants. Also other synergistic molecules and modalities such as busulfan, carmustine (BCNU), and total body irradiation can have some additive effect.

Susceptibility to hepatic toxicity is not increased in patients with underlying liver disease and hepatic dysfunction. (ref A2) A 25% dose reduction is recommended in patients with serum bilirubin concentration between 50 and 85 mmol/L or alanine aminotransferase higher than 180 IU/ml. The drug is not recommended in patients with serum bilirubin levels higher than 85 mmol/L [29].

## Ifosfamide

Ifosfamide is another alkylating agent that requires the hepatic p450 oxidase enzyme system for activation. It is very rarely associated with DILI. The liver dysfunction related to ifosfamide is found in only 3% in a meta-analysis of 30 studies including more than 2000 patients [30].

There is no recommendation about dose reduction in patients with mild to moderate hepatic dysfunction, but 75% dose reduction can be recommended in patients with severe hepatic dysfunction (serum ALT > 300 IU or bilirubin > 50 mmol/L) [31].

## Melphalan

Melphalan is an agent which is rapidly hydrolyzed in plasma. Nearly 15% of the unchanged drug is excreted in the urine, and the remaining part of the drug is excreted through stool. At standard doses, it is not hepatotoxic. But high doses of melphalan (140 mg/m$^2$), which can be used in high-dose regimens for bone marrow transplants, are reported to be associated with mild and transient elevations of serum aminotransferase and bilirubin [32]. No serious liver injury associated with melphalan has been reported, and there is no recommendation for dose modification of this drug in patients with hepatic dysfunction.

## Chlorambucil

Chlorambucil is another derivate of nitrogen mustard and a rare cause of hepatotoxicity. An autopsy series of patients with leukemia and lymphoma showed that three of six patients with cholestatic hepatitis were reported to have this associated with chlorambucil [33]. However, it is important to keep in mind that this is an old review and at the time of publication there were no tests for chronic hepatitis. In another case, reported liver enzymes rose and skin rashes recurred after rechallenging with chlorambucil [34]. There is no recommendation about the dose reduction of chlorambucil in patients with hepatic dysfunction.

## Busulfan

Busulfan is a weak alkylating agent which is rapidly cleared from the plasma by excretion in the urine as methanesulfonic acid. Hepatic metabolism of the drug seems to be unimportant. Busulfan-associated hepatotoxicity is related with oxidative stresses, and this is mostly due to depletion of liver glutathione levels. In case reports as a single agent, high-dose busulfan toxicity is associated with cholestatic hepatitis [35]. Two case reports have described standard doses of busulfan associated with cholestatic hepatitis. The toxicity of busulfan can be increased with concomitant usage of cyclophosphamide or melphalan which are both glutathione detoxified. Busulfan is also associated with hepatic veno-occlusive disease when used in high doses or in combination with cyclophosphamide. Also there is no dose modification recommendation for busulfan in patients with hepatic impairment.

## Bendamustine

Bendamustine is a drug mostly used in the salvage therapy of lymphomas. The drug is primarily metabolized in the liver, and omitting the drug in patients with moderate liver dysfunction (transaminases $\geq$ 2.5 × ULN or total bilirubin $\geq$ 1.5 × ULN) is recommended.

## Dacarbazine

Dacarbazine is a prodrug activated by microsomal liver enzymes. As with busulfan, dacarba-

zine is also toxic for endothelial cells through glutathione depletion. It can also cause hepatic veno-occlusive syndrome at standard doses and is associated with peripheral eosinophilia and thrombosis of the central venules and veins.

### Temozolomide

Temozolomide is an orally active alkylating agent which is commonly used in patients with CNS tumors and malignant melanomas. Metabolism and the toxicity of the drug are not affected by hepatic function, but due to fatal and severe hepatotoxicity related with temozolamide, it is recommended that liver function tests are performed at baseline and before each cycle [36]. There is no recommendation about dose modifying, but omitting if the toxicity was grade 2 or more can be an option.

### Other Alkylating Agents

Carmustine, lomustine, and streptozocin are other alkylating agents which have both alkylating and carbomylating activity. Their hepatotoxic effect is usually associated with glutathione depletion-related oxidative injury. Streptozocin can be associated with a cholestatic pattern of hepatic injury. Toxicities of all of these agents are related to mild or moderate elevation of liver function, and this toxicity usually resolves after cessation of the causative drug. There is no recommendation about dose modification with hepatic impairment, but close monitoring of liver function tests may be necessary during the therapy.

### Antimetabolites

The main antimetabolites that are commonly used in chemotherapeutic regimens are cytosine arabinoside (ara-C), 5-fluorouracil (5-Fu), 6-mercaptopurine, azathioprine, 6-thioguanine, methotrexate, and gemcitabine.

Their hepatotoxic effects are variable, but the common features of these drugs are their metabolism in the liver. Therefore, dose reduction is usually needed in patients with hepatic dysfunction.

### Cytosine Arabinoside

Cytosine arabinoside (ara-C) is a major drug for treating hematologic malignancies. Ara-C is mainly metabolized intracellularly by phosphorylation to ARA-CTP, and this end product inhibits its DNA synthesis. The effect of the drug is limited to cells actively proliferating and synthesizing DNA. The liver plays a major role in detoxification of the cytarabine, and doses of the drug must be reduced in patients with hepatic dysfunction. Otherwise, toxic effects occur, mainly in the nervous system [37].

There were several case reports which showed cytarabine to be associated with abnormal liver function tests. Most of the cases in the literature have hematologic malignancies, and establishing a diagnosis of drug-induced liver injury is very difficult because of confounding risk factors such as sepsis, a multiple transfusion history, and combined use with other drugs.

Cytarabine-related histologically proven cholestasis was reported as a case report [38, 39].

In conclusion, cytarabine may cause transient elevations in liver tests, and this abnormality is generally dose limiting and usually resolves after ending the therapy [40].

This drug should be used cautiously in patients with severe hepatic dysfunction (ALT > 150 IU and/or total bilirubin > 50 mmol/L), and a 25% dose modification is recommended in order to avoid drug-associated myelosuppression and neurotoxicity.

### Fluorouracil and Capecitabine

Fluorouracil (5-FU) is a uracil analogue and mainly eliminated by the liver and peripheral degradation by dihydropyrimidine dehydrogenase enzyme activity. Nearly 15% of the drug is excreted in the urine without change. The active form of the drug (5-fluorodeoxyuridine monophosphate) inhibits thymidylate synthesis in proliferating tissues.

Capecitabine is an oral fluoropyrimidine which is in prodrug form. After absorption from the intestinal system, this prodrug is converted to the active form by thymidine phosphorylase. This enzyme's concentration is higher in tumor tissues than in normal tissues. This feature of the drug is associated with a higher tumor selectivity and better tolerability.

5-FU is shown to be associated with hepatic steatosis [40–42]. In spite of steatohepatitis, this effect is not related with morbidity or mortality [23].

There are some reports about the relation between bilirubin levels and 5-FU clearance. These data have shown that 5-FU doses should be reduced in patients with hepatic dysfunction. Omitting the drug is recommended if bilirubin levels are more than four times the upper limit of normal. An important point for both 5-FU and capecitabine is their interaction with warfarin; this issue is reported in several case reports [43, 44]. Another caution for 5-FU is for its use in combination with levamisole, oxaliplatin, and irinotecan because of the risk of potentiation of their hepatotoxic effects. Despite these data, there is no relation between capecitabine and liver function, so there is no dosage adjustment in case of hepatic dysfunction [45].

## Floxuridine

Floxuridine (FUdr) is a metabolite of 5-FU and commonly used for intra-arterial treatment of isolated liver metastasis in colorectal cancer. FUdr is a much more potent drug than 5-FU, and this is usually associated with more hepatotoxicity. The adverse effects can be developed in two ways:

- Direct toxic effects of the drug to the hepatic cells that are associated with elevations in liver enzymes
- Damage in the intra- or extrahepatic bile ducts

The toxicity of the drug seems to be related to the dose and its duration. Liver transaminase elevations associated with the drug usually resolve after cessation of the drug. It is recommended that liver enzymes be followed at least weekly during therapy with intrahepatic intra-arterial FUdr.

## Gemcitabine

Gemcitabine is a pyrimidine analogue that inhibits DNA synthesis in proliferating cells. It is commonly used in different cancer types such as breast carcinoma, non-small cell lung carcinoma, and pancreatic cancer. It is mainly eliminated by the hepatic cytochrome p450 enzyme system, and 10% of the drug is excreted in the urine without being changed. The drug may cause transient elevations of liver enzymes in up to 60% of patients, but these adverse effects are seldom of clinical significance and rarely associated with severe hepatotoxicity [46, 47]. There is no dose recommendation in this setting, but patients with elevated bilirubin levels at the beginning of the therapy have an increased risk of toxicity, and lower weekly doses such as 800 mg/m$^2$ should be initiated, and gradually escalating doses can be given if therapy is tolerated, so caution is advised [48].

## Mercaptopurine

Mercaptopurine is a purine analogue mainly used in the maintenance therapy of acute lymphocytic leukemia. The drug is activated by the hypoxanthine guanine phosphoribosyl transferase enzyme to the monophosphate nucleotide. The main effect of the drug is inhibition of de novo purine synthesis. It is mainly metabolized in the liver by the xanthine oxidase enzyme; hepatotoxicity of the drug is usually associated with daily dosing, and it is common if the usual daily dose is over 2 mg/kg. The hepatotoxicity may present as cholestatic liver disease and/or hepatocellular injury. Both of these effects are related with drug-associated direct toxicity. Bland cholestasis with minimal hepatic necrosis, but with significant cytologic atypia, and disorganized hepatic cords of cholestatic pattern are seen at biopsy [49].

In hepatocellular injury, most episodes of jaundice occur within 30 days of starting the therapy, and changing the administration route of the drug (oral to intravenous) does not affect the development of hepatotoxicity. In this picture, moderate elevations of aminotransferases, alkaline phosphatase, and serum bilirubin levels are usually between 50 and 100 mmol/L.

In both situations, abnormality in liver function tests usually resolves spontaneously after cessation of the causative drug. There is no recommendation about usage of this drug in patients with hepatic dysfunction, but dose reduction should be considered in order to avoid drug accumulation.

## Azathioprine

Azathioprine is a nitroimidazole derivative of 6-mercaptopurine and commonly used as an immunosuppressive agent in renal transplant recipients and autoimmune diseases. In comparison to 6-MP, hepatotoxicity of the drug is less frequent, milder, and less dose dependent.

Clinical patterns of hepatotoxicity associated with azathioprine are hypersensitivity reactions, idiosyncratic cholestatic reactions, presumed endothelial cell injury with raised portal hypertension, veno-occlusive disease (VOD), or peliosis hepatis [50]. Most of these patterns are reported in renal transplant recipients, and in some of them, progression of liver abnormalities after discontinuation of the drug is reported. There is no specific recommendation about dose modification in patients with hepatic dysfunction, but close monitoring of liver function tests and avoiding use in patients with severe hepatic dysfunction are reasonable.

## 6-Thioguanine

Thioguanine is an antipyrine drug and reported to be associated with hepatic VOD [40]. The drug is rapidly and extensively metabolized in the liver. Elevations of liver enzymes can be seen during the therapy with this drug, but serious hepatic injury is rarely reported. It is recommended to make a 50% dose reduction or avoid use in patients with severe hepatic dysfunction (ALT > 200 IU and/or serum bilirubin > 50 mmol/L).

## Methotrexate

Methotrexate (Mtx) is a folic acid analogue and commonly used in a variety of malignant and nonmalignant diseases. It mainly binds dihydrofolate reductase and inhibits reduction of dihydrofolate to its active form tetrahydrofolic acid. This molecule is important for one-carbon transfer reactions that are required for synthesis of thymidylate which is an important precursor for DNA and RNA.

At usual doses, Mtx is excreted in the urine without changing, but in high doses the drug is partially metabolized to 7-hydroxymethotrexate by the liver [51]. Liver fibrosis and cirrhosis have been reported with maintenance therapy with Mtx in children with acute leukemia. The commonly seen clinical pattern with Mtx therapy is acute transient elevation of liver transaminases. This elevation can be 2–20-fold especially in patients who received high-dose Mtx despite leucovorin rescue. This pattern of injury usually resolves spontaneously within 1–2 weeks after discontinuation of the drug. The risk is higher in patients treated with a daily dose than in those treated on intermittent dosage schedules. In conclusion, chronic usage of this drug may cause acute elevations in liver function tests.

Due to accumulation of the drug in body fluids, especially in third spaces of the body such as ascites or pleural effusions, where these fluids can act as a reservoir for slow distribution of the drug into the plasma, increased systemic exposure with the risk of toxicity can occur [52]. So draining third space fluids or dosage modification of the drug is recommended in patients with malignant effusions. There is no other recommended dose modification in patients with hepatic dysfunction.

## Pemetrexed

Pemetrexed is a novel folate analogue mainly used in nonsquamous non-small cell lung cancer and malignant mesothelioma. Grade 3–4 hepatotoxicity has been reported during pemetrexed therapy. 75% dose reduction is recommended for bilirubin elevation >3 × ULN or AST >5 × ULN. Omitting the drug is recommended in patients with >10 × ULN or AST >20 × ULN.

## Antitumor Antibiotics

Members of this drug family are anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin), mitoxantrone, bleomycin, mitomycin, mithramycin (plicamycin), and dactinomycin.

## Doxorubicin

Doxorubicin is the most widely used member of the family. It acts through DNA intercalation, alteration of membrane function, and formation of free radicals [53]. The drug is mainly metabolized by the liver, and nearly 80% of the total drug dose is excreted in the bile. There are a few case reports in the literature about doxorubicin-related hepatic injury in patients with acute leukemia. As mentioned before, there are multiple factors which may contribute negatively to the effect of the drug on hepatic dysfunction in these patients.

Cholestasis may cause delayed clearance of the drug and its metabolites. This delay can be associated with the development of greater systemic toxicity, such as myelosuppression and mucositis, even in standard doses. However, no increased toxicity has been reported in patients with cirrhosis or isolated elevations in liver transaminases. In conclusion, dosage recommendations for doxorubicin in the context of hepatic function are as follows:

- Bilirubin 20–50 mmol/L or ALT two to four times of upper limit → Administer 50% of the total dose.
- Bilirubin 50–80 mmol/L or ALT more than four times of upper limit → Administer 25% of total dose.
- Bilirubin levels more than 80 mmol/L: it is contraindicated to use.

The other widely used agent in this group is epirubicin, and the recommended dosages are as follows:

- Bilirubin <20 mmol/L no dosage adjustment.
- Bilirubin 20–50 mmol/L or AST 2–4 × ULN 50% of recommended starting dose.
- Bilirubin 50–80 mmol/L or AST >4 × ULN 25% of recommended starting dose.
- Bilirubin levels more than 80 mmol/L: it is contraindicated to use.

## Mitoxantrone

Mitoxantrone is an anthraquinone antibiotic. Mitoxantrone has less toxicity than anthracyclines and usually presents itself with transient elevations in liver enzymes. Owing to interactions between mitoxantrone clearance and hepatic function (especially bilurubin levels), it is recommended to make a 50% dose reduction for mild to moderate dysfunction (bilirubin 25–50 mmol/L) and a 75% dose reduction in those with more severe dysfunction (bilirubin > 50 mmol/L).

## Bleomycin

Bleomycin is an antitumor antibiotic which is used in cancers such as lymphomas, germ cell tumors, and various squamous carcinomas. The main mechanism for the drug's action is through the breakage of double-stranded DNA. Nearly 50% of each administered dose of bleomycin is excreted in the urine without change, and the other part of the drug is inactivated by aminopeptidases present in many tissues including the liver. This enzyme does not exist in the lung and skin, so these parts of the body are most susceptible to bleomycin-associated injury. It is reported that bleomycin-associated liver injury is a very

rare condition, so there is no established recommendation for dosage modification in hepatic injury or dysfunction.

## Mitomycin

Mitomycin is an antitumor antibiotic that disrupts DNA synthesis like other alkylating agents. It is mainly metabolized in the liver, and a small percent (app 10%) of drug is excreted unchanged in the urine. Our present understanding of hepatic function and mitomycin clearance is unclear. There is documented increased myelotoxicity in patients with concomitant hepatic dysfunction [54].

There are no established dose modification recommendations for mitomycin in hepatic dysfunction, but recommendations from reported studies are as follows:

- Fifty percent dose modification at bilirubin levels of 25–50 mmol/L
- Seventy-five percent dose modification at bilirubin levels of >50 mmol/L, hepatic enzymes more than three times of upper limit

## Plicamycin (Mithramycin)

Plicamycin is the most hepatotoxic agent that is used in clinical practice. Nowadays it is only used in the treatment of malignant hypercalcemia in rare conditions, so hepatic injury seen with this drug is reported very rarely. Hepatotoxic effects mainly show themselves by elevations of aminotransferases and depression of the synthesis of the coagulation factors such as II, V, VII, and X. Because of alternative choices for this drug, it is recommended to avoid using it in patients with hepatic dysfunction.

## Dactinomycin

Transient elevations of liver enzymes can be seen during treatment, and this clinical picture appears to be related to the dose. Double doses on alternate days as compared to consecutive 5-day usage showed that hepatotoxicity is more common with consecutive usage. Also this drug is reported to be associated with hepatic VOD. Available data on dose modifications in hepatic dysfunction are limited, but it is recommended that a 50% dose reduction be considered in patients with bilirubin levels more than 50 mmol/L.

## Dacarbazine

Dacarbazine (DTIC) is a potent antitumor antibiotic that is widely used in Hodgkin lymphoma and malignant melanoma. It may cause VOD as a result of hepatic vascular toxicity, and another possible mechanism of hepatic injury associated with dacarbazine is idiosyncratic hypersensitivity reactions. The drug is mainly metabolized in the liver by the hepatic microsomal enzyme system, so clearance of the drug can be affected from hepatocellular damage, but there is no established recommendation about the usage of this drug in patients with hepatic dysfunction.

## Vinca Alkaloids

Drugs in the vinca alkaloid family mainly act on tubulin and microtubules. Vincristine and vinblastine are members of this group. They are primarily metabolized by the liver and excreted through the bile; therefore, in cases of hepatic dysfunction, their metabolism will be affected, and this may cause serious toxic effects. Mild transient elevation of liver enzymes can be seen during the course of therapy, but these are temporary toxic effects. More severe hepatotoxicity can be seen in patients who receive vincristine with concomitant irradiation.

Dose adjustments in hepatic dysfunction are as follows:

- Serum bilirubin 25–50 mmol/L or ALT 60–180 IU/L: 50% dose modification
- Serum bilirubin 50–85 mmol/L: 75% dose modification
- Serum bilirubin >85 mmol/L or ALT >180 IU/L: avoid using

## Etoposide

Etoposide is a topoisomerase II inhibitor. It is extensively protein (albumin) bound (nearly 97%) and primarily metabolized in the liver and excreted by the biliary system. It is not hepatotoxic at standard doses, but higher doses of the drug may cause hyperbilirubinemia and elevation in liver enzymes. All of these effects are reversible. Clearance of the drug is correlated with serum bilirubin levels, so patients with high bilirubin levels are exposed to high levels of the unbound fraction of the drug, and this is associated with subsequent hematologic and other toxic effects of the drug (myelosuppression, mucositis).

Dose recommendations in patients with hepatic dysfunction are as follows:

- Bilirubin levels 25–50 mmol/L or ALT 60–180 IU/L: 50% dose modification
- Bilirubin levels 50–85 mmol/L or ALT >180 IU/L: 75% dose modification
- Bilirubin levels >85 mmol/L: avoid using

## Taxanes

Taxanes are also acting on tubules. However, they bind microtubules rather than tubulin dimers. Both paclitaxel and docetaxel are metabolized by the hepatic cytochrome p450 enzyme system and are excreted through the bile; therefore, both drug clearances are affected by hepatic dysfunction [55] and by other molecules affecting this system. Transient elevations in LFTs have been reported 5–20% of cases during therapy, but there is no reported cumulative toxicity of these drugs [56, 57].

For paclitaxel the dose recommendations for three weekly regimens are as follows:

- Total bilirubin levels <25 mmol/L and ALT more than two times upper limit of normal: total dose 135/mg/m$^2$
- Total bilirubin levels 26–50 mmol/L: total dose <75 mg/m$^2$
- Total bilirubin levels ≥51 mmol/L: total dose <50 mg/m$^2$

For docetaxel, the dose recommendations are stricter than paclitaxel. Docetaxel should not be used in patients with serum bilirubin levels above the upper limit of normal or AST and ALT >1.5 times the upper limit, concomitant with alkaline phosphatase >2.5 times the upper limit of normal value (ULN) because of the higher risk of myelosuppression and treatment-related death [58, 59].

Cabazitaxel is a novel member of taxane group; it is a semisynthetic taxane and mainly used in prostate cancer. In mild hepatic impairment (total bilirubin 1–1.5 ULN or AST >1.5 ULN), reduce dose to 20 mg/m$^2$; in moderate hepatic impairment (total bilirubin 1.5–3 ULN or AST any), reduce dose 15 mg/m$^2$; and in case of severe hepatic impairment (total bilirubin >3 × ULN), avoid using the drug.

## Ixabepilone

Ixabepilone is a microtubule inhibitor and is mainly used in patients with chemotherapy-resistant metastatic breast cancer and prostate cancer. The standard dose is 40 mg/m$^2$ over 3 h every 3 weeks. It is metabolized in the liver, and dosage adjustments in cases with hepatic dysfunction are as follows [60]:

- ALT ≤2.5 times ULN or bilirubin levels ≤1 times ULN: 40 mg/m$^2$
- ALT ≤10 times ULN and bilirubin levels ≤1 times ULN: 32 mg/m$^2$
- ALT ≤10 times ULN and bilirubin levels >1.5–3 times ULN: 20 mg/m$^2$

## Eribulin

Eribulin mesylate is a substrate derived from a marine sponge. It has indications in metastatic breast cancer, sarcoma, and non-small cell lung cancer. In mild hepatic dysfunction (Child-Pugh A) 1.1 mg/m$^2$ and in moderate hepatic dysfunction (Child-Pugh B) 0.7 mg/m$^2$ are the recommended doses. In severe hepatic dysfunction (Child-Pugh C), it is contraindicated due to excessive toxicity.

### Irinotecan and Topotecan

Irinotecan and Topotecan are topoisomerase I inhibitors. Irinotecan is metabolized in different sites of body such as the intestine, plasma, and liver. The drug is metabolized into two metabolites that are either inactive or an active metabolite (SN-38). The active metabolite of the drug is inactivated by glucuronidation in the liver. In patients with colorectal cancer, the combination of irinotecan with 5-FU may cause steatosis and hepatic vascular injury. There is no dose reduction recommendation for topotecan in patients with hepatic dysfunction, but for irinotecan the dosage should be reduced in case of hyperbilirubinemia.

Dose recommendation is as follows: [61]

- Serum bilirubin levels 1.5–3 times ULN: reduction of the starting dosage from 350 mg/m$^2$ to 200 mg/m$^2$ for every 3 weeks
- Serum bilirubin levels >3 times ULN: avoid using

### Platinum Derivatives

Cisplatin, carboplatin, and oxaliplatin are platinum derivatives. All of them are excreted in the urine, but mild transient elevations of the liver enzymes can be seen during therapy with them. In patients with colorectal cancer, combinations of oxaliplatin with 5-FU may cause steatosis, hepatic vascular injury, and nodular regenerative hyperplasia. Oxaliplatin is approximately 85% protein bound in serum, but low albumin levels result in decreased drug plasma concentrations.

There is no established dosage modification for platinum derivatives in patients with hepatic dysfunction.

## Tyrosine Kinase Inhibitors

Small tyrosine kinase inhibitors have a major role in the treatment of many cancers. Despite their positive outcomes, most of them have many toxic effects on a number of vital organs especially the liver. Many of them have been withdrawn from market because of these toxic effects. The onset of TKI-related hepatotoxicity begins within 2 months of starting therapy but occasionally is delayed; it is usually reversible, so careful observation is needed during the treatment period [62]. Most of the tyrosine kinase inhibitors use the cytochrome p450 system for metabolism, and as a result, concomitant usage of other drugs using this pathway may increase the serum concentration of the drug, and it may cause hepatotoxicity [63].

Hy's rule which is named by Professor Hyman Joseph Zimmerman is important for deciding the risk of hepatotoxicity of the treatment. According to this rule, a significant risk of severe hepatotoxicity is associated with concurrent elevation in ALT greater than three times the ULN and bilirubin greater than twice ULN with no evidence of biliary obstruction or other causes to reasonably explain the elevations [64]. Hy's rule predicts a mortality rate exceeding 10%.

The indications and potential toxicity of widely used small tyrosine kinase inhibitors are summarized in Table 30.5 [62].

### Imatinib

Imatinib was the first commercially widely used tyrosine kinase inhibitor. It inhibits BCR-ABL kinase in chronic myeloid leukemia and gastrointestinal stromal tumors.

It is metabolized by the cytochrome p450 enzyme system in the liver. Imatinib may cause mild to moderate elevations of liver enzymes during therapy, and severe and fatal acute hepatic necrosis also has been reported. There is no dosage recommendation for imatinib in patients with hepatic dysfunction.

### Lapatinib

Lapatinib is a widely used tyrosine kinase inhibitor mainly in HER neu (+) breast cancer. The drug is reported to be associated with severe potentially fatal hepatotoxicity, so it is

**Table 30.5** Commonly used TKIs and hepatotoxicity risk

| Drug | Indications | Potential time for hepatic injury | AST/ALT elevations all grades % | AST/ALT elevations grades 3–4% | Fatal cases related with drug? |
|---|---|---|---|---|---|
| *TKIs needing liver function monitoring during clinical usage* | | | | | |
| Lapatinib | Her2 + breast cancer | Days to several months after initiation of treatment | 37–53 | 2–6 | Yes |
| Sunitinib | GİST, RCC, pancreatic neuroendocrine tumors | Within 2 months | 40–60 | 2–5 | Yes |
| Pazopanib | RCC, soft tissue sarcoma | Within 18 weeks | 46–53 | 7–12 | Yes |
| Axitinib | RCC | No information | 20 | 1 | No |
| Erlotinib | NSCLC | Within 2–4 weeks | 35–45 | 10–14 | No |
| Crizotinib | NSCLC | Within first 2 months | 57 | 6 | Yes |
| Regorafenib | Colorectal cancer, GIST | 2–6 weeks | 45–65 | 6 | Yes |
| Vemurafenib | M melanoma | Within 6 weeks | 35–38 | 3 | No |
| *TKIs no routine need of liver function monitoring during clinical usage* | | | | | |
| Cabozantinib | Medullary thyroid cancer, RCC | No information | 86 | 3–6 | No |
| Sorafenib | HCC, RCC | No information | 21–25 | 2 | No |
| Vandetanib | Medullary thyroid cancer | No information | 51 | 2 | No |

recommended that liver enzymes be monitored monthly during the therapy. This hepatotoxicity is probably related with the liver use of the drug for metabolism [65], but it can also occur idiosyncratically [66]. It is recommended to reduce the dose from 1250 mg/day to 750 mg/day in patients with hepatic dysfunction and avoid it using in patients with severe hepatic dysfunction.

## Sorafenib

Sorafenib is a potent inhibitor of multiple tyrosine kinases and is mainly used in renal cell carcinoma, differentiated thyroid cancer, and hepatocellular carcinoma. It is also metabolized in the liver by the cytochrome p450 enzyme system, and its use is contraindicated in patients with Child-Pugh Class C cirrhosis. There is no recommendation for Child-Pugh Class A and B, but results of a phase I study showed that a dose reduction to 200 mg twice daily is needed in patients with a bilirubin 1.5–3 times the upper limit of normal, and cessation of the drug is needed when the bilirubin concentration is in excess of this level [67]. There is a reported fatal outcome secondary to hepatic failure in a patient with thyroid cancer after initiating sorafenib within the 8 weeks of treatment [68–70].

## Erlotinib

Erlotinib is a tyrosine kinase inhibitor that inhibits the epidermal growth factor receptor. It is mainly metabolized in the liver by the cytochrome p450 enzyme system. Clearance of the drug is affected by liver function, so it is important to follow the liver function in patients with hepatic dysfunction. Hepatorenal syndrome and fatal hepatic failure can develop during treatment in patients with preexisting moderate to severe hepatic impairment or with multiple medication use in elderly patients [71]. The drug should be discontinued in patients with elevated bilirubin or transaminase levels [72, 73].

## Axitinib

Axitinib is another VEGFR targeting multikinase inhibitor mainly used in renal cell carcinoma.

The recommendation is to monitor ALT, AST, and bilirubin monthly in the treatment period. Fifty percent dose reduction is recommended in

Child-Pugh B patients, but there is no available data in patients with Child-Pugh C liver disease.

## Crizotinib

Crizotinib is a novel tyrosine kinase inhibitor targeting EML4-ALK fusion oncogene in nonsquamous non-small cell lung cancer. Monitoring liver function tests every month and in grade 2 or more elevations temporarily suspending the drug until the toxicity returns to grade 1 and then reducing the dose can be useful, but in the case of permanent grade 3 or more elevations, the drug should be permanently discontinued.

Ceritinib and alectinib are the other novel ALK inhibitors having indications in ALK rearrangement positive nonsquamous lung cancer. Both drugs must be withheld with AST elevation >5 × ULN and total bilirubin >2 × ULN until the toxicity resolves. In case of permanent elevation, the drug must be discontinued.

## Pazopanib

Pazopanib is another multikinase inhibitor targeting PDGF, VEGF, and cKIT. The most often occurring side effects were elevation of liver function test in up to 18% of patients. Grade 3–4 toxicity occurs in less than 1% of patients. Liver function tests should be done every 4 weeks during the treatment. In cases of liver function, elevations between 3 × ULN and 8 × ULN treatment can be continued with weekly control, but over 8 × ULN treatment should be discontinued until the liver function tests return to grade 1 or baseline [74]. The probability of AST, ALT elevation in Pazopanib, and mTOR inhibitors is much higher than for sunitinib and sorafenib.

## Sunitinib

Sunitinib is a multikinase inhibitor targeting VEGF, PDGF, cKIT, FLT3, and RET kinase. It is a strong inhibitor of CYP3A4, and severe liver damage can be seen during usage of this drug.

Liver function tests should be monitored every cycle during the treatment period, and treatment should be suspended in grade 3 or more elevations of liver function tests.

Vemurafenib is mainly used in BRAF mutant tumors in malignant melanoma and nowadays promising results in colorectal cancer. 2–12% LFT abnormalities may be seen during this drug use. Liver function tests should be monitored every cycle during the treatment period, and treatment should be suspended in grade 3 or more elevations.

## Regorafenib

Regorafenib is a small molecule kinase inhibitor mainly used in metastatic colorectal cancer. Fatal drug-induced liver injury is reported in the literature [75].

Liver function tests should be monitored every 2 weeks in the first 2 months of the treatment period. In cases with grade 1–2 elevations, weekly monitoring, ongoing with treatment, can be an option, but treatment should be suspended with grade 3 or more elevations until the tests return to the normal ranges.

## Mammalian Target of Rapamycin Inhibitors

### Everolimus

The mTOR pathway is one of the main pathways in tumorogenesis. It has a cytoplasmic serine/threonine kinase. Inhibiting this pathway by a macrolide inhibitor everolimus has antiproliferative and antiangiogenic properties. The drug is catabolized by the liver via CYPA4, and dose adjustment is needed in patients with liver dysfunction.

Mild cases (Child-Pugh A): Dose should be decreased to 7.5 mg/daily.

Moderate cases (Child-Pugh B): Dose should be decreased to 5 mg/daily.

Severe hepatic impairment (Child-Pugh C): If benefit outweighs risk, drug can be initiated, but dose should not be more than 2.5 mg/daily.

### Temsirolimus

Temsirolimus is another member of this family and mostly used in high-risk renal cell carcinoma. In mild hepatic impairment, reduce dose to 15 mg weekly. With bilirubin levels greater than 1.5 × ULN, this drug use is not recommended.

## Monoclonal Antibodies

### Bevacizumab

Bevacizumab is a humanized recombinant monoclonal antibody targeting VEGF receptors. To now there is no reported hepatotoxicity related with bevacizumab usage. Also there are no dose restrictions in case of hepatic damage; it has protective effects on hepatic sinusoidal damage of conventional chemotherapeutics [76–78].

### Trastuzumab

Trastuzumab is a humanized monoclonal antibody against her 2 neu receptors on cancer cells, and it is mainly used in breast and gastric cancers. There are case reports concerning drug-induced liver damage associated with use of trastuzumab [74]. There is no known dosage modification in liver damage or failure.

### Cetuximab

Cetuximab is a chimeric monoclonal antibody targeting the RAS pathway in RAS wild-type patients in colorectal cancer and all patients in head and neck cancer. There are some reports of reversible liver function test elevations during drug usage in cancer patients, but for now there is no dosage modification recommendation in patients with liver damage or failure.

### Panitumumab

Panitumumab is a humanized IgG2 antibody against the RAS pathway in colorectal cancer patients. Same as cetuximab, there is no any recommended dosage restrictions in patients with liver damage or failure.

### Pertuzumab

Pertuzumab is a monoclonal antibody that targets the extracellular dimerization domain of the HER2 receptor. Promising results have been observed in combination with trastuzumab in HER2 + breast cancer. There is no known dosage modification in liver damage or failure, and the drug can be used with close follow-up.

### Ramucirumab

Ramucirumab is a monoclonal antibody targeting VEGFR2, mainly used in gastrointestinal system cancers. There is reported worsening encephalopathy, ascites, or hepatorenal syndrome in patients with Child-Pugh B or C receiving this therapy [61]. There is no dose recommendation in patients with hepatic dysfunction.

### Rituximab

Rituximab is a chimerical antibody against membrane antigen CD20, mainly used in B cell malignancies and rheumatologic disease. It has no known hepatotoxic effects, but due to effects on lymphocytes, it may aggravate hepatitis B activation in patients with inactive or active carriers. There are no dose restrictions in patients with hepatic damage, but preemptive antiviral therapy is recommended in patients with HbsAG + and/or antiHbC AB + patients.

## Drug Conjugates

### Ado-Trastuzumab Emtansine (TDM1)

TDM1 is a novel drug conjugate of a microtubule inhibitor and trastuzumab mainly used in HER2 3+ metastatic breast cancer. Usage of this drug in severe hepatic impairment is not studied, but in moderate hepatic impairment, the drug can be used with serial monitoring.

## Brentuximab Vedotin

Brentuximab vedotin is a novel immunotoxin with components of a CD30-directed monoclonal antibody and an antitubulin agent, monomethyl auristatin E. It has indications in refractory Hodgkin lymphoma and anaplastic large cell lymphoma. In mild hepatic impairment, the dose should be decreased to 1.2 mg/kg, maximum 120 mg. It is not recommended to use in patients with moderate or severe hepatic impairment.

## Biologic Response Modifiers

### Interferon

Recombinant interferon alfa (IFNa) is used in various types of malignant or myeloproliferative diseases such as hairy cell leukemia, multiple myeloma, AIDS-related Kaposi's sarcoma, and non-Hodgkin lymphoma. The drug is usually associated with reversible liver enzyme elevations [79]. Hepatotoxicity may be dose limiting at doses above 10 million units daily [80]. The drug is mainly metabolized in the kidney, and there is no dosage reduction in patients with hepatic dysfunction.

### Interleukin 2

Interleukin 2 (IL-2) is another biologic response modifier that is used in the treatment of renal cell carcinoma and malignant melanoma. High-dose intravenous IL-2 therapy is reported to be associated with elevations of serum bilirubin levels between 35 and 100 mmol/L. This clinical picture is thought to be associated with intrahepatic cholestasis [81]. Elevation of liver enzymes, hypoalbuminemia, and prolonged prothrombin time are other adverse effects of the drug. Impairment in sinusoidal perfusion and hypoxic damage due to activation of Kupffer cells, leukocyte, and platelet adhesion to hepatic sinusoidal endothelium are mechanisms of hepatic damage. This toxicity is usually reversible, and spontaneous resolution typically occurs within several days after discontinuation of the drug. There is no recommendation for IL-2 dosage adjustment in patients with hepatic dysfunction.

## Immunotherapy

The last decade in medical oncology has seen hopeful advances in immunotherapy, and for the past 2 years, we have had so many drugs and combination regimens with immunotherapies against most cancer subtypes. This drug group has additive toxic effects to other drugs and extra autoimmune toxicity belonging to their immune system-associated toxic effects. Limited LFT elevations can be seen during the treatment period, but mostly these episodes are asymptomatic and resolve spontaneously. Occasionally serious hepatic injuries have been reported, but most of them are resolved with appropriate medical management.

### Ipilimumab

Ipilimumab is the first member of immune checkpoint inhibitors targeting CTLA4. The main side effect for the liver is immune-mediated hepatitis and has been seen 2–9% of the patients. Combination of this agent with chemotherapeutics or other immune checkpoint inhibitors may increase the risk of hepatotoxicity. Corticosteroids are recommended in patients with grade 3 or more toxicity until it resolves to grade 1. In patients with persistent immune hepatitis despite corticosteroids, mycophenolate has also been used [82–84].

### Nivolumab and Pembrolizumab

Both nivolumab and pembolizumab are second-line immunotherapies targeting PD-1 receptors. The rates of hepatitis are less than 5%, and severe hepatotoxicity is much rarer [85–87]. Combinations with anti-CTLA4 antibodies increase hepatotoxicity. There is generally a delay in the onset of symptoms of 1–8 weeks. The management is to withhold the drug, starting 1 mg/kg steroid tapering gradually to 10 mg/day and then reinstating the drug if the toxicity reduces to grade 1 [88, 89].

## Tamoxifen and Other Hormones

Tamoxifen is a nonsteroidal drug that has both antiestrogenic and estrogenic effects. It is mainly used in breast cancer as a chemopreventive therapy and metabolized by the liver cytochrome p450 enzyme system. Tamoxifen-associated liver injuries are nonalcoholic fatty liver disease, peliosis hepatis, hepatic insufficiency, and rarely hepatocellular cancer.

Nonalcoholic fatty liver disease is the most common form of these injuries. There is no recommendation for tamoxifen dosage modification in patients with hepatic dysfunction.

Flutamide and megestrol acetate are other hormones commonly used in oncologic patients. Both of them are reported to be associated with cholestatic hepatitis. Their reactions are not dose dependent and usually resolve after cessation of the drug.

## Hepatic Veno-occlusive Disease

Hepatic VOD is defined as nonthrombotic occlusion of small intrahepatic veins by subendothelial fibrin [90]. It is associated with congestion and potentially fatal necrosis of centrolobular hepatocytes. Bone marrow transplantation (BMT) is a risk factor for developing hepatic VOD. Symptoms of the disease are painful hepatomegaly, rapidly accumulating ascites, or unexplained weight gain and bilirubin >35 mmol/L within 20 days of BMT [91].

Progression is associated with fibrosis and atrophy of centrilobular hepatocytes [90]. Most cases are thought to be drug-induced, and most suspected drugs are alkylating agents, antimetabolites, high-dose cyclophosphamide, busulfan, dacarbazine, dactinomycin, 6-thioguanine, and azathioprine.

## Combination Chemotherapy Regimens

Combination chemotherapy is a therapeutic choice in the management of different types of cancers especially in the adjuvant setting. Every single agent has different effects on tumors and different toxicity profiles, so combinations of drugs increase both antitumor activity and toxic effects. It is important to follow liver function during therapy with some combinations.

Possible hepatotoxic combination regimens are as follows:

- Cyclophosphamide + methotrexate +5-FU
- Cyclophosphamide + doxorubicin +5-FU
- Doxorubicin + 6-Mercaptopurine
- Busulfan + 6-Thioguanine
- Carmustine + Etoposide
- 5-FU + Levamisole

## Radiotherapy and Hepatotoxicity

Radiotherapy is a hepatotoxic modality if the liver is in the radiotherapy field even when used in tolerable doses and also may potentiate or cause hepatotoxic effects when combined with normally non-hepatotoxic chemotherapeutic agents. Case report series consisting of 35 lymphoma patients showed that liver irradiation and concomitant vincristine usage may cause moderate to serious hepatotoxic effects. This situation was thought to be associated with delayed transportation of vincristine through the liver and its excretion into the bile [92]. A similar effect has been reported with radiation and doxorubicin [93]. It is important to be aware of hepatotoxicity during radiotherapy to the abdominal region, especially around the liver.

### Conclusion

As a single agent or combination with other drugs and radiotherapy, chemotherapeutic agents can be associated with mild to severe hepatotoxicity by idiosyncratic reactions or direct toxic effects. Also preexisting liver disease and hepatic dysfunction may alter drug metabolism and increase the risk of non-hepatotoxic toxicity. Many guidelines about dose modification in hepatic dysfunction seem to be empiric. The main problem is to balance excessive toxicity with undertreatment of the

cancer. Clinicians should be alert when using some possible hepatotoxic agents such as vinca alkaloids, taxanes, anthracyclines, and etoposide and decide individually about dose modification on the basis of clinical and laboratory findings for optimal management of cancer patients. So far new targeted therapies and immunotherapies have added additional toxicity profiles consisting of drug-associated hepatotoxicity and autoimmune hepatitis into the oncology practice which makes clinicians job much more complicated.

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# Part IX

# Urogenital

# Urological Symptoms and Side Effects of Treatment

31

Ehtesham Abdi and Alistair Campbell

## Introduction

Urological problems in patients with advanced cancer are infrequent [1]; however, they cause significant physical and more importantly psychosocial problems. Many urological complications and symptoms can be very serious and life-threatening and can adversely affect a patient's quality of life.

The discussion focuses on symptom control in patients with advanced cancer who have developed urinary tract dysfunction. In the palliative care setting, management decisions and discussions should focus on the appropriate option in the context of the patient's overall situation. Biological, social and spiritual factors need to be taken into account and most importantly the patient's and family's wishes, the premorbid health of the patient and adequacy of existing symptom control, rate of disease progression and the cost-benefit analysis of invasive investigation and intervention. Emphasis is placed on less aggressive but effective interventions in keeping with the general physical health of these patients. However, in some situations, more complex, invasive procedures are appropriate and should primarily be aimed at improving the quality of life and symptomatic improvement. In almost all urological malignancies, newer systemic therapies are now available, and the judicious use of these agents in carefully selected patients will lead to a better quality of life and in some instances improvement in survival of patients with advanced urological malignancies.

## Physiology of Voiding

The normal act of voiding involves a functioning detrusor muscle, an intact bladder wall and integrity of the nerves coordinating detrusor and vesical sphincter activities. The bladder receives its principal nerve supply from one-paired somatic nerves and two-paired autonomic nerves. The hypogastric nerves coordinate sympathetic activity, while the pelvic nerves contain parasympathetic fibres. The pudendal nerves provide non-autonomic fibres. Bladder wall distension leads to stretch receptors that trigger pelvic nerve fibres which, unless inhibited by higher centres, will lead to a parasympathetic motor response and bladder contraction. Parasympathetic system

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activation causes the detrusor muscle to contract and bladder neck sphincter to relax, whereas the sympathetic system has the opposite effect to that of the parasympathetic system.

Metastatic disease may involve the lower thoracic and upper lumbar vertebrae and can cause spinal cord compression or nerve root injury. These neurological complications may interfere with normal voiding. Many drugs, frequently used for palliation of symptoms in advanced cancer, can also affect bladder motility and neuromuscular function. Anticholinergic drugs may cause relaxation of the detrusor muscle associated with contraction of the bladder neck sphincter. Other drugs, such as haloperidol, phenothiazines and tricyclic antidepressant (TCA), have cholinergic properties. Anticholinergic agents are particularly troublesome in the elderly and in patients with pre-existing bladder dysfunction. A few patients, upon first use of opioids, may develop temporary urinary retention. Strong opioids, otherwise, do not affect bladder function unless there are other underlying problems such as faecal impaction.

Acute urinary retention causes distension of the bladder wall, producing significant physical symptoms. Pain and discomfort from urinary tract obstruction, metabolic changes and impaired renal function may all cause mental confusion especially in the elderly.

Cancers involving the retroperitoneum or the pelvis may cause upper urinary tract obstruction, whereas conditions of the bladder neck, prostate or urethra can cause lower tract obstruction. Pelvic tumours may locally infiltrate the bladder wall or other local organs causing fistulae. Haematuria may be caused by upper or lower urinary tract pathology. The possibility of spinal cord or nerve root damage and biochemical abnormalities such as hypercalcaemia, hyperglycaemia and diabetes insipidus presenting as urinary symptoms needs to be kept in mind.

The broad category of urological problems in advanced cancer is as follows:

1. Incontinence
2. Haematuria
3. Bladder outlet obstruction
4. Ureteric obstruction
5. Irritative voiding symptoms
6. Pain

## Urinary Incontinence

Urinary incontinence is defined as the involuntary leakage of urine. If not properly managed, urinary incontinence can lead to perineal rashes, pressure ulcers and urinary tract infections (UTIs) and may increase the risk of urosepsis, falls and fractures [2]. The commonest and the most significant type of urinary incontinence is urethral incontinence or extra-urethral loss from urinary fistulae. Cancers in the pelvic region such as the prostate, uterus, rectum and bladder can increase the risk of incontinence as these cancers may involve the urinary bladder or the urethra. Furthermore, cancers that metastasise to the spinal cord may affect the nerves supplying the urinary bladder or pelvic muscles. Endocrine therapy for breast cancer causes hormonal changes that affect the urethra. Treatment of cancer may also cause urinary incontinence. Irradiation to the pelvis causes irritation of the urinary bladder. Surgery to the pelvic area may also damage pelvic floor muscles or nerves.

### Total Urethral Incontinence

Direct tumour invasion, surgical procedures or neurological damage from malignancy may cause urethral sphincter dysfunction. The external urethral sphincter originates at the ischiopubic ramus and inserts into the intermeshing muscle fibres from the other side. It is controlled by the deep perineal branch of the pudendal nerve. Activity in the nerve fibres constricts the urethra. The internal sphincter muscle of urethra is located at the bladder's inferior end and the urethra's proximal end at the junction of the urethra with the urinary bladder. The internal sphincter is a continuation of the detrusor muscle and is made of smooth muscle; therefore it is under involuntary or autonomic control. This is the primary muscle for prohibiting the release of urine.

*Sphincter urethrae* are located at the bladder's distal inferior end in females and inferior to the prostate in males. It is a secondary sphincter to control the flow of urine through the urethra. Unlike the internal sphincter muscle, the external sphincter is made of skeletal muscle; therefore it is under voluntary control of the somatic nervous system. Some cancers and cancer treatments may result in urinary incontinence as above. A careful history and physical examination, cystoscopic examination and, where appropriate, urodynamic studies confirm urethral sphincter abnormality. Spinal cord or nerve root damage is often associated with other motor or sensory nerve symptoms and signs. Most patients with urethral incontinence require an indwelling catheter; however, some men may manage condom drainage or a penile clamp. In patients with less advanced disease, artificial urethral sphincters may be a consideration [3]. For urethral incontinence a number of procedures are available including the Burch colposuspension procedure, urethral slings and radiofrequency treatments. Patient satisfaction rates are reported to be higher for the Burch procedure than for urethral sling procedures. Although urethral sling procedures are reported to have a high success rate, the adverse events are also more common [4]. The AdVance® male suburethral sling is a trans-obturator suburethral sling placed perineally. The AdVance sling is indicated for men with mild to moderate stress incontinence. For short-term results, the AdVance sling is reported to be very satisfactory [5]. The bone-anchored bulbourethral sling works by providing broad-based compression of the urethra, imparting outlet resistance through a sling that is stably fixed to the urethra. Advantages of this approach include a single perineal incision, stable fixation to the bony pelvis and virtually no risk of injury to the bladder [6]. One popular model is the InVance® implant (American Medical Systems [AMS], Minnetonka, MN) [7]. Another sling for males is the Virtue Male Sling®. This sling has four arms, two of which are passed prepubic and two through the obturator foramen. It is a hybrid device, offering urethral mobilisation through the trans-obturator arms and urethral compression through the prepubic arms [8]. However, a high failure rate of over two-thirds has been reported with this procedure. A few patients reported chronic pain, and several patients required subsequent sling explant due to pain or for failure [9]. The most commonly used device is the AMS 800® artificial urinary sphincter and is considered the standard for the treatment of incontinence caused by intrinsic sphincteric dysfunction. This device consists of a pressure-regulating balloon, an inflatable cuff and a control pump. The balloon has a dual function as a pressure regulator and a fluid reservoir. On long-term follow-up, up to 90% of patients have a functional artificial urinary sphincter, with a somewhat low revision rate of about 25% [10]. The efficacy in women seems comparable to men; however women are more often treated with bladder neck suspension and suburethral sling procedures [6].

## Overflow Incontinence

Bladder outlet or urethral obstruction may lead to overflow incontinence. Overflow incontinence is usually associated with acute pain and distress and urinary retention, and voiding occurs without control and in small amounts. The urinary bladder is usually palpable, distended and tender. Following placement of an indwelling urethral catheter, definitive treatment involves surgical or other means to decompress the bladder. Treatment needs to be individualised but may consist of a long-term suprapubic or urethral catheter, intermittent self-catheterisation or an intraurethral stent.

## Urge Incontinence

Intrinsic or extrinsic bladder tumours, inflammation from radiation or chemotherapy or an active UTI may irritate the trigone or bladder neck causing pain and sudden urge to urinate. The presence of other physical disabilities and immobility may further aggravate urge incontinence. Treatment of urge incontinence includes the use of

anticholinergic drugs, such as oxybutynin to reduce detrusor overactivity (Table 31.1).

## Stress Incontinence

A socially embarrassing problem is that of urinary incontinence with coughing, sneezing or laughing. These physiological acts cause an increase in intra-abdominal pressure with consequent involuntary urinary incontinence. Physiologically, stress incontinence is due to abnormal urethral support. The usual treatment for this condition is surgery; however, in patients with advanced cancer, non-surgical measures need to be considered. Non-surgical treatment options include the use of anticholinergics such as alpha-adrenergic agonists such as phenylpropandamine, antispasmodic agents and tricyclic antidepressants (TCA) [11–13]. Alpha-adrenergic agonists are sympathomimetic agents that selectively stimulate alpha-adrenergic receptors. The alpha-adrenergic receptor has two subclasses $\alpha_1$ and $\alpha_2$. Alpha 2 receptors are associated with sympatholytic properties. Adrenergic agonists have the opposite function of alpha blockers. These agents mimic the actions of adrenaline and noradrenaline in the smooth muscle and central nervous system. Sympathomimetic drugs, oestrogen and tricyclic agents increase bladder outlet resistance to improve symptoms of stress urinary incontinence. When a single drug treatment does not work, a combination therapy such as oxybutynin and imipramine may be used. Although their mechanism of action differs, oxybutynin and imipramine work together to improve urge incontinence. A novel treatment for patients who have failed pharmacological therapies is the intradetrusor injections of botulinum toxin, which has been shown to decrease episodes of urinary leakage in this group of patients [13]. If medical therapy is ineffective, long-term urethral catheterisation may be necessary.

**Table 31.1** Pharmacological management of urological disorders

| Problem | Drug therapy | Usual dose |
|---|---|---|
| Haematuria from prostate | Finasteride | 5 mg daily |
| Haematuria from prostate | Dutasteride | 0.5 mg daily |
| Painful bladder/ interstitial cystitis | Pentosan polysulphate | 100 mg tds |
| Irritative symptoms | Oxybutynin | 2.5–5 mg qid |
| Urge incontinence | Oxybutynin ER | 5–15 mg daily |
| Irritative symptoms | Oxybutynin transdermal patch | Twice per week |
| Bladder antispasmodic | Tolterodine | 2–4 mg bd |
| Bladder antispasmodic | Tolterodine ER | 4–8 mg daily |
| Bladder antispasmodic | Tolterodine transdermal patch | Twice per week |
| Irritative symptoms | Trospium XR | 20 mg daily |
| Detrusor instability | Solifenacin | 5–10 mg daily |
| Extrinsic bladder compression; irritation | Darifenacin | 7.5–15 mg daily |
| Detrusor overactivity | Flavoxate | 100–200 mg PO qid |
| Eosinophilic cystitis | Hyoscyamine | 0.125–0.5 mg oral or sl |
| Detrusor overactivity | Dicyclomine SR | 10–20 mg PO qid |
| Intravesical foreign body/calculus | Phenazopyridine | 200 mg orally tds |
| Atrophic vaginitis | Oral anticholinergics | |
| Detrusor instability | Propantheline bromide | 7.5–15 mg qid |
| Detrusor instability | Imipramine chlorhydrate | 10–25 mg bd |
| Irritative symptoms | Intravesical botulinum toxin A | 100–200 units |

## Haematuria

Gross haematuria can be a very frightening symptom; however, the degree of urinary bleeding does not always correlate with the extent or the seriousness of the underlying aetiology [14]. Some patients with bladder or kidney abnormalities present with frank haematuria. However, many patients only have biochemical or

microscopic haematuria. A positive dipstick test will require microscopic confirmation of the presence of red blood cells in the urine. In most cases, a careful history, including the type and timing of bleeding, presence of clots and association of pain with urination, can point to the site of urinary tract bleeding. The presence of bright red blood suggests bleeding from the prostate or the urinary bladder whereas darker blood often originates from the upper urinary tracts and kidney. Urethral bleeding usually presents with initial haematuria followed by clear urine. If blood is present throughout the urinary stream then bleeding may be from the kidney, ureter or bladder, whereas terminal haematuria is likely to be from the bladder neck or prostatic urethra.

If haematuria is associated with symptoms of dysuria, urinary frequency and urgency, then UTI needs to be excluded. Anticoagulants, non-steroidal anti-inflammatory (NSAID) and anti-platelet drugs may lead to platelet dysfunction and cause microhaematuria. For proper and adequate assessment of the bladder, a complete cystourethroscopy is required when upper tract imaging studies do not establish the cause of haematuria. Treatment needs to be individualised, based on the underlying aetiology.

## Haematuria of the Upper Renal Tract

Investigations for haematuria include microscopy and urine culture; urine cytology; radiological examination of the kidneys, the ureters and the bladder; and almost always a cystoscopy [15]. The urinalysis is a critical component of the workup of gross haematuria and should be an initial test. A fresh, midstream urine specimen must be collected. The presence of white blood cells, leucocyte esterase and nitrites points to an infectious process that should be confirmed by urine culture and treated with antibiotics. Older patients with painless, gross haematuria should be considered at high risk for malignancy, and urine cytology should be performed.

Bleeding from the upper urinary tract is often confused with renal colic or acute ureteric obstruction causing acute flank pain. A clot causing complete ureteric obstruction can present without clinical haematuria. Macroscopic haematuria due to upper renal tract pathology, although uncommon, can occur. A careful history and appropriate radiological studies are able to differentiate between renal colic and complete ureteric obstruction from a clot or a tumour. In a patient with upper urinary tract obstruction, acute onset flank pain and no previous history of renal stones, the problem is more likely caused by clot or tumour than a stone. Imaging is a key part of the evaluation of haematuria and provides structural and functional information about the renal parenchyma and upper urinary tract. Several modalities are available for visualisation of the upper urinary tract, including ultrasonography (US), computed tomographic urography (CTU), magnetic resonance urography (MRU) and intravenous urography (IVU). Nowadays however CTU is the imaging modality of choice, as it provides the greatest anatomical detail and the highest sensitivities and specificities for a range of aetiologies ranging from renal masses to stones to urothelial tumours. CTU, compared with IVU, has a superior ability to characterise renal masses and a higher sensitivity in detecting upper tract urothelial tumours [16–18]. The non-contrast phase of CT can also detect renal stones with sensitivity of 94–98%, compared with 52–59% for IVU [19]. Initial radiological studies to investigate haematuria include standard renal ultrasound or more frequently these days CT scans. The previous standard intravenous pyelogram is rarely performed these days due to the availability of helical CT scans which have higher sensitivity for detecting abnormalities of renal tract. Spiral CT scans can also locate ureteric obstruction and possibly the aetiology of haematuria. Cystoscopy and retrograde pyelogram are almost always required to identify upper urinary tract pathology. A renal arteriogram may occasionally be necessary to exclude an arteriovenous fistula.

In patients with painless haematuria, cystoscopy and retrograde studies may identify the site and source of bleeding if it is performed at the time of active bleeding. However, further diagnostic procedures including selective ureteric catheterisation for cytology, or ureteroscopy,

may be required for definitive therapy for the underlying cause [20].

Renal cell carcinoma of the kidney or transitional cell carcinoma of the renal pelvis, or ureter, or a calculus is the most likely cause of upper renal tract bleeding. If a renal tumour is identified and staging imaging studies show no metastatic disease, a radical nephrectomy is the definitive therapy. For transitional cell carcinoma of the upper tract, radical nephroureterectomy can be performed [21, 22].

In the presence of extensive metastatic disease or if other co-morbid conditions exist, radical surgery would usually be contraindicated. Many patients, however, may tolerate a laparoscopic nephrectomy or nephroureterectomy that cause much less morbidity and seem to achieve as good an outcome as open surgery in some centres [21, 22]. When surgical measures are inappropriate, bleeding from a renal cell carcinoma can be controlled by chemoembolisation of the renal artery [23]. If bleeding persists, palliative nephrectomy may be rarely required despite the presence of metastases; however there is no survival advantage with nephrectomy in this setting; therefore careful consideration needs to be made as to the role of invasive procedures in this setting [24, 25]. For patients who have indwelling ureteric stents and develop frank haematuria, arteriography is needed to exclude a potential iliac vessel fistula in the ureter.

Medical management of controlling haemorrhage from upper urinary tracts may be necessary under certain situations when surgical means are inappropriate. Forced diuresis by increasing oral and intravenous fluids may help dilute the blood and prevent clot formation. Anti-fibrinolytics, such as ε-aminocaproic acid (EACA) and tranexamic acid, are used as inhibitors of fibrinolysis [26]. These lysine-like drugs interfere with the formation of the fibrinolytic enzyme plasmin from its precursor plasminogen, by plasminogen activators, which take place mainly in lysine-rich areas on the surface of fibrin. These drugs block the binding sites of the enzymes or plasminogen respectively and thus stop plasmin formation. Tranexamic acid is an anti-fibrinolytic that competitively inhibits the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. It has roughly eight times the anti-fibrinolytic activity of the older analogue, EACA. Systemic EACA administration can, in rare situations, be considered for upper renal tract haemorrhage; however, this approach needs very careful consideration. EACA administration may lead to the formation of large tenacious clots that can produce ureteric obstruction. Side effects of EACA are uncommon but can be serious. Thrombotic complications, myopathy, rhabdomyolysis and renal and hepatic failure have been observed with the use of EACA [27, 28].

If no obvious cause or location of upper renal tract haemorrhage is identified in a patient who is very symptomatic from the bleeding and when all other conservative measures have failed, nephrectomy or ureterectomy is a ‘last resort’ option. Patients with advanced renal cell carcinoma may develop bleeding and clot formation. Palliative measures in this situation include newer targeted systemic therapies [29, 30] or infrequently radiation therapy [31]. With laparoscopic and partial nephrectomy being used more frequently and successfully, surgical means to deal with bleeding from renal cell carcinoma remains a viable option [32].

## Haematuria from Lower Renal Tract

A majority of patients who present with microscopic haematuria are clinically asymptomatic. The source of this microscopic bleeding is usually the lower urinary tract. Microscopic haematuria rarely leads to anaemia. Non-invasive procedures such as renal ultrasound and CT scans may detect pathologies that may obviate the need for invasive procedures such as a cystoscopy. However, ureterocystoscopy may detect a malignancy such as transitional cell carcinoma (TCC) of the ureter that radiological studies may not identify. Flexible cystoscopy is now widely available and is a much better tolerated procedure [33] in frail patients, and it may not be any more uncomfortable than simple urethral catheterisation.

## Symptomatic Lower Tract Haematuria

Macroscopic haematuria may occur without a change in the voiding pattern. Clot retention causes painful and tender bladder distension due to accumulation of blood clots and urine. If prolonged and untreated, clot retention may lead to renal failure. Pain and discomfort causes patients to become restless. In general, most patients do not lose much blood in their urine, although it might be a frightening experience; however, in a number of patients, bleeding may be severe enough to cause hypotension and shock. Physical examination should include rectal examination in men for prostatic abnormalities and of the pelvis in women for gynaecological causes. Patients with frank haematuria need increased fluid intake to dilute the blood in the bladder and reduce clot formation. All anticoagulants should be ceased to minimise ongoing bleeding. A large-bore multi-eyed urethral catheter (24F or 26F) is required to completely evacuate the clots from the bladder and for subsequent vigorous bladder irrigation with water or saline to keep the bladder free of clots. After satisfactory manual irrigation, a 22F or 24F three-way indwelling catheter is inserted for cold water or saline continuous bladder irrigation (CBI). Suprapubic catheters are not large enough to provide adequate irrigation for evacuation of clots. A small number of patients, however, may continue to bleed or have obstruction of the irrigating catheter from clots and require evacuation of clots by cystoscopy or cautery. Various treatments for gross haematuria from advanced prostate cancer are available including hormonal manipulation, anti-fibrinolytics, embolisation of the internal iliac arteries and intravesical instillations of various agents [34, 35].

Palliative radiotherapy can control haematuria in a significant proportion of patients in the short term, but responses are short-lived; after 6 months less than one-third of patients are free of recurrent bleeding. Furthermore, patients who have been previously irradiated have limited options for further palliative radiation therapy. Transurethral surgery however is very effective therapy for haematuria in patients with locally advanced prostate cancer and hence is the primary therapeutic modality [36].

Apart from malignancies of urological tract, lower urinary tract haematuria can occur due to other causes. Haemorrhagic cystitis often occurs following treatment for cancer. Haematuria caused by cytotoxic drugs does not usually cause irritative voiding symptoms. Cyclophosphamide and ifosphamide are the agents most likely to cause haemorrhagic cystitis. The risk of haemorrhagic cystitis after cyclophosphamide is reported to be between 12% and 41% [37]; however, with most standard doses, the expected risk is about 5%. The active metabolite of cyclophosphamide is acrolein, and this agent is believed responsible for causing mucosal damage [38, 39]. 2-Mercaptoethane sulphonate (mesna) is a sulphydryl compound that reacts with the metabolites of cyclophosphamide that may produce bladder wall irritation. Mesna is converted in the blood to a biochemically inactive compound that is reduced back to mesna in the kidneys. In vivo mesna is a chelating agent that binds acrolein; hence it protects the bladder mucosa without interfering with the cytotoxic effect of cyclophosphamide or ifosphamide [40, 41].

For bleeding refractory to conservative measures, topical agents can be used with varying degrees of success. Intravesical administration of formalin is one of the most effective but also the most toxic treatments for haemorrhagic cystitis. Formalin stops bleeding by fixing the bladder mucosa by cross-linking proteins, thereby preventing necrosis, sloughing, blood loss, occlusion and fixation of telangiectatic tissue and small capillaries [42–44]. A 2.5–10% formalin solution is instilled passively into the bladder using low-pressure gravity feed over 15–30 min. The bladder is then irrigated continuously with normal saline. Relief of haematuria is seen within 1–5 days, with a mean duration of 4 months, without general complications. The method has been widely used with mostly good outcomes. In a study of 14 patients, treated with 1% formalin instillation, 10 patients were responsive to the first instillation and a further two to the second instillation. Cessation of haematuria was achieved in the remaining two patients by another treatment

with 2% formalin. Severe side effects however are frequently observed with formalin instillation in patients with persistent gross haematuria. Reflux of formalin to the ureters and kidneys can lead to ureteral stenosis, fibrosis, obstruction, hydronephrosis and renal papillary necrosis. The prophylaxis against vesicoureteral reflux requires prophylactic ureteric balloon catheters to prevent retrograde flow of formalin. Other toxicities reported with intravesical formalin therapy include renal failure, clinically significant reduction of bladder capacity to <100 mL in many, urinary incontinence, urgency and nocturia and possibly retroperitoneal fibrosis [45, 46]. Intravesical formalin has also been reported to cause hydronephrosis and vesico-ureteric reflux, perforation and bladder fibrosis. Although the incidence of complications appears to be lower if formalin solutions of 4% are used, the effectiveness of this treatment seems to be inferior. Although the technique of formalin instillation is simple enough, the procedure itself is painful and requires general or spinal anaesthesia, and a catheter has to be left in the bladder after the procedure for bleeding control. There are no studies comparing the effectiveness of formalin instillation to catheterisation alone [47–50]. However, case reports and non-randomised studies report up to 80% efficacy of formalin in controlling haemorrhage from the bladder [51–53]. It is an interesting observation that for controlling haematuria caused by either cyclophosphamide cystitis or unresectable carcinomas of the bladder, generally lower concentrations of formalin seem effective. In contrast, higher formalin concentrations may be required to control bleeding due to radiation cystitis. An interesting modification of intravesical formalin instillation is the endoscopic intravesical placement of 10% formalin-soaked pledgets rather than the standard 4% formalin instillation. This modification had fewer toxicities and was still effective in controlling bleeding in up to 82% of patients [53]. Overall however the use of intravesical formalin has substantially declined over the years as less toxic therapies have become available. This therapy must be reserved for haemorrhagic cystitis that is truly refractory to all other treatments. Another intravesical treatment for acute vesical haemorrhage is a 10–20 min instillation of 0.5–1.0% silver nitrate in sterile water. In refractory cases, multiple instillations of silver nitrate may be required [54]. No controlled randomised trials of silver nitrate have been done.

Other agents that have been used in managing lower urinary tract bleeding have also been used in controlling bleeding from upper urinary tract. EACA works as an anti-fibrinolytic or anti-proteolytic agent and can be used to treat bladder mucosal haemorrhage. EACA can be given either orally, parenterally or intravesically [55–57]. Although most of the reports of use of EACA for vesical bleeding have been pilot studies, case studies or uncontrolled studies, there has been widespread use of EACA. Clinical experience of many years' duration may justify its use for severe haemorrhagic cystitis. A loading dose of 5 g is given followed by hourly doses of 1.00–1.25 g. Bleeding should stop within 8–12 h. If bleeding is successfully controlled, maintenance EACA therapy with total oral daily dosage of 6–8 g divided into four doses is given. If administered intravesically, EACA is given as continuous irrigation (CBI). To each litre of normal saline 200 mg, EACA is added, and the irrigant is administered as CBI. However, EACA causes thick clots, which are very difficult to irrigate in patients with normal urethral catheters. To control haemorrhage from upper renal tracts, EACA is therefore contraindicated as the thick clots cause upper renal tract obstruction, clot colic and, potentially, renal failure.

Another topical agent, ammonium salt of aluminium, 1% solution of alum, administered intravesically and CBI, also has shown modest efficacy in stopping bleeding from the urinary tract [58]. Alum is composed of either aluminium ammonium sulphate or aluminium potassium sulphate. As an astringent, aluminium acts by precipitating protein over bleeding surfaces. Its action is limited to the cell surface and interstitial spaces, and due to its low cell permeability, cells remain viable. Hardening of the capillary endothelium occurs leading to decreased capillary permeability, contraction of intercellular space and vasoconstriction. As a result, local oedema,

inflammation and exudation are also reduced. Compared to formalin the systemic absorption of alum is also lower [59–61]. Alum excretion proceeds through a renal route, and increased serum levels can result in prolonged prothrombin times [62]. In the pilot study of intravesical administration of 1% alum solution, complete response to haematuria, from massive bladder haemorrhage, over various periods was observed [59]. No side effects were observed, and treatment could be given without anaesthesia. Since the initial publication, several studies on small numbers of patients have been reported [63–65]. Alum administration is relatively safe and non-toxic and does not require general anaesthesia. Normally, serum aluminium is excreted rapidly by the kidneys, with a potential excretion reserve of up to 30 times normal values. Renal insufficiency, accumulative absorption or massive absorption due to large absorptive surfaces, like a large bladder tumour, may cause aluminium toxicity. Aluminium toxicity causes neurofibrillary degeneration in the central nervous system, which can lead to encephalopathy, malaise, speech disorders, dementia, convulsions and vomiting. It can also cause severe allergic reaction in susceptible individuals [66, 67]. Intravesical alum has success rates between 66% and 100% using 1% alum solutions. However, no hard definitions of success and relapse are available. Bladder spasms and suprapubic pain are common during alum treatment. These symptoms are obviously caused by the acidity of the alum solution but can be effectively managed by antispasmodics. Serious side effects of alum irrigation have only been reported in isolated cases. Encephalopathy and acute aluminium intoxication occurred predominantly in patients with renal dysfunction [68–71]. To avoid systemic side effects, serum aluminium can be monitored during treatment. Signs of clinical toxicity seem to occur at a mean serum aluminium concentration of 7.4 mmol/L, and surveillance of patients is recommended when concentrations exceed 3.7 mmol/L [72, 73]. Patients with normal renal function and no clinical evidence of aluminium toxicity have only a modest increase of serum aluminium (from 1.68 mmol/L at baseline to 3.36 mmol/L on treatment with alum [62]. On balance, a 1% alum solution can be considered to be a treatment option, at least in patients without renal dysfunction. Measurement of serum aluminium would not appear to be necessary provided usual concentrations and amounts of alum irrigation are used.

Prostaglandins can cause constriction of vascular smooth muscle cells and aggregation of platelets. Intravesical administration of carboprost tromethamine, an F2-α prostaglandin, has been used to treat cyclophosphamide-induced haemorrhagic cystitis. Carboprost tromethamine is administered as intravesical solution at a concentration of 0.4–1.0 mg/dL for 2 h, four times per day, alternating with continuous saline bladder irrigation for 2 h, during 4–5 days [74, 75]. Only one study compared the effect of intravesical instillation of PGF2 alpha with alum on haematuria caused by bladder cancer. In a study of ten patients treated with 1 mg PGF2 alpha daily for a maximum of 5 days, there were six complete controls of macroscopic haematuria, and two had partial control. PGF2 treatment did not have any advantage compared to alum. In both groups, patients had only local side effects such as bladder spasms or catheter blockage. In view of the high cost, low availability and stringent storage conditions for PGF2 alpha, these agents should only be considered in patients who have failed alum treatment. Several studies have been carried out on the use of prostaglandin for the treatment of haemorrhagic cystitis caused by radiation, cyclophosphamide and bone marrow transplantation. Prostaglandin was effective in these studies, although the detailed mechanism of prostaglandin action on the bladder epithelium remains unclear.

Both external beam radiation and brachytherapy for cancers of genitourinary tract, cervix, rectum or other pelvic cancers may cause haemorrhagic cystitis. Haemorrhagic cystitis can occur 6 months to 10 years after pelvic radiation therapy with moderate to severe rates of haematuria at 3–5% after radiotherapy for pelvic malignancies [76]. Radiation cystitis usually presents with haematuria, dysuria, urinary frequency and urgency. Late effects of radiation therapy

generally result from a combination of vascular damage through radiation endarteritis in combination with a loss of parenchymal cells. Radiation endarteritis leads to significant vascular changes with consequent hypoxia, telangiectasia, hypovascularity and hypocellularity several years after initial therapy. Radiation therapy may also cause depletion of the stem cell population below levels needed for tissue repair [77]. Such loss of stem cells leads to an inability to replace normal collagen and cellular losses leading to tissue breakdown and healing. If severe, these changes may eventually result in tissue fibrosis. Unlike chemotherapy-induced haemorrhagic cystitis, there are no preventative agents or measures in common use. For radiation-induced haemorrhagic cystitis, aggressive symptomatic therapy is needed, and further radiation exposure is to be avoided.

Radiation-induced haemorrhagic cystitis has been treated with hyperbaric oxygen with significant success [76]. Obliterate endarteritis secondary to ionising radiation leads to tissue hypoxia and poor healing. Hyperbaric oxygen therapy has been demonstrated to improve angiogenesis and promote healing in radiation injured tissue by formation of healthy granulation tissue, including the bladder [78]. Hyperbaric oxygen given at the time of initial radiation therapy may also prevent the long-term risk of haemorrhagic cystitis [78]. Hyperbaric oxygen can reverse some of the ischaemic changes caused by radiation therapy. Furthermore, hyperbaric oxygen induces vasoconstriction with direct effects on bleeding from the bladder mucosa. Hyperbaric oxygen therapy is effective in up to 75–80% of treated patients especially if commenced within 6 months of the development of radiation-induced haemorrhagic cystitis. Treatment efficacy seems to be independent of prior intravesical therapy and the timing of radiotherapy [78, 79].

Conjugated oestrogens have also been used for the treatment of cancer therapy-induced haemorrhagic cystitis [80, 81]. The recommended starting dose of conjugated oestrogens is 2.5 mg twice daily followed by a maintenance dose of 0.625–1.25 mg daily. Due to the cardiovascular toxicities of conjugated oestrogens, the lowest effective dose of oestrogen should be used. However, in a patient with poor performance status and uncontrolled urinary tract haemorrhage, conjugated oestrogen therapy may be a consideration.

Recurrent haemorrhagic cystitis due to locally advanced unresectable cancer may respond to oral pentosan polysulphate [77]. Rarely oral tranexamic acid could be used as this drug can cause clot formation [26, 82]. Rarely hypogastric artery ligation or embolisation or proximal urinary diversion with or without cystectomy may be the procedures of last resort. Sodium hyaluronate, a derivative of hyaluronic acid, can replenish the deficient surface glycosaminoglycan (GAG) layer [83]. For the treatment of refractory interstitial cystitis intravesical, sodium hyaluronate has been quite effective [84, 85] and has been investigated as preventive treatment of radiation-induced haemorrhagic cystitis. In a pilot study of sodium hyaluronate, in patients with advanced cervical cancer treated with pelvic radiotherapy, weekly chemotherapy and high-dose rate brachytherapy, the protective effect of this agent on the urinary bladder mucosa was confirmed [86]. The intravesical instillations with 40 mg/50 mL sodium hyaluronate solution prior to each brachytherapy session significantly reduced the incidence of radiation-induced cystitis in patients with cervical and endometrial cancer [87]. Weekly instillations of sodium hyaluronate solution have a protective effect on the bladder, reducing the incidence and severity of radiation-induced cystitis [88]. The treatments are generally well tolerated, and no related adverse events were reported [87, 88]. A novel use of intravesical tacrolimus, an immunosuppressive drug used mainly after allogeneic organ transplant to lower the risk of organ rejection, in treatment of radiation-induced haemorrhagic cystitis has been reported and needs further investigation [89].

If the bleeding is coming from the prostate or bladder neck, a TURP is required to resect the abnormal prostatic tissue. The friable area is electrocoagulated to prevent further bleeding. A urethral catheter on traction may further compress the bleeding vessels in the prostate and

bladder neck. However, despite TURP or TURBT, chronic haematuria secondary to abnormal prostatic pathology may recur. Finasteride, a synthetic anti-androgen, inhibits type II 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT). Finasteride is used in treating benign prostatic hyperplasia for decreasing the risk of urinary retention and haematuria as well as for the treatment of hair loss. Finasteride decreases suburethral prostatic microvessel density and significantly lowers VEGF expression at the suburethral but not at the hyperplastic prostate level. Bleeding observed in patients with BPH and obstructive voiding symptoms may be due to increased neovascularity within the prostatic urethra rather than the hyperplastic prostate zone [90]. Finasteride induces a reduction in the density of prostatic microvessels, thereby helping to reduce bleeding [90]. A few non-randomised clinical studies confirm that finasteride reduces the severity and frequency of recurrent haematuria due to bleeding from the prostate [91, 92]. However, most of the clinical trials of finasteride have been in benign prostatic hyperplasia, and its role and effectiveness in haematuria caused by prostate cancer have not been confirmed. As finasteride has relatively few side effects, in recurrent prostatic bleeding, it could be used empirically (Fig. 31.1).

Patients, who fail conservative measures, may require total cystectomy and urinary diversion to control refractory haemorrhagic cystitis. However, the outlook of these patients is extremely poor, and most of these patients are poor surgical candidates because of ongoing haemorrhage and coagulopathy.

In seriously ill patients, who are not suitable for major surgical intervention, selective embolisation of branches of the hypogastric arteries may be successful in stopping bleeding. Selective embolisation works best when arteriography demonstrates a discreet vessel responsible for the bleeding; however, in most patients, such discreet sources of bleeding cannot be identified as the entire bladder urothelium is usually involved in bleeding. Permanent embolotherapy is now carried out with new, more thrombogenic coils made of either platinum or titanium [93]. Complications of arterial embolisation include claudication of the gluteal muscles, temporary lower extremity paralysis and even necrosis of the bladder [93–96].

## Urinary Outlet Obstruction

Urinary tract obstruction can occur throughout the urinary tract, from the kidneys to the urethral meatus. Causes of unilateral or bilateral obstruction include calculi, tumours, strictures and anatomical abnormalities and malignant retroperitoneal fibrosis [97].

Anatomically, certain parts of the urinary tract are more susceptible to obstruction. Narrowing of the ureters can occur at the pelviureteric junction, the pelvic brim and the ureterovesical junction. In women, the distal ureter, as it crosses posterior to the pelvic blood vessels and the broad ligament in the posterior pelvis, is another potential site of obstruction. Furthermore, urinary tract obstruction can also occur due to the external compression of the ureters by gynaecologic malignancies.

### Bladder Neck and Lower Urinary Tract Obstruction

In men, common causes of lower urinary tract obstruction include BPH, malignancies of the prostate gland as well as local invasion of tumours of the rectum or urethra. Bladder neck obstruction occurs much less frequently in women than in men. In women, locally advanced cancers of the ovary, cervix or the uterus can also cause bladder neck obstruction. Prolonged complete bladder neck obstruction may lead to renal failure due to chronic urinary retention and especially if sepsis is superimposed. In the presence of bladder neck obstruction, detrusor muscles may not be able to overcome urethral resistance; hence, the bladder is unable to be emptied. Neuropathic causes may lead to primary failure of detrusor muscles. Patients with symptoms of urinary frequency, urgency, nocturia and a poor urinary stream, with or without haematuria, frequently

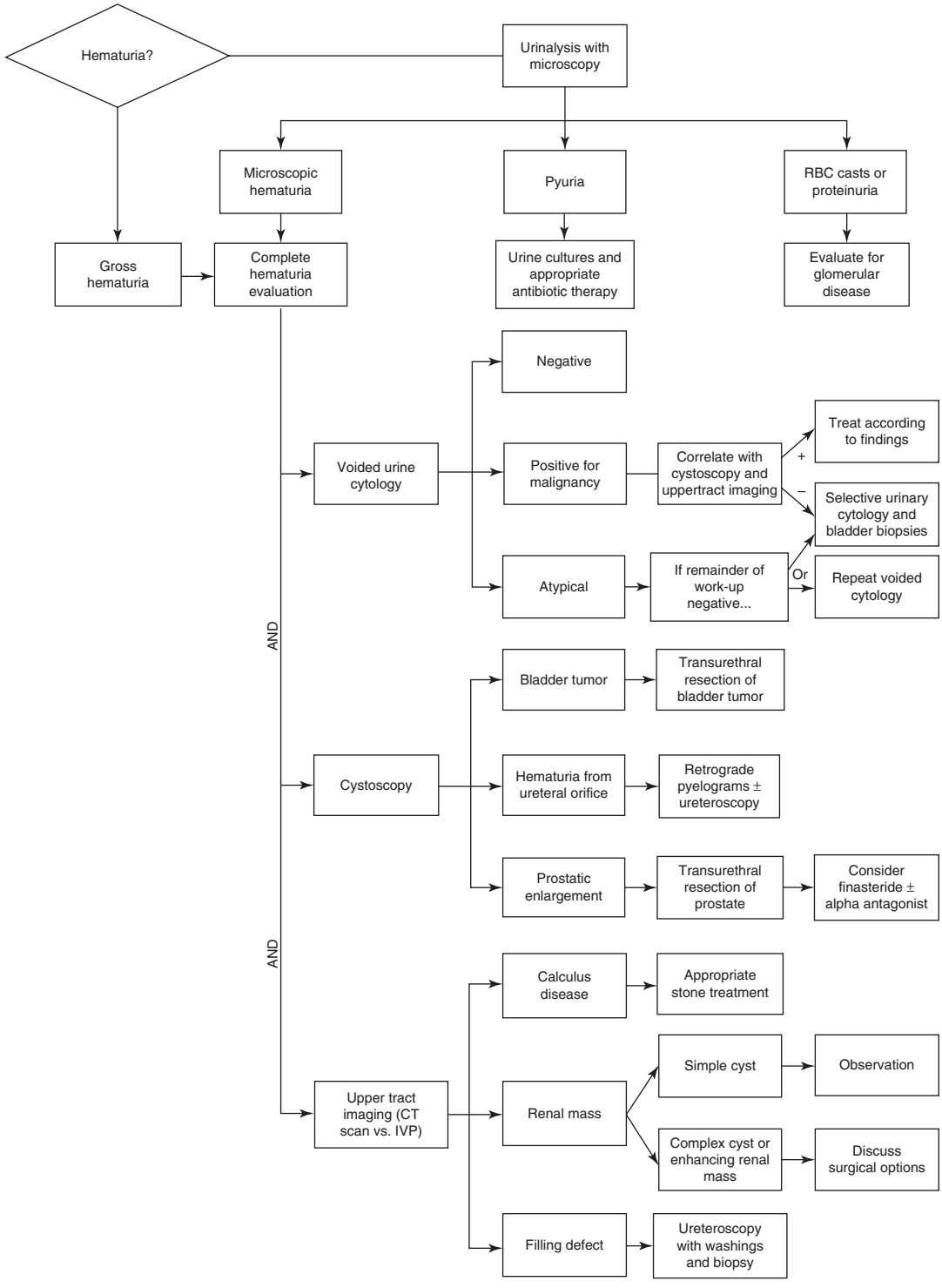


**Fig. 31.1** From Chap. 32 Urologic Issues in Palliative Care Editors: Berger AM, Shuster JL, Von Roenn JH. *Principles & Practice of Palliative Care & Supportive Oncology, 3rd Edition*. Copyright ©2007 Lippincott Williams & Wilkins

have mechanical lower urinary tract obstruction. Patients with a poor urinary stream, abnormal voiding urgency or sensation and decreased urinary frequency have primary detrusor failure. Cannabinoid receptors and their agonists, endocannabinoids, can be detected throughout the urinary tract. However, despite a paucity of well-tolerated agents for patients with lower urinary tract symptoms (LUTS), clinical targeting of this system has remained largely overlooked. In this review, the authors describe the current evidence for a role of cannabinoids in micturition and as a treatment for LUTS [98].

As the management of these disorders differs significantly, it is critical to make an appropriate diagnosis before initiating therapy (Table 31.1).

## Alpha-Blockers for Prostatic Bladder Neck Obstruction

Alpha-blockers (e.g. preposing, tamsulosin, finasteride/dutasteride) have been shown to significantly improve the symptoms of benign prostatic hypertrophy and are considered first-line treatment [99]. 5-Alpha-reductase inhibitors can also be used to treat lower urinary tract symptoms. This family of drugs has been shown to improve symptoms as well as decrease the risk of acute urinary retention and the need for surgery. Long-term combination therapy has been shown to reduce clinical progression of benign prostatic hypertrophy [100]. 5-Alpha-reductase inhibitors can also manage prostate-related haematuria by reducing the vascularity of the prostate. The mechanism of action for this is uncertain [101, 102]. 5-Alpha-reductase inhibitors should, however, only be commenced under the recommendation of a urologist [99].

A comprehensive history of presentation, use of medication (e.g. anticholinergics, opioids), past medical history (diabetes, calculi, tumours, radiation therapy, retroperitoneal fibrosis and neurologic disorders) and past surgical history are helpful in identifying potential causes of obstruction.

Complete urinary retention is usually preceded by gradually progressive symptoms of urinary obstruction including urinary hesitancy, frequency, nocturia, incontinence, UTI, poor urinary stream and incomplete bladder emptying.

Urethral stricture may occur due to previous urethral trauma, surgery or infection. Furthermore, anticholinergic or α-adrenergic drug use may also cause urinary bladder obstruction. Usually, the bladder is palpable and painfully distended. Cystoscopic studies are required to diagnose meatal stenosis, urethral fibrosis, induration or tumour-related stricture.

A urethral or, more frequently, a suprapubic catheter will decompress the bladder. If the bladder obstruction has been present for some time, the sudden relief of obstruction may lead to a significant post-obstructive diuresis. In the event of prostatic enlargement causing urinary obstruction, a limited transurethral prostatectomy ('channel TURP') may achieve good palliation; however, surgical procedures in these patients may be associated with increased risk of bleeding, clot retention, infection and persistent failure to void.

## Symptomatic Treatment

Bladder neck obstruction due to prostatic enlargement requires urethral catheterisation for symptom relief. In addition, medical therapy using one of the selective α-1 antagonists may be required. These drugs work by blocking the action of adrenaline on the smooth muscle of the bladder and the blood vessel wall. Drugs of this family include terazosin, doxazosin, alfuzosin or tamsulosin. The efficacy of these drugs in advanced prostate cancer or in patients with other co-morbidities, debility and poor performance status is less well known, but the likelihood of recovery of adequate bladder detrusor function is small.

If conservative measures fail to decompress the obstruction, more-invasive measures including long-term urethral or suprapubic catheterisation, intermittent self-catheterisation, urethral stenting, urinary diversion or resection of the obstructing lesion may be needed. In patients with malignant tumours, definitive measures should be considered much earlier as recovery of

bladder function in this setting is much slower and often incomplete.

## Androgen Suppression Therapies

A majority of patients with newly diagnosed and locally advanced and metastatic prostate cancer respond to androgen suppression therapy, and this treatment may be preferable to surgery [103, 104]. Luteinising hormone stimulates Leydig cells in the testes to produce testosterone, which is converted to dihydrotestosterone (DHT) by the action of 5α-reductase [105]. DHT binds to intracellular androgen receptors. Androgen suppression therapy for prostate cancer is aimed at reducing circulating testosterone to levels seen in castrate men. Low testosterone levels cause apoptosis in neoplastic prostate cells, with little or no acute effect on non-androgen target tissues. Although androgen deprivation therapy (ADT) can be achieved by bilateral orchidectomy, medical castration with luteinising hormone-releasing hormone (LHRH or GnRH) analogues with or without an anti-androgen therapy is nowadays the preferred approach. Immediately after commencement of LHRH analogue therapy, there is a surge in testosterone levels, which may cause spinal cord compression from vertebral metastases as well as aggravate bone pain. Concomitant administration of an anti-androgen agent, 1–2 weeks prior to the start of GnRH therapy, avoids the flare phenomenon. Since 2010, several new drugs have been approved by regulatory authorities, which include abiraterone and enzalutamide. These drugs enable more effective inhibition of intraprostatic androgen production or the androgen receptor itself [106].

If satisfactory voiding does not occur within 2–3 weeks, a TURP, other surgical treatments or long-term catheterisation will be required. Patients with advanced prostate cancer, who either develop obstructive uropathy while on ADT or whose obstructive uropathy fails to adequately respond to ADT, have very poor survival [107].

## Self-Catheterisation

For patients with mechanical bladder outlet obstruction, self-catheterisation or a chronic indwelling catheter is not appropriate and is best for those with urinary retention due to detrusor failure. Patients with urinary retention who are physically capable and motivated may be suitable for clean intermittent self-catheterisation. This approach causes less urinary tract infection than either urinary retention or an indwelling catheter and allows the patient to spend most of the day without a urethral catheter [108]. Chronic indwelling urethral catheters can be associated with infection, urethral stricture, epididymitis and symptoms associated with a dysfunctional bladder. These methods are suitable for patients who are unfit for surgery or those who choose not to undergo a surgical procedure to decompress the bladder. The amount of residual urine in the bladder must be monitored to prevent upper urinary tract complications due to residual urine at high pressures. Despite clean intermittent catheterisation, most patients develop asymptomatic pyuria and bacteriuria. Empirical broad-spectrum antibiotic therapy should be avoided unless there is systemic evidence of urinary infection. Chronic low-dose antibiotics may be justified in patients with recurrent symptomatic urosepsis.

## Long-Term Intravesical Catheters

For patients with acute urinary retention, regardless of the underlying cause, short-term indwelling catheters are necessary for immediate decompression of a distended and tender bladder. For sick and medically unfit patients with poor performance status a long-term permanent catheter may be the best palliative choice. Modern long-term urethral catheters need to be replaced approximately every 6 weeks and therefore may be the best choice for patients who are technically difficult to catheterise. However, encrustation and the subsequent blockage of indwelling urinary catheters are common problems affecting up to 50% of long-term catheterised patients [109]. Patients who develop catheter blockage

due to encrustation are classified as 'blockers'. 'Blockers' have a high urinary pH and ammonium concentration and are often women with poor mobility and often have urinary leakage or urinary retention. Urethral catheters cause significant discomfort in patients with bladder spasms. In this group of patients, urine may leak around the urethral catheter, and they may experience severe suprapubic pain or discomfort. A combination of oral anticholinergic, analgesic and antispasmodic drugs may be effective in pain control. Long-term indwelling catheters may become calcified paradoxically causing urinary obstruction, urethral stricture and calcification of the catheter balloon, urethritis, epididymitis, urosepsis and urethral erosion. Suprapubic catheters avoid some of the complications of a urethral catheter; however, long-term catheters are still associated with many other complications.

## Surgery for Urinary Obstruction

### Transurethral Resection of the Prostate

TURP is a surprisingly challenging procedure, technically. The procedure is usually required in older, less healthy men. However, continuing improvements in surgical technique and instruments allow this procedure to be done more safely and easily. Approximately 25% of all candidates for TURP present with urinary retention and require preoperative catheter drainage. Some of these men may develop post-obstructive diuresis and other electrolyte disturbances. Abnormal electrolyte and elevated BUN and creatinine levels should be corrected. The use of preoperative finasteride may reduce bleeding during and after TURP surgery, although the optimal timing is unclear. Significant amounts of fluid may be absorbed during a TURP, especially if venous sinuses are opened early or when the operation is prolonged. On an average, during a TURP, approximately 1.0–1.2 L fluid is absorbed in the first hour, the so-called TURP syndrome [110]. This may lead to dilutional hyponatraemia, which causes mental confusion, nausea, vomiting, visual disturbances, haemolysis, haemoglobin nephropathy, coma, cardiac failure and shock. Haemodynamically, this is characterised initially by increased central venous pressures, hypertension, bradycardia and other signs of early vascular overload, including restlessness, tachypnoea and, sometimes, dusky skin changes of the conjunctivae, mucous membranes or fingernails. Symptoms of TUR syndrome generally do not occur until the serum sodium level has decreased to 125 mmol/L or less. Therefore, a TURP is recommended only when the procedure is expected to last no longer than 90 min [111, 112]. Other expected and mostly manageable complications following TURP include bladder perforation and urinary tract infection. Most TURPs are done with saline resection (Gyrus); hence TUR syndrome is less common. Recent technological advances have led to the development of new bipolar resection systems that permit normal saline to be used as an irrigant [113, 114]. Bipolar resectoscopes have undergone evaluation for safety and efficacy and are reported to have advantages over standard monopolar resection [114–119]. As the bipolar system uses physiologic saline as the irrigation fluid, the dangers of TUR syndrome are minimised, and the usual time limit of resection is increased. The bipolar system can be used safely and effectively in the resection of glands of any size [119]. Even resecting large prostate glands leads only to a small fall in haematocrit [113, 114]. In general, most patients do not require a blood transfusion. A fall of 1.3 mEq/L in the serum sodium concentration in the saline bipolar group has been reported. In a small pilot study, it was observed that despite a prolonged resection time, the mean drop in serum sodium concentration was only 1.6 mEq/L [120]. In comparison, the glycine monopolar group showed an appreciable decline in sodium levels (4.12 mEq/L).

### Resection of the Prostate

In patients with prostate cancer, particularly those with locally advanced disease, obstructive voiding symptoms are common. In newly diagnosed prostate cancer, up to 82% of men present with obstructive symptoms. Approximately one-third of patients with prostate cancer, on an observation treatment plan, develop bladder neck

obstruction and require TURP [36]. Even after radiotherapy for stage C prostate cancer, many patients subsequently require TURP for symptomatic local progression. When assessing the role of TURP, three aspects need to be considered: (a) the safety of the procedure, (b) the functional outcome and (c) oncological aspects [121]. For many patients, with symptomatic locally advanced prostate cancer, a channel TURP is a very good option. Channel TURP removes only the obstructing prostatic tissue and does not resect all of the malignant prostatic tissue. A channel TURP procedure has less operative morbidity, but this technique is suitable only for a proportion of patients due to the increased risk of bleeding, clot retention, infection and persistent failure to void [122]. Other complications of channel TURP include urinary incontinence, although uncommon at <5%, due to the procedure cutting through malignant prostatic tissue and the normal anatomic structures being disturbed. Tumour may also directly invade the external urethral sphincter. In carefully selected patients, channel TURP for prostate cancer results in satisfactory voiding; however, about one in five patients will require other procedures several months later [123, 124]. TURP therefore is a suitable option for symptomatic relief of bladder outlet obstruction from locally advanced prostate cancer. A risk of tumour dissemination through prostatic venous channels exists when TURP is performed through malignant tissue. Nevertheless, there is no evidence that patients undergoing palliative TURP have worse survival than those who do not. Robotic radical prostatectomy is now being used more often as it offers the advantages of minimally invasive laparoscopic approach. This technique has been gaining widespread acceptance in the United States and Europe and is increasing in penetration worldwide [125].

A TURP is occasionally indicated after brachytherapy, as monotherapy for the treatment of localised prostate cancer. The indications for TURP are acute urinary retention and failure to resume micturition after catheter removal or bothersome urinary symptoms refractory to medical treatment. Urinary retention has been reported in 1.5–22% of patients after brachytherapy, and post-implant TURP rates range from 0 to 8.7% [126]. If possible, TURP should be deferred for at least 6 months following brachytherapy to allow delivery of over 90% of the intended radiation dose. If TURP is performed after brachytherapy, the post-operative urinary incontinence rates are between 0% and 18% [124, 127].

Alternatives to surgical prostatectomy include intraurethral stent, transurethral microwave therapy, transurethral needle ablation and holmium [128] and GreenLight (ablative) biolitec thulium laser enucleation [129]. Drug therapy, such as the use of α-blockers and 5α-reductase inhibitors, may be used for symptomatic prostatic hyperplasia but may not be effective in men with refractory urinary retention from prostate cancer.

## Newer Treatments for Urinary Obstructions

Newer, minimally invasive therapeutic procedures minimise complications of bladder and prostate surgery. These procedures can resect, evaporate or coagulate the prostatic lesions and include electrosurgical vapourisation of the prostate, transurethral needle ablation, microwave therapy and high-frequency radio wave ablation. These outpatient-based treatments are transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA). TUMT provides very good treatment of LUTS as an alternative to drug therapy, TURP, transurethral needle ablation (TUNA), photoselective vapourisation of the prostate (PVP), open prostatic enucleation or other surgical therapies. TUMT is appropriate therapy for patients with moderate to severe LUTS, for those in whom medical therapy has failed and for those who are averse to drug therapy. A few randomised clinical trials have compared TUMT with TURP [130]. Symptomatic improvement and durability was greater after TURP than after TUMT and better objective response as measured by maximal flow rate. However TUMT has a lower incidence of retrograde ejaculation, erectile dysfunction, TURP syndrome, clot retention and transfusion requirement [131]. Similar to TUMT, in comparison to

TUNA, clinical trials have shown TURP to be superior to TUNA. With TUNA procedure, a 58% improvement in symptoms was reported, but the retreatment rate was high in the TUNA patients at 21.2–51% [131, 132]. A meta-analysis confirms these findings, showing that TUNA does provide symptomatic improvement but symptom and quality-of-life scores were all higher with TURP [132, 133]. Patients undergoing TUNA had fewer complications, lower incidence of retrograde ejaculation, erectile dysfunction and strictures in comparison to TURP. Both TUMT and TUNA procedures deliver high energy to the prostate to create heat and cause tissue necrosis. The necrotic tissue is subsequently reabsorbed leading to shrinkage of the prostate gland resulting in relieving urethral obstruction [133, 134].

Other less-invasive procedures for resection of prostatic utilise lasers. The visual laser ablation of the prostate (VLAP) technique involves the use of Nd:YAG lasers for treatment of benign prostatomegaly [135]. Potassium-titanyl-phosphate (KTP (GreenLight)) and holmium lasers vapourise benign prostatic tissue rather than resect it. Photoselective vapourisation of the prostate (PVP) with the GreenLight (KTP) laser uses a high-power 80 W laser. A 550 μm KTP laser fibre is inserted into the prostate to vapourise most of the prostatic tissue [136, 137]. KTP lasers can penetrate to a depth of 2.0 mm. Holmium laser ablation of the prostate (HoLAP) is a similar procedure [138]. The HoLAP procedures direct the beam from a high-power 100 W laser at a 70° angle using a 550 μm side-firing fibre. The holmium wavelength is invisible to the naked eye. Whereas KTP relies on haemoglobin as a chromophore, for holmium lasers, water within the target tissue is the chromophore. The penetration depth of holmium lasers is <0.5 mm, avoiding complications associated with tissue necrosis often found with the deeper penetration and lower peak powers of KTP.

These less-invasive procedures reduce the risks of complications and decrease post-operative catheter times when compared to standard TURP. These newer techniques, although developed for the treatment of benign disease, may have a role in the management of prostate cancer that remains undefined and experimental [139]. Overall, these alternative methods seem promising in providing a quick relief of symptoms from urinary outlet obstruction, with relatively low morbidity. However, long-term results of the benefits and limitations of these techniques require further follow-up.

## Urethral Stents

Self-expanding metal stents are now widely used for the palliation of obstructed organs and viscera in multiple organ systems, including the urinary tract [140]. These devices are relatively easily inserted under local anaesthetic with minimal sedation [141, 142]. With further improvement in technology, newer stents are exemplified by the nickel-titanium shape-memory alloy stent (Memokath 051 Stents) [143]. These stents are particularly useful for patients with poor performance status and with a limited life expectancy. These self-expanding stents may obviate the need for placement of long-term indwelling urethral or suprapubic catheters and external urine collection. Newer double flange stents are also available which have fewer complications and less stent migration [144]. However, stent migration has been reported in a number of patients [143]. Almost all the patients initially achieve successful voiding with insertion of a urethral stent; however, about 25% of patients subsequently re-obstruct due to stent migration. The presence of the stent provides a framework for deposition of urine constituents. Over time, this will occur with any stent. To prevent encrustation, dilution of the urine with high fluid intake and aggressive treatment of any urinary tract infection should be undertaken [145]. Prevention of encrustation and possible stent occlusion is also one of the major indications for prophylactic exchange of ureteral stents as recommended by the manufacturer. In benign prostatic hyperplasia, 23% of the stents need removal, as do 5% of those implanted in patients with bulbar urethral stricture and 22% of those in patients with detrusor sphincter dyssynergia. Of the explantations, about 44% need to be

done during the first year. Migration and/or inappropriate placement is the cause for explantation in up to 38.4% of cases [146]. These stents seem to be more durable and more successful in benign than in malignant prostatic enlargement [146–149]. Patients, who have intrinsic obstruction as well as detrusor muscle dysfunction, only have a modest improvement in their voiding. The procedure is safe and has minimal long-term complications. The stent also provides a sustained, good quality of life for patients and avoids the necessity of long-term catheterisation. Intra-prostatic stents therefore are very promising for the management of urinary outflow obstruction in the medically ill patient who has bladder neck obstruction, as long as the technique of stent insertion is correct and the chosen stent is of the right length.

## Ureteric and PUJ Obstruction

Acute renal failure secondary to bilateral ureteric obstruction is a common problem in palliative care. Obstruction may be secondary to pelvic tumour invasion, compression of both ureters by retroperitoneal tumour or metastatic pelvic lymph nodes and, rarely, by direct metastases to the ureters. In the majority of patients, an underlying malignancy will be diagnosed [150]. In almost one-half, the development of bilateral ureteric obstruction is the initial manifestation of the underlying cancer. The commonest cancer in women is carcinoma of the cervix and, in men, carcinoma of the prostate.

Pelviureteric junction (PUJ) obstruction is defined as an obstruction of the flow of urine from the renal pelvis to the proximal ureter. This condition is often congenital and benign. The critical decision to be made in dealing with suspected PUJ obstruction is whether the radiologic findings correlate with the physiologic picture. The role of the medical treatment of hydronephrosis and hydroureter is limited to pain control and treatment or prevention of infection. Most conditions require either minimally invasive or rarely surgical treatment. Bulky tumour in the pelvis or in the retroperitoneum may present with unilateral or bilateral extrinsic ureteric obstruction. Conservative therapy is the preferred approach for a patient with limited life expectancy, poor performance status, other co-morbidities and a poor quality of life. Surgical urinary diversion for symptomatic progressive upper urinary tract obstruction is of minimal or no benefit for patients who have no further anticancer therapy options and who have a limited life expectancy. Conservative measures may allow a comfortable, peaceful and predictable death. Patients with tumour-related urinary tract obstruction have severe pain, and surgical urinary diversion does not improve pain control. Untreated bilateral ureteric obstruction will lead to anuria, uraemia, renal failure, anorexia, fatigue, nausea, vomiting and, eventually, death. The potential for durable benefits after surgical treatment for ureteric obstruction depends mainly on the type and severity of the underlying disease process and whether there are any further therapeutic options. Surgical procedures to treat PUJ obstruction include laparoscopic pyeloplasty, open pyeloplasty, endopyelotomy, endopyeloplasty and robotic-assisted laparoscopic pyeloplasty.

In patients with advanced cancer, suitable for surgical intervention, stenting is the treatment of choice. Metallic ureteric stenting using the Cook Resonance metallic stent is safe and effective for ureteric obstruction from both malignant and malignant causes with a high success rate. One advantage of this stent over traditional polymer-based stents is much better intraluminal flow as well as reduced incidence of encrustation with stone material, which allows longer dwell times and less frequent exchange procedures [151].

## Internal Ureteric Stents

In patients with intrinsic and extrinsic causes of hydronephrosis, ureteral stent placement is standard practice. The procedure requires cystoscopy and retrograde pyelography. For obstructed ureters, endoscopic insertion of a ureteric stent can achieve internal urinary diversion. However, internal ureteral stents (IUS) need to be changed

every 6–12 months to prevent encrustation. Internal urinary diversion for malignant ureteric obstruction can be a difficult procedure, failures are frequent, and often the obstruction is only partially relieved, with a success rate of approximately 80–90% for extrinsic ureteric obstruction [152, 153]. Morbidities after internal or external diversion are minimal in cases of malignant obstruction. However, ongoing obstruction following IUS is more frequent than for percutaneous nephrostomy tube placement.

### Self-Expanding Ureteric Stents

Recently, self-expanding metallic ureteric stents have become available for external ureteric obstruction. Insertion of the stent still requires a general anaesthetic. In a study of 28 patients, insertion of a self-expanding ureteric stent was successful in almost all of the patients. At almost 19 months follow-up, the stent remained patent and functional in over 80% of patients [154]. Self-expanding ureteric stents are therefore another option for treating obstructed ureters once these stents become more widely available [154, 155].

### Unilateral Ureteric Obstruction

Unilateral ureteric obstruction by primary or secondary cancers is slowly progressive and usually asymptomatic. However, occasionally unilateral ureteric obstruction is sudden and causes pain similar to renal colic. Imaging studies such as renal ultrasound or helical CT of the abdomen may demonstrate ureteric obstruction as well as the underlying cause. If imaging studies do not demonstrate the site of obstruction, cystourethroscopy with a retrograde study is required. In the presence of symptomatic obstruction or if the contralateral side is non-functioning, an internal ureteric stent can be inserted for the relief of obstruction. In many patients, advanced underlying malignancy precludes major surgical procedures to divert the urine or to lyse the ureters. If the contralateral kidney is functioning well and if internal or external drainage of the obstructed kidney has failed, removal of the involved kidney and ureter may need to be considered. If the obstructed kidney is completely asymptomatic and the contralateral kidney is functioning well, intervention may not be required.

## Urinary Diversion

The traditional treatment for patients with bilateral ureteric obstruction with renal failure or those with symptomatic unilateral obstruction is open nephrostomy. However, the median survival following urinary diversion by open procedures is about 6 months, morbidity is about 50%, and there is a 3–8% mortality rate and about 30% satisfactory outcome from surgery [156]. A study of 47 patients undergoing palliative urinary diversion for ureteral obstruction due to pelvic cancers reported the average survival time at 5.3 months, with only half of the patients alive at 3 months and only about 20% alive at 6 months. After urinary diversion, about two-thirds of the survival time was spent in the hospital [157]. Therefore, open nephrostomy is associated with significant operative and perioperative risks, without durable benefits. Recent advances in percutaneous nephrostomy, retrograde and antegrade stenting and stenting biomaterial itself have dramatically changed the indications for and the results of urinary diversion in the management of malignant ureteric obstruction. In cases of advanced urologic malignancies with impairment of renal function secondary to tumour infiltration in high-risk patients, a laparoscopic instead of an open cutaneous ureterostomy has been performed [158].

Percutaneous external urinary drainage using a nephrostomy tube for obstructed ureters is now common practice and is an alternative to endoscopic ureteric stenting. Modern percutaneous external urinary diversion techniques for malignant ureteric obstruction can be performed with minimal procedural morbidity, and it does improve renal function and provide significant clinical and quality-of-life improvement with minimal morbidity; however, there is no

improvement in overall survival. Compared to internal stenting, percutaneous nephrostomy is more invasive, with an associated risk of tube dislodgement; and the diverted urine needs to be collected externally [159]. A large proportion of patients will achieve improvement of renal function. Nevertheless, the median survival of patients undergoing nephrostomy is still very poor, and post-procedure hospitalisation rates are substantial [160]. Patients with prostate cancer or gynaecologic malignancy seem to have better survival than those with bladder cancer [161, 162]. Also, patients with earlier-stage disease or those with newly diagnosed advanced disease have better outcomes [163]. Patients without prior systemic therapy also have better survival, and the perioperative cardiac, pulmonary or haemorrhagic complications are low. The risk of post-procedure complications, fever or acute pyelonephritis following an endoscopic stent insertion or percutaneous catheter insertion seems similar [152]. However, internal stents have a higher failure rate (11%) than percutaneous nephrostomy (1.3%). For longer-term survivors of percutaneous nephrostomy tubes, internalisation of the nephrostomy tube is another option. The technique involves antegrade placement of a stent into the ureter through the existing nephrostomy tract. A nephroureteral stent can also be placed through the percutaneous approach into the bladder. This technique allows antegrade flow of urine from the kidney into the bladder obviating the need for an external collection bag.

## Irritative Voiding Symptoms

Irritative voiding symptoms such as dysuria, nocturia, urgency or urge incontinence have many causes. Most of the patients presenting with irritative voiding symptoms do not have a serious underlying condition. Most commonly irritative voiding symptoms are caused by conditions such as BPH, atrophic vaginitis or idiopathic detrusor instability. The management of such cases must focus on identifying and treating the underlying disorder.

Tumour in the lower urinary tract, including carcinoma in situ of bladder, can cause irritative symptoms. Chemotherapeutic and biological agents can cause similar difficulties, as can neurological involvement. Neurological involvement, more typically, causes an atonic bladder and later frequently becomes irritative. Inflammation of the bladder is most often due to infection, and symptoms consist of excessive urinary frequency, dysuria and urge incontinence.

## Urinary Tract Infection

The diagnosis of symptomatic urinary tract infection (UTI) may be complicated by the high prevalence of asymptomatic bacteriuria, which does not require any treatment, and the difficulty in interpreting the signs and symptoms of UTI in a population in which significant co-morbidities exist. For a patient presenting with symptoms of acute irritative voiding, urinary tract infection should be among the first diagnoses to be considered. Classic symptoms and signs for UTI include dysuria, incontinence, increased frequency, urgency, haematuria and suprapubic pain; when pyelonephritis is present, flank tenderness and fever are usually encountered [164]. A diagnosis of UTI should be based on a thorough clinical evaluation, the exclusion of other possible diagnoses and the presence of new signs and symptoms localised to the genitourinary tract. A new onset of urinary tract symptoms can indicate the presence of a UTI, although attention should be given to differentiating these symptoms from chronic symptoms. In general, a biochemical and microscopic urine examination is necessary before starting any antibiotic therapy. Patients who have recurrent urinary tract symptoms or those who have been recently hospitalised should also have a urine culture and sensitivity performed. In the aged and patients with disabilities, however, the cause of urinary tract infection is often iatrogenic, secondary to long-term indwelling urinary bladder catheters. The incidence of urinary tract infections in patients with indwelling urinary catheters is related to the duration of catheterisation [165]. This acquired bacteriuria

occurs at a rate of about 5–10% per day of catheterisation, with more than one-half of patients with indwelling catheter developing bacteriuria within 10–14 days and virtually all by 6 weeks. Since it is impossible to eliminate catheter-associated infections and the bacterial flora changes rapidly in patients with chronic indwelling urethral catheters, treatment of asymptomatic bladder bacteriuria or funguria is not recommended [166]. Antibiotic prophylaxis simply promotes the emergence of antibiotic-resistant microbes.

For antibiotic therapy to be effective, proper collection of the urine specimen is very important. Clean-catch specimens are not easily obtained from patients who have physical or other functional impairments. Under certain circumstances, therefore, a clean catheterised specimen may be required to obtain proper bacteriological information. The urine of many patients, who have an indwelling catheter or condom catheter, is almost always colonised with bacteria, and therefore bacteriuria alone, in the absence of other features of urinary tract infection, does not require active treatment. However, a negative urine culture is often considered adequate to rule out infection. Pathogenic bacteria readily proliferate in the presence of urinary stasis at any level of the urinary tract. Anatomic abnormalities of the urinary tract, obstructing stone or neoplasm and benign or malignant bladder outlet obstruction may all predispose to urinary stasis or even obstruction. Immunosuppression, due to cancer or its therapies, other acquired or inherited immune deficiency syndromes, chronic steroid administration and diabetes mellitus may also increase the risk of urinary tract infection.

Patients with recurrent urinary tract infections require further investigations to rule out anatomical or other structural abnormalities of the urinary tract. A post-voiding residual urine volume exceeding approximately 150–200 mL requires further evaluation. Imaging studies include renal ultrasound or non-contrast CT scan and cystoscopy for evaluation of calculi, hydronephrosis or bladder diverticula.

## Non-infective Irritative Voiding Symptoms

Irritative voiding symptoms or symptoms in patients without infection are treated symptomatically with agents such as phenazopyridine, 200 mg orally three times a day, or flavoxate, one tablet daily. Symptomatic and conservative treatments of irritative voiding symptoms include anticholinergics such as oxybutynin, flavoxate and solifenacin and antimuscarinics such as tolterodine, darifenacin and trospium. Bladder anticholinergic agents block the binding of acetylcholine at bladder muscarinic receptors. Acetylcholine stimulates muscarinic receptors, resulting in contraction of the bladder detrusor muscle and an urge to urinate [167]. Anticholinergic drugs cause contraction of the bladder neck sphincter and relaxation of the detrusor muscle. Long-term use of anticholinergics can cause a decline in cognitive function. Patients with advanced cancer may also be on a number of other drugs with anticholinergic properties that may potentially aggravate the anticholinergic symptoms. These drugs include benzodiazepines, antipsychotics, hypnotics, TCAs, skeletal muscle relaxants, antihistamines and anticonvulsants. The cholinesterase inhibitors often used to treat dementia can also worsen incontinence [168].

New anticholinergics, solifenacin, darifenacin and trospium, appear to have different side effects and may be safer alternatives to tolterodine and oxybutynin [169]. The M3 receptor-specific agents, darifenacin and solifenacin, may have the least effect on cognitive function; however, dry mouth and constipation remain side effects. Paradoxically in patients with severe and disabling irritative voiding symptoms, anticholinergic drugs can be used to induce urinary retention, so to allow the patient to manage intermittent catheterisation. Urinary analgesic drugs such as flavoxate or phenazopyridine may partially relieve irritative voiding symptoms. Flavoxate seems to be a more effective agent with less toxicity than phenazopyridine [170]. A combination of urinary analgesics and an anticholinergic agent

may be quite effective in managing these symptoms (Table 31.1).

## Tumour-Related Irritating Symptoms

Intravesical or extravesical tumours may produce irritative bladder symptoms and, along with other agents, may be responsible for the development of painful bladder spasms. Carcinoma in situ of the bladder commonly presents with irritative voiding symptoms and haematuria. Low-grade TCC of the bladder, on the other hand, is often asymptomatic. Locally invasive tumour in the pelvis, e.g. cancers of the ovary, cervix, uterus, rectum, prostate and colon, may involve the serosa or even the mucosa of the urinary bladder. It is important to differentiate between tumour infiltration and urinary tract infection from the history, examination and additional investigations. Although some of the urinary symptoms may be quite similar, direct tumour invasion often causes painless haematuria. Patients with irritative voiding symptoms, haematuria and sterile urine cultures require investigation for upper and lower urinary tract pathology. Investigations include urine cytology and cystoscopy. Urine cytology sensitivities vary between 4% and 69% depending on the grade of the tumour. However, the specificity of urine cytology in bladder cancer is 99% [171]. A negative cytology does not exclude malignancy. Less-invasive procedures may be needed for patients with poor performance status or those with advanced disease. Fibre-optic and flexible cystoscopes cause minimal discomfort and do not require full anaesthesia. Renal and bladder ultrasound and spiral CT scans are also minimally invasive and can define the entire urinary system with minimal inconvenience.

If a tumour invading the bladder wall is identified and is causing irritative voiding symptoms, then transurethral resection of the bladder tumour (TURBT) is required. Full thickness resection of the tumour will also provide additional histological and prognostic information. One of the distinctive features of TCC is that multiple metachronous or synchronous cancers frequently develop. These have either a polyclonal origin or arise from metastasis from a single clone. Patients with bladder cancer, therefore, need to have a long-term follow-up with repeated urine cytology and cystoscopy for monitoring. More sensitive and non-invasive methods for bladder cancer detection are required. A number of urinary markers are under investigation for the early diagnosis of carcinoma in situ, including nuclear matrix protein-22 [172], hyaluronic acid-hyaluronidase, BTA stat [173], urinary bladder cancer antigen [174] and multi-target fluorescence in situ hybridisation (FISH) probe [175].

## Post-radiation Cystitis

Tumours of the pelvic organs (i.e. prostate, bladder, colon, rectum) are common in men, constituting 35% of expected new cancer diagnoses for 2017. In women, cancer of the colon and rectum, bladder and genital tract (uterus, ovary and vagina/vulva) are expected to make up 17% of new cancer diagnoses in 2017. Radiation therapy is an important management tool for the treatment of these malignancies, creating significant potential for the development of radiation injury to the bladder [176]. Radiation morbidity is due to incidental treatment of healthy organs. Delivery mechanisms of radiation to the target organ have been improved to reduce the complications of radiation to healthy normal tissues. Wide-field treatment was the standard of care, but it is associated with high morbidity. Until relatively recently, many centres were still using cobalt therapy with low energy. Therefore, it required high doses of RT to deliver adequate radiation to the tumour and high doses to healthy structures near the target. Late genitourinary complications of RT include persistent irritative voiding symptoms. Urinary incontinence may be precipitated or exacerbated, particularly in men with prior prostatectomy. Severe late radiation cystitis and haematuria may occur in 3–5% of patients [177]. However, many of the symptoms may also be caused by residual tumour. The incidence and severity of acute radiation cystitis is dose-related with most cases occurring with RT

doses of 60.00–65.00 Gy [178–180]. Newer techniques and energy sources focus therapy on the target, minimising collateral radiation to healthy structures. These include conformal beam therapy and computed tomography (CT) or ultrasound-guided brachytherapy [181]. Newer radiation equipment, which provide higher energies, produce better tissue penetration, resulting in smaller doses to the surrounding normal tissues. Newer RT techniques also utilise more beams, which allow a lower dose per beam, thus reducing the maximum dose to normal structures beyond the target tissues. With conformal beam therapy for prostate cancer, rectal complications are much lower than with four-box, small-field therapy; however, the incidence of bladder complications is unchanged, probably because of the proximity of the bladder neck and unavoidable exposure to the urethra. IMRT (intensity-modulated radiation therapy) has also demonstrated a significant improvement in rectal complications compared with 3D conformal radiation therapy. Fewer grade 2 bladder complications occur with IMRT, but the rates of grade 3 complications are similar. In patients with prostate cancer, GI symptoms can be reduced by the use of fiducial marker-based position verification [182]. Symptoms of acute radiation injury to the bladder are of short duration and often respond to symptomatic therapy, such as anticholinergic medications and analgesics. Severe complications of chronic radiation injuries are difficult to manage because they tend to be recurrent and are sometimes refractory to therapy. There are very few follow-up studies of small number of patients for proper interpretation of these toxicities. A few follow-up studies performed with various treatment regimens show that although all have some effectiveness, no single modality is superior. They also show the recurrent nature of radiation complications of the bladder. Complications of radiation cystitis include haemorrhagic cystitis (3–5%), vesical fistula (2%) and bladder neck contracture (3–5%). Cancer and contracted bladder can also occur but are rare. Grade 1 and 2 symptoms need treatment only if they bother the patient. These can be managed medically. Management of grade 3 and higher clinical presentations depends on the type of symptom. Voiding dysfunction can be managed medically if the patient desires. Fistula formation usually requires surgical intervention. Contracted bladder and incontinence require evaluation to determine the degree of disability, bladder compromise and potential need for surgery. The use of endoscopic injection sclerotherapy has been reported with good results in a limited number of patients with intractable haemorrhagic cystitis [183]. This treatment involves the injection of a sclerosing agent (e.g. 1% ethoxysclerol) into the bleeding areas to control the severe haematuria in patients with otherwise intractable bleeding that is not responding to simpler methods. Therapy for radiation cystitis is primarily aimed at relief of symptoms. The exception is HBO (hyperbaric oxygen) therapy, which can potentially reverse the changes caused by radiation. HBO therapy stimulates angiogenesis, which reverses the vascular changes induced by ionising radiation [184]. For persistent or more severe symptoms, HBO therapy seems to provide the most consistent benefits [185]. The ability of HBO to preserve bladder function and the non-invasive nature of this treatment are features that favour its use. However, if significant fibrosis and ischaemia have already occurred, HBO therapy does not reverse the changes and only prevents further injury [186, 187]. HBO therapy has a reported response rate of 27–92%, and the recurrence rate is 8–63% [188, 189]. In adults, HBO is administered as 100% oxygen at 2–2.5 atm. Each session lasts from 90–120 min, and patients receive HBO sessions 5 days weekly for a total of 40–60 sessions [188].

Treatment of symptomatic acute radiation cystitis requires analgesics such as phenazopyridine in combination with an anticholinergic. Phenazopyridine is a compound which, when secreted into the urine, has a local analgesic effect. Some patients do not adequately respond to these therapies. Some of the patients can become quite debilitated due to severe urinary frequency, urgency, dysuria, nocturia and, at times, urge incontinence. Occasionally, urinary diversion with a urethral catheter improves symptoms temporarily, although frequently the bladder

pain is aggravated by the catheter itself. Small suprapubic catheters and bilateral percutaneous nephrostomy diversions have been used. More definitive but also more-invasive procedures involve diverting the urine or enlarging the bladder. These are major procedures and require open abdominal surgery. Any urological surgery following radiation therapy is relatively difficult and potentially has more peri- or post-operative complications. For augmentation, cystoplasty or urinary diversion peri- or post-operative complications are dramatically increased in patients with irradiated bowel or bladder due to underlying radiation-induced vasculitis. In practice, however, very few patients are likely candidates for these interventions because of the associated surgical morbidity and mortality.

## Nonbacterial Cystitis

Nonbacterial cystitis is a term that comprises various medical disorders, including nonbacterial infectious (viral, mycobacterial, chlamydial, fungal) and non-infectious (radiation, chemical, autoimmune, hypersensitivity) cystitis, as well as interstitial cystitis. This term also includes painful bladder syndrome/interstitial cystitis (PBS/IC); a syndrome of genitourinary symptoms, such as frequency, urgency, pain, dysuria, nocturia, dyspareunia, abdominal cramps and/or bladder pain; and spasms for which no aetiology can be found. Establishing a specific diagnosis often requires urine cultures and various urologic procedures, including cystoscopy and tests of immunological function. Intravesically administered biological or cytotoxic drugs to treat superficial or multifocal transitional cell carcinoma of the bladder or carcinoma in situ can be potentially quite irritating, inducing varying degrees of chemical cystitis. Intravesical bacillus Calmette-Guerin (BCG) is the most common and the most effective agent for the treatment of superficial and in situ bladder carcinoma. Since the late 1980s, evidence has become available that instillation of BCG into the bladder is an effective form of immunotherapy in this disease [190]. While the mechanism is unclear, it appears that a local immune reaction is mounted against the tumour. Immunotherapy with BCG prevents recurrence in up to 67% of cases of superficial bladder cancer. In addition to the usual weekly intravesical instillations, maintenance therapy may continue after the initial 6-week regimen. Symptoms of urinary frequency, dysuria and haematuria may develop after two or three instillations and last for approximately 2 days after each treatment. These symptoms are expected as BCG therapy elicits an immune stimulatory and inflammatory reaction. Following intravesical BCG therapy, dysuria may occur in up to 91% of patients, urinary frequency in 90% and haematuria in 43% [191]. A combination of phenazopyridine and anticholinergic drugs seems to be quite effective in controlling these symptoms for the initial 6-week course of therapy. Although there have been no randomised controlled trials of these drugs, either singly or in combination, empiric treatment supports their routine use. For patients not responding to this regimen, treatment with isoniazid, paracetamol, diphenhydramine and non-steroidal anti-inflammatory agents may be helpful.

Intravesical chemotherapy drugs, such as mitomycin C, doxorubicin, ethoglucid, epirubicin or thiotepa, may reduce tumour recurrence but have no effect on disease progression to muscle invasion [192, 193]. The most commonly used intravesical chemotherapy drug is mitomycin, and because of its high molecular weight and minimal systemic absorption, it has few local or systemic side effects. Increasing the drug concentration, decreasing urine volume and alkalinising the urine to stabilise the drug may improve the therapeutic effectiveness of mitomycin [194]. Cytotoxic agents used as topical therapy are ineffective when administered as systemic therapy, and agents effective as systemic therapy are ineffective as intravesical treatments.

Unlike BCG, intravesical cytotoxic drugs are usually better tolerated. Mitomycin C may cause chemical cystitis in only 10–15% of patients and rarely leads to a contracted bladder. Doxorubicin has also been associated with chemical cystitis. Treatment of cystitis due to these agents is similar

to that for BCG, except that isoniazid is not required.

Systemic administration of cyclophosphamide and ifosphamide, busulphan and methenamine mandelate may cause irritative symptoms. Concomitant administration of mesna during cyclophosphamide and ifosphamide seems quite effective in preventing these complications. Mesna is a chelating agent that binds acrolein, a toxic by-product of phosphamides, thereby decreasing its toxic effects [195]. In rare cases, irritative voiding symptoms can be refractory to conservative management, and urinary diversion may need to be considered. The standard form of urinary diversion with the lowest risk of short-term morbidity is the ileal conduit.

Many oral agents have been used for the treatment of PBS/IC, with varying success. Medications often used as first-line therapy include TCAs such as amitriptyline and imipramine, which have bladder-relaxing and analgesic properties. In the bladder wall of patients with PBS/IC, often there are increased numbers of mast cells. Whether these mast cells have any pathological basis to PBS/IC is unclear; however, these mast cells contain large amounts of histamine, a vasoactive substance that causes itching and swelling while promoting inflammatory cell infiltration. Antihistamines could therefore be used as first- or second-line therapy. Hydroxyzine, a first-generation antihistamine, blocks mast cell activation and, in uncontrolled studies, was reported effective in interstitial cystitis. However, randomised controlled trials subsequently failed to demonstrate hydroxyzine to be superior to placebo [196]. Another first- or second-line therapy is pentosan polysulphate, an oral restorative for the bladder lining's damaged, (iAluRai) attenuated or missing glycosaminoglycans barrier. The usual dose of pentosan polysulphate is 100–200 mg bd [196]. Approximately 20–30% of patients experience pain and symptom relief with pentosan, although it may take as long as 6 months for adequate relief of symptoms. Several recent randomised double-blind trials of pentosan polysulphate have been published. A dose-finding study did not show any difference in symptom control between 300, 600 or 900 mg of pentosan polysulphate. After 7 months, symptom scores decreased by similar amounts in about 20% of patients; improvement usually occurred within the first 4 weeks. A small trial of oral pentosan polysulphate, with or without hydroxyzine, showed a low response rate and non-significant differences between the groups [197]. Calcium channel blockers inhibit detrusor muscle contraction and downregulate lymphocyte production of interleukin (IL)-2. In a small trial using the calcium channel blocker nifedipine, eight out of nine patients reported improvement of symptoms for at least 4 months, but only about half reported longer-term improvement [198, 199]. In many patients, especially those who are normotensive, the drug is better tolerated in the extended-release form.

Apart from orally administered agents, for symptomatic relief of PBS/IC, a number of topical agents have also been used including capsaicin [200] and resiniferatoxin. However, in a prospectively randomised trial, **resiniferatoxin** failed to show efficacy in treatment of interstitial cystitis [201]. Another agent is RIMSO-50, a purified form of the industrial solvent DMSO. In approximately 50–70% of cases, DMSO has been shown to have therapeutic benefit [202]. Its presumed mechanism of action is multifactorial; the agent has anti-inflammatory, analgesic, muscle-relaxant, collagen-degrading and bacteriostatic properties and causes mucosal injury [189, 203]. For treatment of PBS/IC, 50 mL DMSO is instilled into the bladder. It needs to be retained for 15 min and then excreted. This procedure is repeated for 6–8 weeks, followed by a maintenance regimen of 50 mL every 1–2 week for 3–12 months. The addition of sodium bicarbonate, a steroid such as triamcinolone and heparin to the DMSO solution may improve its effectiveness. About half the patients treated with this combination regimen obtain significant pain relief. However, treatments generally become less effective over time. Adverse effects include transient worsening of bladder symptoms, probably due to histamine release, and minor haematologic, renal and hepatic dysfunction. Intravesical heparin added to RIMSO-50 may be even more effective in reducing relapse rates.

Heparin is a polyanionic compound that is thought to mimic the anti-adherence characteristics of the glycosaminoglycans of the bladder mucosal lining.

Intravesical instillation of 20,000 units of heparin in 10–20 mL of sterile water is used as initial therapy while waiting for other treatments to take effect. While this treatment helps some patients immediately, it usually takes 2–3 weeks before definitive response is seen. Corticosteroids and/or lignocaine has also been used to improve the anti-inflammatory and analgesic response of RIMSO-50.

## Urinary Fistulae

Malignancy-associated urinary tract fistulae in patients with advanced cancer can be very difficult to manage both physically and psychologically. These fistulae can cause patients, their families and their caregivers significant distress and a sense of hopelessness. From the urinary tract, locally invasive cancer may cause rectourethral, urethrocutaneous, vesicovaginal and vesicoenteric fistulae.

One of the uncommon complications of radical prostatectomy is the development of a rectourethral fistula; however, occasionally these may also develop due to locally invasive prostate or rectal cancer. Symptoms of a rectourethral fistula include passage of urine per rectum, faeces per urethra and pneumaturia. Cystoscopy or proctoscopy is required to confirm the diagnosis. A small fistula may close spontaneously following a diverting colostomy and bladder catheterisation; however, in most patients, surgical repair may be needed if there is no underlying active malignancy. For an active malignant fistula, the underlying malignancy may require appropriate therapy; otherwise urinary and/or faecal diversion may be necessary.

### Urethrocutaneous Fistulae

In the rare cases of primary or secondary urethral or penile malignancies, urethrocutaneous fistulae may develop. There may be a localised penile mass, and the urine may drain through the urethrocutaneous tract. Surgical treatment depends on the location of the fistula but includes proximal, total or partial penectomy followed by other local or pharmacological treatment, depending on the underlying cause. If the definitive surgical option is not appropriate, urinary diversion through a percutaneous suprapubic cystostomy may be an option.

### Vesicovaginal Fistulae

A fistulous tract between the urinary bladder and the vagina is often a consequence of gynaecological surgery or puerperal trauma [204]. Presenting symptoms include the passage of urine from the bladder into the vagina through the fistulous tract. Pelvic examination is usually non-contributory as no specific abnormalities are seen unless there is a large fungating tumour. Contrast imaging of the renal tract will exclude the presence of ureteric abnormalities. Cystoscopy can assess the size, site and number of fistulous tracts. More often than not, these fistulae are seen on the posterior bladder wall. However, for planning corrective surgery, information regarding the extent of the tumour including its proximity to a ureteric orifice is required. If the irrigating fluid escapes from the vagina during the cystoscopy, the diagnosis of a vesicovaginal fistula can be confirmed. A speculum examination of the vagina may be useful. Methylene blue dye can also be injected into the bladder to see if it escapes into the vagina through a fistulous tract. During cystoscopy, biopsies of any suspicious areas may also confirm a specific diagnosis.

For small benign fistulae, 4–6 weeks of urethral or suprapubic catheter drainage may be sufficient for spontaneous closure of the tract. In most patients, however, transvaginal or transabdominal surgical repair is necessary with interposition of an omental pedicle graft. Surgery for repair of a vesicovaginal fistula needs careful and selective tissue handling, layered closure of the wound, low tension along suture lines, use of

absorbable sutures, post-operative suprapubic catheter drainage and perioperative use of antibiotics [205]. However, most patients with symptomatic vesicovaginal fistula have extensive pelvic disease. In most people, urinary diversion rather than surgical procedures is the best palliative option. In patients with widespread local disease or disseminated metastases or those who are not candidates for major surgery, bilateral nephrostomy tubes with subcutaneous tunnelling will provide good palliation and quality of life.

### Vesicoenteric Fistulae

Fistulae can form between the bladder and any part of the GI tract. Both benign and malignant large bowel and inflammatory small bowel conditions may lead to vesicoenteric fistula. Most patients complain of dysuria followed by pneumaturia [206]. Vesicoenteric fistulae lead to the risk of recurrent urinary tract infections, especially for fistulae between the GI tract and the bladder. Vesicocolic fistula may also present with the passage of faecal matter in the urine. Cystoscopy may visualise the fistulous tract in up to two-thirds of the patients [207]. These fistulae usually present high on the posterior wall of the bladder as an area of erythema, and small amounts of faecal matter may be seen extruding from the tract. There may be only local or generalised inflammation of the bladder mucosa. If the fistula cannot be seen on cystoscopy, other diagnostic procedures including imaging and dye studies may be required. Spiral CT scans and MRI are the most sensitive methods used to detect enterovesical fistulae. In general, CT scans with oral and rectal contrast, together with cystoscopy, are able to identify most enterovesical fistulae. Occasionally however, the fistulous site is very small when other contrast-imaging studies may be needed to identify the location of the tract. These studies include cystography, upper and lower GI barium studies and $^{51}$Cr-labelled sodium chromate [208]. The treatment of symptomatic enterovesical fistulae is dependent on the abnormality of the GI tract and the general condition of the patient. If possible, en bloc surgical excision of the segment of bowel and bladder is the ideal therapy. This will allow normal bowel and bladder function to return. If the poor general physical health or the extent of local disease prevents this procedure, intestinal diversion may be required to redirect the faecal matter and hence reduce the urinary symptoms. Very rarely a total cystectomy with ileal conduit urinary diversion may be performed. This type of procedure, however, may need to be accompanied by complete pelvic exenteration. A simpler option may therefore be the placement of bilateral nephrostomy tubes, with subcutaneous tunnelling and external urinary diversion.

## Pain

Pain is a major problem in advanced malignancy. The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30–40% [209]. Skeletal complications due to metastatic bone disease (MBD) have a detrimental effect on pain and QoL and are also associated with increased mortality [210]. Prostate, kidney and urinary bladder cancer all have a high probability of painful bony metastases. Prostate, kidney and urinary bladder cancer all have a high probability of painful bony metastases. Management of pain from bone metastases as well as other obstructive visceral pain requires treatment as per standard WHO analgesic guidelines. In recent times, for patients who have developed hormone refractory prostate cancer with bone metastases, bisphosphonate therapy, especially zoledronic acid (ZA), has been demonstrated to be effective in reducing the risk of skeletal-related events and mean skeletal morbidity rate and, hence, aid in pain control from bone metastases from prostate cancer. It is noteworthy that pamidronate sodium was not shown to be superior to placebo in the same setting [211]. Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with metastatic breast cancer, SREs caused by bone metastases were delayed [212]. Denosumab is a fully human monoclonal antibody

that binds to and neutralises RANKL (receptor activator of nuclear factor-KB ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to ZA in preventing or delaying SREs in patients with advanced MBD, including patients with urothelial carcinoma [213]. Denosumab has been approved for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [210]. Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for osteonecrosis of the jaw and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions [214]. For denosumab, no dose adjustments are required for variations in renal function. In addition, radiation therapy for pain from bony metastases is extremely effective. Also pain from spinal cord compression requires therapy with steroids and either surgical spinal decompression or radiation therapy. For other pains related to advanced cancer, standard WHO pain ladder should be used. However newer studies suggest that strong opioids may be preferable to weak opioids effectively eliminating the second step of WHO ladder [215].

## Renal Colic

Renal colic is one of the most painful conditions experienced by patients. Ureteric obstruction, caused by a calculus, blood clot or rarely a tumour, causes capsular distension resulting in severe pain in renal distribution. The pain is colicky in nature due to ureteric muscle spasm and extends from the flank radiating to the testis or the perineum. The pain is severe enough to generate an autonomic response with severe restlessness, pallor and diaphoresis. Relief from this pain requires parenteral administration of an opioid, such as morphine or a non-steroidal anti-inflammatory drug such as ketorolac or diclofenac [216, 217].

## Obstructive Bladder Pain

Acute urinary retention causes severe lower abdominal pain, restlessness and a constant and compelling urge to void. Uncommonly, the obstruction is relieved spontaneously; however, in most instances, a urethral catheter needs to be inserted to relieve this pain. If the obstruction is not relieved, the acute urge will gradually subside, but bladder distension will persist. The elderly patients as well as those on opioids may not present with these symptoms but instead may have confusion as the main or only presenting symptom. Chronic urinary obstruction, causing gradual bladder distension over time, may present with just a sense of fullness, symptoms of chronic urinary retention and overflow incontinence.

### Conclusions

Like most palliative approaches, the aim of managing urologic complications in patients with progressive and incurable diseases is to maintain and possibly improve the quality of life of a patient while maintaining the quantity of life. Urological symptoms and complications may develop due to the underlying benign or malignant disease or due to the treatments required for the urological or other malignancy. With significant improvement in imaging modalities, newer devices and medications and surgical interventions, patients with advanced disease now can enjoy a better quality of life, and the morbidities associated with underlying illness and previous treatments can be minimised.

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# Gynecological Symptoms

# 32

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## Introduction

Gynecologic cancer comprises cervical cancer, ovarian cancer, fallopian tube cancer, cancer of the uterus, and cancers of the vagina and vulva. Furthermore, a number of small disease groups such as gestational trophoblastic disease are included.

In high-economic countries, the incidence of cervical cancer is decreasing, whereas in many low-economic countries, cervical cancer is among the most common of all cancer types. Almost 9 out of 10 deaths from cervical cancer occur in less developed regions and mortality differs 18-fold from regions with rates below 2 pr 100,000 (Australia, Western Europe, and Western Asia) to regions with high rates of over 20 pr 100,000 (Africa and Melanesia) [1]. Due to the development of a human papilloma virus vaccine, it is expected that the incidence of cervical cancer will decrease further in countries with access to a vaccination program. Cervical cancer is diagnosed in women aged 25–70 years and is more prevalent in lower socioeconomic groups and in women with multiple sexual partners. The most frequent symptom at the time of diagnoses is postcoital vaginal bleeding [2].

Ovarian cancer is most common in high-economic countries and is worldwide the seventh most common cancer in women. The incidence has been slowly increasing, and the risk of dying before the age of 75 from ovarian cancer is almost twice as high if residing in a more developed region than in less developed regions [1, 2]. Because of the lack of symptoms in early-stage disease, ovarian cancer has been called the "silent killer." Several studies have shown that women with newly diagnosed ovarian cancer can report uncharacteristic symptoms up to 2 years prior to diagnosis. These symptoms include unusual abdominal or lower back pain, distended abdomen, bloating, gastrointestinal problems, urinary symptoms, and vaginal bleeding [3, 4]. Age distribution is typically 35–75 years with epithelial cancers primarily diagnosed in women older than 50 years and germ cell tumors primarily diagnosed in younger women.

The incidence of carcinoma of the uterus almost displays the same geographical distribution as ovarian cancer and is most commonly diagnosed in women between 40 and 70 years of age. Due to early onset of symptoms (often postmenopausal bleeding) and a much lower tendency to distant metastases, survival is significantly superior as compared to women diagnosed with ovarian cancer [2].

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This chapter will focus on symptoms and supportive care in patients with cervical cancer, ovarian cancer, and cancer of the uterus. Prophylaxis and management of complications due to the cancer and of side effects from cancer therapies will be described. Patients suffer from different problems at the time of diagnosis, after surgery, during chemotherapy and/or radiotherapy, and in the phase of survivorship. Furthermore, a variety of symptoms occur in gynecologic cancer patients at the end of life.

## Specific Symptoms and Complications in Gynecologic Cancer

In general, patients with gynecologic cancer experience a high number of different symptoms, and the need for supportive care is significant. The most common disease-specific symptoms in gynecologic cancer patients are lymphedema of the lower extremities, vaginal bleeding, bowel obstruction, ascites (ovarian cancer), and fistulas.

Lymph node dissection, in particular, in women who have had inguinal (cancer of the vagina or vulva) or deep pelvic node dissection with or without postoperative radiotherapy (cancer of the vulva or cervical cancer), often results in subsequent *lymphedema* of one or both of the lower extremities. Lymphedema may have a huge impact on daily activities and quality of life and typically develops within the first 12 months posttreatment. The risk varies substantially in the literature. It has been reported in 36–69% of women with cancer of the vulva [5, 6], in 8–12% of those with cervical cancer or cancer of the uterus, and in 5–7% of women undergoing surgery for ovarian cancer [5]. Postoperative radiotherapy increases the risk 3.5-fold in women with cancer of the vulva or cervical cancer, and the more frequent use of extensive surgery in ovarian cancer will undoubtedly increase the risk of lymphedema as well. Fortunately, the introduction of the sentinel node technique (e.g., in cancer of the vulva) [7]) is a landmark and will significantly reduce the risk of surgery-induced lymphedema. Treatment of manifest lymphedema is difficult [5, 6] and is described in detail in Chap. 19.

*Malignant intestinal obstruction* is a particular problem in advanced ovarian cancer [8, 9]. Both direct obstruction (due to invasive tumor) and peritoneal carcinomatosis are frequent causes. Symptoms are nausea and vomiting, constipation or partial-overflow diarrhea, and pain. The management is challenging because of the impact on quality of life and the often short life expectancy. Surgical intervention is often indicated if symptoms occur at the time of diagnosis, but in advanced ovarian cancer, surgery should be reserved for patients with a good performance status, a single well-defined obstruction, and with no prior surgery due to intestinal obstruction. In patients with a single obstruction, available for endoscopic intervention, self-expanding metallic stents (SEMS) can be used as an alternative to surgery or in cases where surgery is not indicated [9]. Due to the high frequency of peritoneal carcinomatosis as the cause of obstruction in advanced ovarian cancer, the first choice of treatment will often be conservative limited to medical management and/or a percutaneous endoscopically placed gastrostomy.

As described above, *vaginal bleeding* is a common presenting symptom in women with cervical cancer or cancer of the uterus. In rare cases, bleeding could be severe due to cervical cancer eroding into a small artery, but most commonly the bleeding is slow, and patients suffer the symptoms of chronic anemia. Bleeding complications can also occur after diagnosis, e.g., during radiotherapy. Control of bleeding can in most cases be obtained with a vaginal pack stuffing the entire vagina. If this is not successful, surgery should be considered. Palliative radiotherapy to the pelvis given as 15 Gy in three fractions or 30 Gy in ten fractions is effective in most cases. Selective embolization of the hypogastric or uterine arteries can be helpful in patients not suitable for surgery or radiotherapy or in patients with persistent bleeding. In mild cases, e.g., in patients undergoing radiotherapy, treatment with oral or intravenous tranexamic acid is often useful. In case of massive intractable bleeding in patients

with incurable cancer, best supportive care is sedation with midazolam [10, 11].

Management of patients with *fistulas* is reviewed in the section of radiotherapy-induced side effects, and *ascites* is described in Chap. 27.

## Complications Following Surgery

The therapeutic approach in gynecologic cancer has changed markedly during the past years. In many countries, surgical treatment of gynecological cancer has been centralized to specialized departments, thereby increasing the volume of patients and number of operations per surgeon. This has resulted in better outcomes for the patients.

In cervical cancer and cancer of the uterus, clinical staging (not involving radiology) was previously done prior to surgery. Low-stage disease patients were offered surgery, and high-stage disease patients were offered radiotherapy. Staging in cervical cancer is still clinical (supplemented by radiology), but today, the majority of patients with endometrial cancer have surgical staging performed. Also surgery has become more extensive in many patients, in particular, as concerns pelvic and/or aortic node dissection. Furthermore, concomitant cisplatin (or cisplatin-based combination chemotherapy) is routinely offered to high-risk cervical cancer patients. Pre-/postoperative chemoradiations have improved treatment results but have also increased the risk of side effects. In ovarian cancer surgery aims for a macroscopically radical operation, either as the primary treatment or as interval debulking after neo-adjuvant chemotherapy, meaning that many of these women undergo extensive surgery.

New techniques such as robotic surgery can in some cases be an alternative to open abdominal laparotomy or conventional laparoscopic surgery. Although robotic surgery often prolongs the mean operative time, robotic surgery is less invasive and can be offered to some patients not suitable for open abdominal surgery. For example, robot-assisted hysterectomy in endometrial cancer can often be carried out in older patients, who can typically be discharged from hospital within 1–2 days postsurgery. Unfortunately, good quality trials involving robotic surgery in gynecologic cancer patients are sparse. Several randomized trials are ongoing, but none have been published today to the best of our knowledge. Because the majority of women with ovarian cancer is diagnosed with stages III–IV disease often requiring extensive surgery, robot-assisted surgery in ovarian cancer has only been investigated in small trials involving patients diagnosed at an earlier stage.

A total of 1894 patients with cervical cancer were included in a retrospective study published in 2012, comparing open abdominal surgery, laparoscopic surgery, and robot-assisted laparoscopic surgery [12]. In 2006 (start of inclusion), 98% of the women included underwent open abdominal surgery, but 4 years later, 23% of the women included in the study had laparoscopic surgery, while robot-assisted surgery was performed in 10% of patients. Overall complications were 15.8% for open surgery, 13.4% for robot-assisted surgery, and 9.2% for laparoscopic surgery. The significant differences in complications included a lower requirement for transfusions in the group undergoing minimally invasive procedures compared to open surgery and fewer days of hospital stay (3 days for open, 2 days for laparoscopic, and 1 day for robot-assisted).

In endometrial cancer, the use of robot-assisted surgery is increasing with a rise from 12.6% of cases in 2008 to 44.2% of cases 5 years later [13]. In a retrospective study including more than 10,000 women, patients undergoing robot-assisted surgery had significantly more comorbidities including obesity and cardiovascular and pulmonary disease than patients undergoing laparoscopic surgery [13]. Despite this, no significant differences were found when comparing complications during or following robot-assisted and laparoscopic surgery, and there was even a lower risk of remaining at the hospital for 3 days or more for patients treated with robot-assisted surgery.

Two reviews involving patients with cervical or endometrial cancer published in July and August 2016 [14, 15] both conclude that the current level of evidence is too low to determine

safety and clinical effect of robot-assisted surgery. Both reviews did find a trend toward lower complications when comparing to open surgery but no established differences when comparing to laparoscopy with the exception of estimated blood loss which was lower in the robotic-assisted surgery group. Before definitive conclusions can be drawn, more and higher-quality research is needed, including registration of long-term adverse effects and survival data.

The following complications to surgery are primarily derived from open abdominal surgery. The most frequent complications are hemorrhage, intraoperative genitourinary (bladder or ureteral injury) and gastrointestinal injuries, deep venous thrombosis, pulmonary embolism, and various infections including wound infections. The risk of lymphedema has been described earlier. The complication rate is dependent on the aggressiveness of surgery and the skills of the surgeon.

Bladder and intestinal dysfunction including bowel obstruction are frequently observed following surgery [16]. These complications are believed to be the result of surgical trauma involving the sympathetic and parasympathetic nerve branches innervating pelvic organs.

Different kinds of medications have been used to minimize lower urinary tract symptoms (LUTS) that can persist for months (detrusor hypertonia resulting in voiding dysfunction) or, in some patients, for years. Muscarinic receptor antagonists (if symptoms are due to bladder dysfunction) and serotonin or noradrenaline reuptake inhibitors (if symptoms are due to dysfunction of the urethra) can be helpful. Also perioperative anorectal symptoms like constipation, bloating, and the feeling of incomplete evacuation affect a number of women.

Sexual dysfunction includes coital and orgasmic problems, dyspareunia, and sexual dissatisfaction. This can be due to surgery involving the top of vagina, surrounding parametrial tissues, or oophorectomy. The reduction of the vagina and damage to the pelvic nerves can cause sexual dysfunction. Major gynecologic surgery can result in disturbances of vaginal blood flow to the vagina which can cause decreased sexual arousal. In a prospective study in 173 women undergoing radical hysterectomy and compared with matched controls, short-term (up to 6 months postsurgery) sexual problems included orgasmic difficulties, dyspareunia, sexual dissatisfaction, distress during intercourse because of a reduced vaginal size, and problems with completing intercourse, while long-term problems (up to 2 years postsurgery) included a negative impact on sexual interest and lubrication of the vagina [17, 18].

## Side Effects Induced by Chemotherapy

The most commonly used chemotherapeutic agents in gynecologic oncology and the most frequently observed side effects are summarized in Table 32.1.

Almost all women with a diagnosis of epithelial ovarian cancer are offered chemotherapy either as neo-adjuvant or postoperative chemotherapy. Only those with stage I A or B and grade 1, non-clear cell histology are treated by surgery alone. As concerns endometrial cancer, the role of therapy after surgery has been intensively discussed during recent years. Adjuvant radiotherapy decreases the risk of local recurrence but does not seem to have an impact on survival. Therefore, some use external beam radiation therapy with or without brachytherapy, whereas other prefer adjuvant chemotherapy in high-risk patients. Women with cervical cancer, who need adjuvant radiotherapy and those in whom radiotherapy is the primary treatment, will benefit from concomitant platinum-based chemotherapy.

The primary approach to best supportive care is to use the least toxic regimen, provided efficacy is maintained. Cisplatin-based chemotherapy was for many years the gold standard in ovarian cancer treatment, but several studies have shown that cisplatin can be replaced by the much less toxic carboplatin without loss of effect [19]. Unfortunately, this is not the case in cervical cancer, and cisplatin (alone or in combination) is still the preferred antineoplastic agent in these patients. Chemotherapy in cancer of the uterus has not

**Table 32.1** Incidence of side effects induced by antineoplastic agents frequently used in gynecologic cancer (for CINV is referred to Table 32.2)

| Antineoplastic agent | Anemia | Neutropenia | Thrombopenia | Neurotoxicity | Ototoxicity | Nephrotoxicity | Alopecia | Constipation | Diarrhea | PPE |
|---|---|---|---|---|---|---|---|---|---|---|
| Cisplatin | ++ | ++ | ++ | +++ | +++ | +++ | + | ++ | ++ | 0 |
| Carboplatin | +++ | ++ | +++ | + | ++ | ++ | + | + | + | 0 |
| Oxaliplatin | ++ | +++ | ++ | +++ | + | + | + | + | +++ | + |
| Doxo−/epirubicin | +++ | +++ | +++ | 0 | 0 | + | +++ | 0 | ++ | 0 |
| Paclitaxel | +++ | +++ | +++ | +++ | + | 0 | +++ | 0 | ++ | 0 |
| Docetaxel | +++ | +++ | +++ | ++ | 0 | 0 | +++ | 0 | ++ | + |
| Topotecan | ++ | ++ | ++ | 0 | 0 | + | ++ | + | ++ | 0 |
| Gemcitabine | ++ | ++ | ++ | + | 0 | + | + | + | + | 0 |
| Pegylated liposomal doxorubicin | + | + | + | 0 | 0 | 0 | + | + | + | +++ |
| Vinorelbine | ++ | ++ | + | ++ | 0 | + | ++ | ++ | + | 0 |
| Trabectedin | ++ | ++ | ++ | + | 0 | 0 | ++ | ++ | ++ | ++ |

+++ Side effects may occur in more than 30%. ++ Side effects may occur in 10–30%. + Side effects may occur in 1–10%. 0 Side effects may occur in less than 1%. *CINV* chemotherapy-induced nausea and vomiting, *PPE* palmar-plantar erythema

been intensively investigated, and many use the same regimens as in ovarian cancer [20, 21].

Guidelines recommend six courses of carboplatin and paclitaxel as first-line treatment in patients with ovarian cancer. This regimen is tolerable to most patients. Addition of a third drug should be avoided (topotecan, etoposide, doxorubicin, or gemcitabine) because this does not improve progression-free or overall survival but is more toxic [22]. The JGOG-3016 study [23] compared the standard three-weekly schedule of carboplatin and paclitaxel with a dose-dense regimen (three-weekly carboplatin and weekly paclitaxel) and found that the dose-dense regimen improved both PFS and OS but also induced more grade 3–4 anemia. The GOG-0662 trial, published in 2016, randomized 692 patients with ovarian cancer to carboplatin every third week and paclitaxel either weekly or every third week [24]. The patients could receive bevacizumab at their own discretion (84% opted for this), and the randomization was stratified accordingly. Again the PFS survival was significantly longer in those who received dose-dense paclitaxel (without bevacizumab), but this difference was not seen, when patients received bevacizumab in addition. Also in this study, more patients had grade 3–4 anemia in the dose-dense regimen, and also more grade 2–4 sensory neuropathy was seen, but a lower rate of grade 3–4 neutropenia. Intraperitoneal chemotherapy in ovarian cancer has in a few trials resulted in improvement of PFS and OS compared to intravenous chemotherapy, but differences in the doses of chemotherapeutic agents have made results difficult to interpret, and high rates of serious adverse events in the intraperitoneal chemotherapy groups including fever, fatigue, gastrointestinal AE's, infection, metabolic AE's, and pain have prevented this regimen from becoming a standard recommendation [25].

## Side Effects Induced by Platinum Compounds

Platinum compounds comprise *cisplatin*, *carboplatin*, and *oxaliplatin* of which the first two are most frequently used in the treatment of gynecologic cancer.

The dose-limiting drug adverse event of cisplatin is nephrotoxicity. Cisplatin is excreted largely unchanged in the urine primarily within the first 24 h after infusion. Nephrotoxicity is expressed as a reduction in glomerular filtration rate (GFR) due to severe renal tubular damage. For each treatment course, there can be a decline in GFR, and this can lead to irreversible toxicity or partial recovery after termination of therapy. Women with advanced-stage cervical cancer often have impaired renal function before the start of treatment, and a possible uni- or bilateral ureteral obstruction should be explored and relieved before starting cisplatin therapy. Cystoscopy insertion of ureteral stents is preferable, but a percutaneous nephrostomy can be used instead.

Renal function should not be based on the measurement of serum creatinine only, but calculation of the glomerular filtration rate (GFR) using the Cockcroft-Gault formula. In the elderly and in patients with an extreme body surface area (very small or very large), the use of the Cockcroft-Gault formula leads to inaccurate estimation of renal function, and measurement of GFR is mandatory. There have been several attempts to reduce nephrotoxicity by coadministration of specific compounds, but none of these are routinely used. The dose of cisplatin should be adjusted according to the renal function, and cisplatin therapy should be avoided if the GFR is lower than 50–60 mL/h (measured by Cr-EDTA clearance). Hydration with normal saline is important in maintaining a urinary flow of 100 mL/h, and concomitant administration of other nephrotoxic agents such as aminoglycosides and loop diuretics should be avoided. Cisplatin leads to magnesium depletion, which can be avoided by adding 40–80 mmol of magnesium in the hydration fluid per cycle of chemotherapy [26]. Carboplatin has limited nephrotoxicity, with the exception of magnesium depletion, when dosing is based on GFR, and the third platinum analog, oxaliplatin, is devoid of significant nephrotoxicity.

Cisplatin exhibits preferential uptake in the dorsal root ganglia and produces a dose-related large fiber sensory neuropathy [27]. There is an increasing risk of symptoms with dose, but severe symptoms are rarely seen in patients who have received a total dose less than 300 mg/m$^2$ [28]. Symptoms are first characterized by painful paresthesia and numbness. Later on symptoms like loss of vibration sense, severe paresthesia, and ataxia can be apparent. Loss of motor function has been reported, but the motor system is rarely affected. High BMI, diabetes, and high age all promote neuropathy, while physical exercise and having an autoimmune disease seem to be protective [29–31]. Many studies have examined the effectiveness of potential neuroprotective agents such as amifostine, growth factors, glutathione, Org 2766, acetyl-L-carnitine, and vitamin E, but none of these seem to significantly prevent or limit neurotoxicity, and guidelines do not recommend the use of any of them [32]. Neurotoxicity is much less pronounced with carboplatin but can be dose-limiting with oxaliplatin. Oxaliplatin can provoke muscle cramps resembling Raynaud's phenomenon and pharyngeal-laryngeal dysesthesias which can be triggered by drinking cold liquids or touching cold surfaces.

Cisplatin-induced hearing loss is usually bilateral and often irreversible. Hearing loss and tinnitus is related to the cumulative dose of cisplatin, patients' age (children and elderly have a higher risk), and pre-therapeutic hearing impairment [33, 34]. Symptoms can occur within hours to days after cisplatin administration. The formation of radical oxygen species (ROS) induced by cisplatin may play a role in ototoxicity. Therefore, a number of free-radical scavengers, such as amifostine, acetylcysteine, salicylates, and vitamin E, have been tested in animals [34]. So far only amifostine has been investigated in humans, but two randomized trials were unable to demonstrate any significant effect, and a recent Cochrane review (on prevention of platinum-induced hearing loss in children) found no evidence of effect [35]. Some studies primarily in testicular patients indicate that cisplatin-induced hearing impairment could be due to genetic predisposition [36].

Chemotherapy-induced nausea and vomiting (CINV) is not a life-threatening side effect and seldom dose-limiting. Nausea and vomiting are, however, two of the most feared side effects induced by chemotherapy [37]. Cisplatin has the highest risk of CINV (almost 100% if no prophylactic antiemetics are provided to the patient), but also carboplatin and oxaliplatin induce a considerable risk of 30–90% of vomiting depending on the dosage [38]. Two new neurokinin $(NK)_1$-receptor antagonists netupitant and rolapitant have been investigated in patients receiving cisplatin-based chemotherapy, and both significantly improve the antiemetic effect of a 5-hydroxytryptamine $(5\text{-HT})_3$-receptor antagonist and dexamethasone [39, 40]. Recent studies and subanalysis from previously published large-scale studies suggest that patients receiving carboplatin-based chemotherapy will benefit from the addition of an $NK_1$-receptor antagonist to the previously recommended regimen consisting of a single dose of a $5\text{-HT}_3$-receptor antagonist plus dexamethasone [41]. Younger women with advanced cervical cancer are at a particular high risk, because young age and the female gender are risk factors for CINV and because they receive a combination of fractionated radiotherapy to the pelvis and concomitant weekly cisplatin. A multinational phase III trial randomized 246 patients to antiemetic prophylaxis with palonosetron plus dexamethasone plus placebo versus palonosetron, dexamethasone, and, the $NK_1$-receptor antagonist, fosaprepitant [42]. Patients completed a daily diary for the entire course of fractionated radiotherapy and concomitant weekly cisplatin. The primary parameter, the sustained no emesis rate during 35 days, was 49% in the standard arm and 66% in patients receiving fosaprepitant (subhazard ratio 0.58 [95% CI 0.39–0.87], $p = 0.008$). An update of the MASCC/ESMO antiemetic guidelines was published on August 2016 [43]. Detailed recommendations for the antiemetic prophylaxis in gynecologic cancer patients are based on this update (Table 32.2).

**Table 32.2** Antiemetic prophylaxis in gynecologic cancer patients receiving chemotherapy

| Emetic risk group | Antineoplastic agents (iv) frequently used in gynecologic cancer[a] | Prophylaxis of acute CINV (0–24 h) | Prophylaxis of delayed CINV (24–120 h) |
|---|---|---|---|
| High (>90% risk) | Cisplatin[b] | $NK_1$-receptor antagonist + 5-$HT_3$-receptor antagonist + dexamethasone | Aprepitant days 2–3 + dexamethasone days 2–4 or dexamethasone alone if NEPA or rolapitant was used in day 1 |
| Moderate (30–90% risk) | Carboplatin | $NK_1$-receptor antagonist + 5-$HT_3$-receptor antagonist + dexamethasone | Aprepitant days 2–3 + or none if NEPA or rolapitant was used in day 1 |
| | Oxaliplatin<br>Epirubicin<br>Doxorubicin<br>Trabectidin | 5-$HT_3$-receptor antagonist + dexamethasone | Oxaliplatin, doxorubicin, epirubicin: dexamethasone can be considered<br>Trabectidin: none |
| Low (10–30% risk) | Topotecan[c]<br>Gemcitabine<br>Pegylated liposomal doxorubicin | Dexamethasone or a 5-$HT_3$-receptor antagonist or a dopamine receptor antagonist such as metoclopramide | No routine prophylaxis |
| | Paclitaxel<br>Docetaxel | The prophylactic corticosteroid used to avoid allergic reactions is usually enough as antiemetics | |
| | Olaparib, rucaparib, or niraparib (oral) | Maintenance of single agent therapy: antiemetics should only be administered on demand | |
| Minimal (<10% risk) | Bevacizumab<br>Vinorelbine | No routine prophylaxis | No routine prophylaxis |

*NEPA* a combination of netupitant ($NK_1$-receptor antagonist) and palonosetron (5-$HT_3$-receptor antagonist)
[a]When combination chemotherapy is used, prophylaxis follows recommendation for the agent with the highest emetic risk
[b]Only aprepitant has been investigated in patients receiving the low dose of weekly cisplatin (40 mg/$m^2$) used in cervical cancer [42]
[c]Antiemetics should be given on each day of topotecan therapy

Carboplatin induces a higher risk of myelosuppression than cisplatin. Both have a moderate-to-high risk of thrombocytopenia and anemia, whereas the risk of neutropenia is less pronounced. The indications for blood transfusion and use of hematopoietic growth factors are described elsewhere. It should be emphasized that women treated with pelvic radiation should avoid anemia, due to the decrease in the efficacy of radiotherapy. Gynecologic patients in whom the maintenance of dose intensity and dose density is important (first-line chemotherapy in ovarian cancer and first-line chemoradiation in cervical cancer) should receive prophylactic and/or therapeutic granulocyte colony-stimulating factors according to guidelines [44].

## Side Effects Induced by Taxanes

Premedication with corticosteroids (both *paclitaxel* and *docetaxel*) and $H_1$ and $H_2$ inhibitors (paclitaxel) are necessary to avoid allergic reactions (both) and fluid retention (docetaxel). The risk of myelotoxicity, in particular neutropenia, is high with both (most pronounced with docetaxel). Also neurotoxicity is a frequent side effect, primarily with the use of paclitaxel. Taxanes have a low emetic risk potential (10–30% risk), and the premedication (corticosteroids) is sufficient as antiemetic prophylaxis, when taxanes are given as single agents [45]. Diarrhea is a frequent side effect and responds to treatment with low doses of loperamide. Alopecia is seen in more than 80% (Table 32.1).

## Side Effects Induced by Anthracyclines

The risk of myelosuppression is moderate (when given as single agents), but both anemia and neutropenia as well as thrombocytopenia are seen. Oral mucositis is a problem in approximately 40% of patients, and nausea and vomiting can be severe, in particular, if doxorubicin or epirubicin is combined with cyclophosphamide. Actually, the newly updated MASCC/ESMO guidelines classify the combination of an anthracycline and cyclophosphamide as highly emetogenic [38] and recommend a combination of an $NK_1$-receptor antagonist, a 5-$HT_3$-receptor antagonist, and dexamethasone as antiemetic prophylaxis [41]. The dose-limiting side effect is cardiomyopathy. Maximum cumulative (lifelong) doses of doxorubicin and epirubicin have been defined (450–500 mg/m$^2$ and 850–900 mg/m$^2$, respectively). Patients should be monitored using multiple-gated acquisition (MUGA) scanning or echocardiography [46].

Alopecia is ranked as one of the most troublesome side effects by women receiving chemotherapy, and complete alopecia is seen in almost 100% of patients after the first course of anthracycline-based chemotherapy. No pharmacologic treatment is available, but scalp cooling can prevent or decrease alopecia in as many as 80% [47].

Liposomal doxorubicin has a side-effect profile completely different from the other anthracyclines. Palmar-plantar erythema (PPE) is dose-limiting, but myelosuppression and mucositis are mild; alopecia is a rare problem, and cardiotoxicity is much less frequent than with conventional anthracyclines [48].

## Side Effects Induced by Other Cytotoxics Frequently Used in Gynecologic Oncology

The topoisomerase-1 inhibitor, *topotecan*, is used in the treatment of resistant or recurrent ovarian cancer and in cervical cancer. Myelosuppression, in rare cases complicated with neutropenic enterocolitis, and fatigue are most frequent. Nausea, vomiting, diarrhea, and alopecia are seen in less than 30% of patients.

The antimetabolite, *gemcitabine*, induces mild-to-moderate myelosuppression, but used as part of a combination chemotherapy regimen, this can be severe and necessitate omission of gemcitabine day 8 in a treatment course in a significant number of patients. Fever and dyspnea are frequently seen within the first 24 h after administration, whereas nausea, vomiting, and mucositis are seen in less than 30%. Hemolytic uremic syndrome and/or lung toxicity are rare side effects but can be severe. Drug-drug interactions with oral anticoagulants can be a problem, but as recommended in the chapter on thrombosis, cancer patients with thrombosis should not receive oral anticoagulants, but low-molecular-weight heparin which can be administered safely concomitantly with gemcitabine.

In recurrent platinum-sensitive ovarian cancer, trabectedin is being used along with pegylated liposomal doxorubicin to prolong the platinum-free interval in order to improve the response rate to platinum at a later time [49]. Adverse events to trabectedin primarily include hematologic and hepatic, with the dose-limiting adverse events being neutropenia and elevation of liver enzymes [50].

## Side Effects Induced by Targeted Therapy

Targeted therapy has recently been included in the armamentarium of medical treatment in gynecologic cancer. The antiangiogenic agent, bevacizumab, has been approved by the FDA and EMA in 2014 for use in recurrent platinum-resistant ovarian cancer and cervical cancer and in advanced primary and recurrent platinum-sensitive ovarian cancer (EMA). The FDA has recently (December 2016) improved bevacizumab for use in recurrent platinum-sensitive ovarian cancer as well. The most recent findings include the effect of the poly (ADP-ribose) polymerase (PARP) inhibitors olaparib, rucaparib, and niraparib. Olaparib has been approved as maintenance therapy in BRCA-mutated advanced ovarian cancer

patients, who have responded to platinum-based chemotherapy (FDA and EMA) or as monotherapy in BRCA-mutated patients who have received three or more lines of chemotherapy (FDA). Rucaparib has been approved (FDA 2016 and EMA 2018) as monotherapy in BRCA-mutated patients who have progressed on two or more lines of chemotherapy. Niraparib was approved by FDA and EMA in 2017 as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

## Antiangiogenic Therapy Including Multikinase Inhibitors

These agents include *bevacizumab, aflibercept, pazopanib, nintedanib, trebananib, sunitinib, sorafenib,* and *cediranib* (Table 32.3).

Angiogenic activity not only plays a significant role in tumor growth but also in the development of ascites, a highly prevalent and troublesome symptom [51]. *Bevacizumab* is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) and is recommended in combination with chemotherapy and as maintenance for both primary ovarian cancer in patients with poor prognostic factors and in recurrent disease [52]. The pivotal trials were ICON7 [53] and GOG 0218 [54] in ovarian cancer first-line therapy, the OCEANS trial in platinum-sensitive recurrent ovarian cancer [55], the Aurelia trial in recurrent platinum-resistant ovarian cancer [56], and the GOG 0240 trial in recurrent, persistent, or metastatic cervical cancer [57]. The major benefits from these trials were an increase in PFS, whereas OS was only significantly increased in the study in cervical cancer [57] and in a subgroup of high-risk patients in the ICON 7 trial [53]. Adding bevacizumab to standard chemotherapy resulted in an increase in grade 1–2 mucocutaneous bleeding, grade 2 or above hypertension, grade 3 or above thromboembolic events, and grade 3 or above gastrointestinal perforations.

Multikinase inhibitors not only targeting VEGF but also other receptors such as the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR) include pazopanib, cediranib, nintedanib, and trebananib [58, 59].

*Pazopanib*, targeting VEGFR, PDGFR, and c-KIT, was investigated as maintenance therapy in a randomized, double-blind study (AGO-OVAR 16) including 940 patients with advanced ovarian cancer who did not progress on first-line chemotherapy [60]. Even though a 5.6 month prolongation of PFS in patients receiving pazopanib (versus placebo) was found, no effect on overall survival was obtained. Significant adverse events were seen in patients randomized to pazopanib. Treatment discontinuation was significantly higher (33.3% vs. 5.6%) in the group receiving pazopanib as was grade 3–4 adverse events including hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythema (1.9%). Pazopanib has been approved by the FDA and EMA for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma but not yet for use in gynecologic cancer. The adverse event profile may, however, prohibit routine use, because FDA has released warnings against severe and fatal hepatotoxicity and interstitial lung diseases or pneumonitis.

The ICON6 trial investigated *cediranib* (VEGFR-1, VEGFR-2, VEGFR-3, and c-KIT inhibitor) in combination with platinum-based chemotherapy in patients with relapsed ovarian cancer [61]. A total of 486 patients were randomly assigned upfront to either placebo or cediranib given concomitantly with chemotherapy only or to cediranib given both concomitantly and as maintenance therapy. Cediranib prolonged time to progression, but overall survival data has not yet been published. Significantly more patients in the cediranib arms compared to the placebo arm discontinued treatment early due to adverse events. Toxicity occurring more frequently in patients receiving cediranib included diarrhea, neutropenia, hypertension, and voice changes, during chemotherapy, and diarrhea,

**Table 32.3** Incidence of side effects induced by targeted agents frequently used in gynecologic cancer (for CINV is referred to Table 32.2)

| Targeted agents | Anemia | ↓ ANC | Thrombopenia | ↑ BT | Dizziness | Fatigue | Headache | Constipation | Proteinuria | ↑ ALT/ AST | Diarrhea | GI-perforation | Bleeding | Dyspepsia | ATE VTE | PPE | MDS LEU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bevacizumab | + | ++ | ++ | +++ | 0 | ++ | ++ | ++ | +++ | 0 | ++ | + | ++ | + | + | + | 0 |
| Olaparib | +++ | ++ | ++ | 0 | ++ | +++ | ++ | ++ | 0 | 0 | +++ | 0 | 0 | ++ | + | 0 | + |
| Rucaparib | +++ | ++ | ++ | 0 | ++ | +++ | ++ | +++ | 0 | +++ | +++ | 0 | + | + | 0 | + | + |
| Niraparib | +++ | ++ | +++ | ++ | ++ | +++ | ++ | +++ | 0 | + | ++ | 0 | + | ++ | 0 | 0 | + |

+++ Side effects may occur in more than 30%. ++ Side effects may occur in 10–30%. + Side effects may occur in 1–10%. 0 Side effects may occur in less than 1%
*CINV* chemotherapy-induced nausea and vomiting, *ANC* neutrophile count, *ALT/AST* alanine/aspartate aminotransferase, *PPE* palmar-plantar erythema, *ATE* arterial thromboembolic event, *VTE* venous thromboembolic event, *MDS* myelodysplastic syndrome, *LEU* leukemia

hypothyroidism, and voice changes, during maintenance therapy. Based on the ICON 6 study, an application for marketing authorization was submitted to EMA but subsequently withdrawn due to a number of unanswered questions (e.g., concerning diarrhea and tiredness leading to early treatment discontinuation).

In a double-blind trial (AGO-OVAR12), 1366 patients with ovarian cancer were randomized 2:1 between *nintedanib* 200 mg (inhibitor of VEGFRs, PDGFRs, and fibroblast growth factor receptors) and placebo in addition to carboplatin and paclitaxel [62]. Progression-free survival reached statistical (but probably not clinical) significance with 17.2 months in the nintedanib group versus 16.6 months in the placebo group. Overall survival data has not yet been published (December 2017). Significantly more diarrhea was seen in patients receiving nintedanib with grades 3–4 reported in 22% versus 2% in the placebo arm. Also nausea, vomiting, and decrease of appetite were more frequent in the nintedanib group, and a total of 24% of patients receiving nintedanib had adverse events leading to drug discontinuation versus 15% in patients receiving placebo. Nintedanib has been approved by FDA and EMA for treatment of idiopathic pulmonary fibrosis, but not yet for ovarian cancer.

*Trebananib*, an antagonist to the angiopoietins Ang1 and Ang2 on the Tie2 receptor and as such a VEGF-independent antiangiogenic agent, has been investigated in two phase III trials in ovarian cancer. In the randomized, double-blind TRINOVA-1 trial, trebananib plus weekly paclitaxel was compared to placebo plus weekly paclitaxel in 919 patients with recurrent disease and a platinum-free interval of less than 12 months [63]. Trebananib improved PFS with 2.8 months, whereas no increase in OS was seen in the intention to treat population. An exploratory analysis in patients with ascites at baseline [64] showed a significant prolongation of OS in the trebananib-treated patients (14.5 months versus 12.5). The most frequent adverse events were edema (64% in the trebananib group versus 28% in the placebo group), ascites, and pleural effusion. Trebananib was also associated with more adverse event-related treatment discontinuations than placebo (17% versus 6%).

The TRINOVA-3 trial randomized 223 women with recurrent ovarian cancer and a platinum-free interval of <12 months to pegylated liposomal doxorubicin plus either trebananib or placebo [65]. No significant difference in PFS (primary parameter) was seen. As in the TRINOVA-1 trial, significantly more edema and ascites were reported among patients receiving trebananib.

*Aflibercept*, *sorafenib*, and *sunitinib* have only been investigated in phase II trials in gynecologic cancer [66–68], but the adverse event profile is well-known from multiple studies including phase III studies in other cancer diseases.

## Poly (Adenosine Diphosphate [ADP]-Ribose) Polymerase (PARP) Inhibitors

BRCA1 and BRCA2 proteins are critical in the homologous repair pathway, but BRCA-defective cells can normally use the base excess repair pathway, which is dependent on PARP proteins. Inhibiting PARP enzymes in BRCA-defective cancer cells is therefore thought to lead to cancer cell death. Because normal tissue contains at least one functional allele of BRCA1 or BRCA2 with which to repair its DNA, normal cells are, in theory, spared when exposed to a PARP inhibitor [69]. Recently, it has been demonstrated that the effect of PARP inhibitors such as olaparib, rucaparib, and niraparib is not restricted to patients with BRCA mutations. Some patients with high-grade serous ovarian cancer, but without BRCA mutations, have tumors with homologous recombination deficiency (HRD) and respond to PARP inhibition, in particular if they are platinum-sensitive [70].

The first clinical study with *olaparib* was a phase 1 study in which the dose-limiting toxicities observed with a 600 mg oral dose were grade 4 thrombocytopenia, grade 3 mood alterations, grade 3 fatigue, and grade 3 somnolence [71]. The marketed dose of 400 mg × 2 orally primarily caused grade 1–2 adverse events (Table 32.3). A subsequent larger phase II, randomized, double-blind study investigated olaparib 400 mg × 2

orally versus placebo as maintenance therapy in 265 patients, who had received at least two platinum-based regimens and who had had a partial or complete response to the most recent treatment [72, 73]. Progression-free survival increased from 4.8 months in the placebo group to 8.4 months in the group receiving olaparib (HR = 0.35; 95% CI, 0.25–0.49; $P < 0.001$), but no significant differences in OS was seen (median 27.8 months in the placebo-group versus 29.8 months in the olaparib group) [72]. Grade 3–4 adverse events were reported in 35.3% of the patients in the olaparib group versus 20.3% in the placebo group with fatigue and anemia in 7% and 5%, respectively, in the olaparib group. Any grade (total adverse events) of nausea (68.4% versus 35.2%), fatigue (48.5% versus 37.5%), anemia (16.9% versus 4.7%), and vomiting (31.6% versus 14.1%) were the only adverse events reported at least 10% higher in the olaparib group. Recently a randomized, double-blind phase III study (SOLO-2/ENGOT-Ov21) in BRCA-mutated, platinum-sensitive recurrent ovarian cancer was published [74]. The median progression-free survival was 19.1 months with olaparib as compared to 5.5 months with placebo (HR = 0.30; 95% CI, 0.22–0.41; $P < 0.0001$). Grade 3–4 adverse events were reported by 36% in the olaparib group and 18% in the placebo group. The most frequently grade 3–4 adverse event in the olaparib group was anemia (19%).

Rucaparib received accelerated FDA approval in December 2016 based on phase I–II trials in a total of 377 patients including 106 patients eligible for response rate and response duration in two phase II trials in which anemia (in 22%) and elevations in liver transaminases (in 12%) were the most frequent grade 3–4 adverse events [75, 76]. In 2017, a large, randomized, double-blind, phase III study in women with high-grade serous or endometrioid ovarian cancer, who had platinum-sensitive recurrent disease, was published [77]. Progression-free survival was improved by rucaparib both in the BRCA-mutant group (16.6 months versus 5.4 months, HR = 0.23; 95% CI 0.16–0.34, $P < 0.0001$) and in the homologous-recombination-deficient group (13.6 versus 5.4 months, HR = 0.32; 95% CI 0.24–0.42, $P < 0.0001$). Grade 3–4 adverse events were reported by 56% in the rucaparib group compared to 15% in the placebo group. The most frequently reported grade 3–4 adverse events were the same as seen in earlier phase studies with anemia reported by 19% and elevations in liver transaminases in 10%.

*Niraparib* was investigated in a randomized, double-blind phase III study in 553 patients, stratified according to BRCA status and randomly assigned to either niraparib or placebo as maintenance therapy following platinum-sensitive recurrent ovarian cancer [78]. Median progression-free survival was prolonged in both the group with a germline BRCA mutation (21.0 versus 5.5 months, HR = 0.27; 95% confidence interval [CI], 0.17–0.41) but also significantly in both the non-germline BRCA cohort, but with HRD (12.9 versus 3.8 months) and in the overall non-germline BRCA cohort (9.3 versus 3.9 months). Survival data are still immature. The most frequent grade 3–4 adverse events were thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%) in the niraparib group (Table 32.3).

The extent and severity of long-term adverse events induced by PARP inhibitors are not yet known. In particular, special notice should be assigned to the risk of myelodysplastic syndrome, a potential life-threatening adverse event that has been described in studies with PARP inhibitors. Two recently developed treatment strategies underline the need for careful monitoring of long-term adverse events, namely, the tendency to prolong treatment duration with PARP inhibitors and the ongoing studies investigating the effect of combinations of a PARP inhibitor with cediranib and bevacizumab, respectively.

## Side Effects Induced by Radiotherapy

Radiotherapy given with curative intent is used in women with low-stage cervical cancer, as an alternative to surgery; in low-stage patients with risk factors, as adjuvant therapy following surgery; and in high-stage inoperable patients. As

mentioned before, also women with cancer of the uterus receive multiple fractionation radiotherapy, but this primarily results in a decrease in local recurrence, not in prolongation of survival. Palliative radiotherapy is useful despite the diagnosis and can be helpful against bleeding complications and pain.

Side effects induced by radiotherapy depend on the dose, the size, the location of the radiation field, and the radiation technique applied. Both external beam radiation and intracavitary brachytherapy are used, often in combination. Concomitant cisplatin improves survival in locally advanced cervical cancer by 10–13% [79] but also increases toxicity. Organs at risk from radiotherapy of gynecologic cancer are the skin and mucosa, bladder, kidneys, small bowel, rectum, and bone marrow.

For a number of patients, surgery or radiotherapy can be optional. The decision whether to choose surgery or radiotherapy depends on several factors like age, comorbidity, and patients' preference. In younger women with low-stage disease (IB1) and a desire to maintain fertility, fertility-sparing surgery (radical trachelectomy and lymph node dissection) can be performed with recurrence rates comparable with radical hysterectomy [80]. This will also eliminate the risk of a radiation-induced second malignancy, which is estimated to be 1%.

## Acute Radiotherapy-Induced Side Effects

Definition of acute toxicity differs but is in most trials defined as toxicity appearing during radiotherapy, or shortly after, and lasting for less than 3 months. The most common acute toxicities include skin and mucosal toxicity which can cause pain; ulceration and dryness of the vagina; enteritis with diarrhea, abdominal pain, and fecal incontinence; and bladder symptoms with urinal incontinence, urgency with pain, and bone marrow toxicity. The risk of proctitis and/or enteritis during external radiotherapy to the pelvis is high and is often complicated with diarrhea and abdominal pain. Diarrhea usually begins after 2 weeks of radiotherapy and resolves within 10 days after completion and can be managed with dietary modifications and antidiarrheal medication. Loperamide is more effective than diphenoxylate. The risk of nausea and vomiting induced by pelvic external beam radiation is 30–60% and is most often effectively prevented with a serotonin receptor antagonist [37]. In combined chemoradiation, the risk of emesis will most often depend on the antineoplastic agent used, and antiemetic therapy recommendations will be directed toward the emetic risk of chemotherapy [81].

Urologic toxicity is reported in 8–12% of patients and includes bladder irritation (dysuria and frequency) and hematuria. Symptoms of cystitis are frequent but rarely accompanied by bacterial growth. Dysuria can be managed with phenazopyridine hydrochloride [82].

Concomitant chemoradiation (e.g., weekly cisplatin during fractionation radiotherapy) increases gastrointestinal toxicity and the risk of myelosuppression, primarily leukopenia, and thrombocytopenia [83, 84]. The use of intensity-modulated radiotherapy (IMRT) decreases the risk of acute hematologic toxicity and the number of missed chemotherapy cycles [85].

## Late and Chronic Radiotherapy-Induced Toxicity

The risk of late radiotherapy-induced toxicity is highly dependent on the radiation technique used. Changing from conventional 3D conformal radiotherapy to intensity-modulated radiation therapy (IMRT) seems to reduce late toxicities with a HR of 0.42 [84].

Common late toxicities include dryness, fibrosis and agglutination of the vagina, shortening of the vaginal canal or stenosis, postcoital bleeding, and pain during and after intercourse; gastrointestinal side effects such as small bowel obstruction, fistulae, rectal bleeding, rectosigmoid stenosis; and urinary symptoms like hematuria and ureteric stricture [80]. Symptomatic pelvic insufficiency fracture is reported in 8–13% at 5 years [80] but increases to a 5-year cumulative

fracture prevalence of 45.2% if fractures diagnosed with MRI in asymptomatic patients are included [86]. The risk of having a pelvic insufficiency fracture is not increased by the use of concomitant chemotherapy [86].

Vaginal stenosis and vaginal shortening have a specific impact on quality of life. Radiation-induced fibrosis will lead to vaginal dryness. Stenosis occurs as a result of adhesions and fibrosis in the upper vaginal tissue. These factors will compromise the sexual activities for many women because of pain, bleeding, or even low self-esteem. Vaginal dilators can be effective in prevention of vaginal stenosis, and patients should be informed about their use prior to the start of radiotherapy [87].

Although gastrointestinal toxicity can become symptomatic more than 20 years after completion of radiotherapy, most women will develop mild-to-moderate symptoms during the first 2 years after treatment. Up to 80% of all patients will experience a permanent change in bowel habits after radiotherapy, and in some cases, this will affect physical, psychological, and social aspects of their lives. Small bowel obstruction is caused by adhesions leading to mechanical obstruction and has been described in a little more than 5% after 20 years [88].

Chronic enteritis has been reported in as many as 20% of patients who have received pelvic radiotherapy [89]. There is little evidence on which to base treatment. Potential therapeutic options include nutritional therapy, antidiarrheals, corticosteroids and other anti-inflammatory agents, antibiotics, cholestyramine, pentoxifylline, and tocopherol. Hyperbaric oxygen provides a promising treatment but is expensive and requires access to specialized centers for administration [89].

One of the most disabling late complications is a vesicovaginal or rectovaginal fistula. In a retrospective trial in 1784 patients with cervical cancer treated with external beam irradiation delivered as anterior and posterior opposed fields plus brachytherapy, the overall risk of fistula formation was 3.1% at 20 years, and new occurrences were observed as late as 29 years after treatment [88]. Fistula formation often requires surgery which can be difficult because of diminished blood supply in an irradiated area. Fistulae can cause serious distress, and especially the odor can compromise well-being and lead to a disrupted social life. Metronidazole can be helpful due to the effect on anaerobic bacteria.

Symptoms of late radiation effects to the bladder appear with a median of 2–3 years after the completion of radiotherapy and include dysuria, urgency, hematuria, infections, urethral stenosis, and fistula formation [90]. Antimuscarinics can reduce bladder (detrusor) contractions, thereby relieving urgency and urge incontinence and increasing capacity in the bladder. Symptoms of reduced bladder capacity can also be treated with antispasmodics such as oxybutynin or tolterodine [90].

Today most centers use intensity-modulated radiotherapy (IMRT) which makes it possible to treat tumors with high doses of radiation and at the same time limits the volume of surrounding areas that receive high doses of radiation. This limits the toxicity of the treatment and may insure higher tumor control, but compared with previously used techniques, larger volumes of normal tissue will receive small doses of radiation. The experience with IMRT is limited to 10–15 years, and it is unknown if the larger volumes of low doses of radiation will influence the risk of very long-term adverse effects such as radiotherapy-induced intestinal fistula and secondary cancers. Other novel radiation techniques include the use of image-guided radiotherapy (IGRT) and adaptive techniques which allows, on a continuous basis, to treat the tumor target in a very precise manner even if the position and size of the tumor and the anatomy of the patients change during the treatment course. How this will impact the need for supportive care in these patients is unknown.

## Survivorship Problems

Survivorship is in this chapter defined as patients who have completed oncologic treatment and have no sign of disease, whereas others define survivorship as starting at the time of diagnosis and refer to all patients alive, whether they have

active disease or not. Gynecologic cancer patients report specific survivorship problems dependent on the diagnosis, stage of disease, treatment, treatment result, and time since completion of treatment. The most frequently reported health issues are fatigue, sleep disturbance, urinary difficulties, sexual dysfunction, neurological issues, bowel complains, depression, and memory loss [91].

## Survivorship Problems During the First 6 Months After Completion of Treatment

In a study in 1425 patients, including 90 with gynecologic cancer, patients receiving radiotherapy, chemotherapy, or both were assessed at the end of treatment and again 6 months later. All patients were metastases-free and had not experienced relapse during treatment [92]. One-third of the patients reported five or more moderate-to-severe unmet needs, and for 60% of these, the situation did not improve during the 6-month period. Both at baseline and after 6 months, the five most frequently reported unmet needs were "fears about the cancer spreading," "concerns about the worries of those close to you," "uncertainty about the future," "worry that the results of the treatment are beyond your control," and "lack of energy/tiredness." It is noteworthy that except the lack of energy/tiredness, the most frequently endorsed unmet needs were all psychological, and "fear about cancer spreading" was most frequently scored both at baseline and after 6 months [92].

## Survivorship Problems 2–25 Years After Completion of Treatment

In a study, 5836 long-term cancer survivors completed a health survey. Overall, the interval between a cancer diagnosis and the completion of the survey was at least 5 years with a mean time of 18.0 +/−8.5 years. A total of 970 gynecologic cancer survivors responded, and 28.1% of these indicated that cancer had affected their overall health. The most frequently reported health problems in gynecologic cancer survivors were arthritis/osteoporosis (31.1%), urinary (18.5%), cataracts (16.3%), and heart (13.3%), respectively. It must be emphasized that some of these problems could be due to comorbidities at the time of diagnosis or due to aging [93]. Chemotherapy-induced peripheral neurotoxicity (CIPN) was not among the most frequent adverse drug reactions in the above study, in which most of the patients received chemotherapy, before paclitaxel was part of the standard treatment of ovarian cancer. A recent study investigated the frequency and severity of CIPN and the impact on health-related quality of life among ovarian cancer survivors, who had all (more than 95%) received paclitaxel [94]. CIPN was experienced by 51% of the patients up to 12 years after end of chemotherapy, and this severely affected their quality of life. The risk and severity of CIPN was higher in 25% of the patients who received more than 6 cycles of chemotherapy. There is no method to prevent CIPN, but one option could be to substitute paclitaxel with a drug known to cause less CIPN such as docetaxel [95] or pegylated liposomal doxorubicin [96] in the treatment of recurrent ovarian cancer. The only evidence-based treatment of the pain induced by CIPN is oral duloxetine [97].

## Specific Survivorship Problems in Gynecologic Cancer

Many gynecologic cancer survivors adjust well as they recover, but a significant number have physical and/or psychosocial problems [98]. This can be explained by the combination of the impact of being diagnosed with a cancer, undergoing surgery, receiving chemotherapy and/or radiotherapy, and the fear of recurrence.

Surgery with bilateral oophorectomy in premenopausal women causes premature menopause and may induce symptoms such as hot flashes, vaginal dryness and atrophy, loss of libido, urinary incontinence, and depression. Loss of estrogen production can also lead to mood changes and changes of the hair and skin.

Systemic estrogen can be considered but topical estrogen can be useful as well. In addition, loss of fertility can be a psychological challenge. In all, this may have a significant negative impact on quality of life (QoL).

Survivorship problems can be disease-related, and ovarian cancer survivors seem to report a higher level of unmet needs than endometrial cancer survivors [99]. Choice of treatment may not only be important for the risk of CIPN but can also impact other survivorship problems. A study [98] compared survivorship problems in women with uterine cervical cancer treated with surgery ($n$ = 99, included 26–82 [median 42] months after surgery) or radiotherapy ($n$ = 111, included 25–85 [median 46] months after completion of radiotherapy). The most common side effects after surgery were constipation (70.3%), urinary incontinence (42.9%), fatigue (41.8%), dysuria (41.8%), and vaginal dryness (35.2%). Women treated with radiotherapy most frequently reported fatigue (49.5%), diarrhea (42.2%), urinary frequency (31.5%), lower abdominal skin dryness (28.8%), and urinary incontinence (25.2%). Patients who underwent surgery had a significantly higher incidence of constipation, flushing, dysuria, urinary incontinence, dysparia, and vaginal dryness, whereas women in the radiotherapy group had more diarrhea, bloody stools, and abdominal pain [100]. Neural dysfunction was significantly higher in surgical patients, whereas intestinal dysfunction was higher in radiotherapy patients. Sexual dysfunction was reported by both groups, but without significant difference.

Sexual dysfunction is reported by almost half of the patients treated with surgery or radiotherapy for cervical cancer [100]. Sexual dysfunction from surgery is caused by vaginal shortening, vaginal dryness, and decreased libido, and radiotherapy-induced sexual dysfunction is primarily due to vaginal stenosis which often causes dyspareunia and difficulty in orgasm. Also ovarian cancer survivors have a high frequency of sexual problems, and only approximately 50% are sexually active of which three out of four report pain and discomfort during intercourse and 87% describe vaginal dryness [101].

In conclusion, gynecologic cancer survivors will have a high risk of experiencing depression and anxiety, chronic fear of recurrent disease, and sexual dysfunction. Supportive care should be initiated early in the treatment phase, and counseling should not be restricted to the cancer patient only but also include the partner. A recent study emphasizes that social support is of general benefit for depressive symptoms [102].

## End-of-Life Issues in Gynecologic Cancer

In women receiving optimal therapy, the overall 5-year survival rates in cervical, endometrial, and ovarian cancer are approximately 70%, 85%, and 45%, respectively.

Consequently, more than 50% of ovarian cancer patients and a significant number of women with cervical and endometrial cancer will develop recurrent disease and eventually die from their cancer. These women will need palliative care, including guidance concerning pain, anorexia and cancer cachexia, bowel obstruction, ascites, psychosocial problems, and spiritual issues all described in other chapters.

Today we have a large number of palliative therapies, including surgery, radiotherapy, and chemotherapy. The clinician should continuously protect patients against therapies that will not improve survival or reduce complications and symptoms from the cancer but undoubtedly will induce side effects (medical futility) [103]. This is not an easy task, because the patient at that stage has to accept that therapy with a curative intent is no longer an option [104, 105].

A number of end-of-life complications are frequent in patients with gynecologic cancer. Patients with advanced uterine or cervical cancer have a risk of bilateral ureteral obstruction and uremia due to extension of their cancer. In patients who have not received prior radiotherapy, this modality could be a reasonable treatment option. In patients who have recurrent disease in a previously irradiated area, the decision of whether or not to offer urinary diversion is difficult. Expiration due to uremia (in case uri-

nary diversion is not carried out) could be more beneficial to the patient. This difficult decision should be made in close consultation with the patient and the family. Another problem in cervical and uterine cancer patients is urinary or colonic fistulas. Both types of fistulas have a significant negative impact on patients' quality of life, and every effort should be done to relieve this situation.

Specific problems in advanced ovarian cancer are bowel obstruction and recurrent ascites. These problems are reviewed elsewhere.

## Conclusion

This chapter reviewed supportive care in gynecologic oncology. The conditions for optimal supportive care have changed significantly during the past years due to the inclusion of targeted therapy as part of the routine treatment.

In ovarian cancer, extensive surgery, with the purpose of increasing the numbers of patients who can be macroscopically cleared, has become standard. We still know very little about long-term complications in these patients.

In patients with cervical cancer, the use of image-guided planning and new radiation techniques such as IMRT and IGRT has led to a decrease in acute side effects, but the extent of long-term toxicity is unknown. In particular, it is unknown if the risk of inducing a secondary tumor will increase.

Targeted therapy has become of considerable use in gynecologic cancer. We do not know how the well-known hypertension and proteinuria induced by bevacizumab and other angiogenesis inhibitors will affect patients in the long run, and also the true risk of myelodysplastic syndrome after long-term use of a PARP inhibitor is unknown. Immunotherapy has been a major advantage in cancer diseases like malignant melanoma and lung cancer, and studies are ongoing in gynecologic cancer patients. This will further increase the need for supportive care.

Fortunately survival rates continue to increase due to more effective therapy. Today, many patients with a gynecologic cancer will have to consider themselves as having a chronic disease. This should reinforce the attention on rehabilitation and survivorship issues. It is important that rehabilitation does not continue to be a kind of "damage control" after the end of cancer therapy; instead rehabilitation plans should be initiated at the time of diagnosis and start of therapy. Furthermore the advantage of using "individualized or personal medicine" should be taken into account, whenever possible.

Pharmacogenetics is useful in defining patients who can benefit from individual cancer therapy, but in the future, prediction of individual side-effect profiles of cancer therapy will also be possible. Hopefully, this will lead to an optimization of supportive care in gynecologic cancer patients.

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# Part X

# Neurologic and Muscular

# 33

# Central Nervous System Symptoms: Headache, Seizures, Encephalopathy, and Memory Impairment

Elizabeth Cathcart-Rake, Roxana Dronca, and Charles L. Loprinzi

## Introduction

Central nervous system (CNS) complications are an important cause of morbidity and mortality in patients with cancer. The pathogenetic mechanisms are heterogeneous and may involve direct and indirect tumor effects or may be the result of antineoplastic therapy. Over the past few decades, major advances have been made in the development of more potent and effective treatment techniques, resulting in improved cure rates and increased survival in many malignancies. Although the exact incidence is difficult to assess, the long-term morbidity of cancer-related neurotoxicity is becoming increasingly prevalent and can significantly affect patients' quality of life and functional ability. The clinical manifestations are pleomorphic—headache, seizures, focal neurological deficits, or acute encephalopathy—and even chronic neurocognitive changes including dementia.

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## Headache

Headache is a common symptom in patients with cancer and can result from tumor involvement of the brain or surrounding structures or as a consequence of cancer-related treatment. Up to 60% of patients with primary brain tumors [1] and 48% or more of patients with cerebral metastases [2] experience chronic or frequent headaches. The prevalence of headache depends on tumor type, the location and structures involved, as well as the patient's age and previous headache history. For example, slow-growing low-grade gliomas are less likely to cause headache than high-grade anaplastic gliomas or glioblastomas; these patients usually present with seizures before developing headaches [2]. Previous studies have also reported that elderly patients are less likely to present with headache and more likely to develop confusion, aphasia, or memory loss as compared to their younger counterparts [3]. Infratentorial and intraventricular tumors tend to be accompanied by headache more often than those located supratentorially, probably secondary to the disturbance of CNS flow and development of hydrocephalus and increased intracranial pressure.

Many headache patterns have been described, including some which are indistinguishable from common migraine and tension-type headache. However, the development of an atypical, new (less than 10 weeks) [4], or progressive headache



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[5], especially if unresponsive to general therapy, is particularly worrisome for CNS involvement and warrants careful scrutiny, particularly in patients with known systemic malignancies. In patients with primary or metastatic tumors, the headache is typically moderate to severe in intensity, lasts for hours at a time, and is usually intermittent without having a regular daily occurrence [5]. Contrary to the classical teaching, the typical "morning or nocturnal headache" is uncommon and occurs in only a minority of adult patients with brain tumors [2]. Unlike tension-type headaches, brain tumor headaches are worse ipsilaterally on the side of the tumor, are often exacerbated by bending over or Valsalva-type maneuvers, and are frequently associated with nausea and/or vomiting, mental status or personality changes, and other focal neurological symptoms [2]. Headaches caused by elevated intracranial pressure from mass effect are often widespread and cause diffuse pain due to activation of pain receptors throughout the brain [6]. It is generally uncommon for a patient to present with isolated headache as the only symptom of a brain mass. This was illustrated in a study of 3291 children with primary brain tumors, of whom less than 1% had isolated headache and less than 3% had a normal neurological examination [1]. Symptoms most commonly associated with headache include seizures, fatigue, cognitive dysfunction, or focal weakness [7]. These associations have prompted the International Headache Society to create specific diagnostic criteria for headache attributed to neoplasm [8]. A de novo headache occurring temporally with an intracranial neoplasm should be defined differently than other forms of headache.

As cancer treatments have evolved, so has the incidence and prevalence of intracranial disease among tumor subtypes. Central nervous system metastases have become a more prominent problem in patients with HER-2 positive breast cancers, concurrent with the development of effective systemic drugs for this disorder which provide substantial control of non-CNS disease. Now, approximately a third of patients dying of HER-2 positive metastatic breast cancer develop CNS disease [9]. Unfortunately, temozolomide, which effectively targets intracranial metastasis in metastatic melanoma, has not been effective in preventing intracranial breast cancer [10]. According to one retrospective study, the antiangiogenic agent, sorafenib, may decrease the incidence of intracranial metastases in patients with unresectable and/or metastatic renal cell carcinoma, as only 3% of the patients treated with sorafenib developed brain lesions compared to 12% of placebo group at 2-year follow-up [11]. While many targeted therapies, such as dabrafenib, have shown promise in the treatment of brain metastases [12], further research into their role in the prevention of intracranial disease is needed. Apart from primary and metastatic tumors, other causes of headache in patients with cancer include ischemic or hemorrhagic strokes, dural sinus thrombosis, posterior reversible encephalopathy syndrome (PRES), meningeal carcinomatosis [13] (secondary to disturbance of CSF circulation or infiltration of pain-sensitive structures in the brain or of cranial nerves), or base of the skull metastases. In a seminal paper, Greenberg et al. [14] described five bases (no "s") of the skull metastases syndromes: an orbital and parasellar syndrome characterized by frontal headache, diplopia, and first-division trigeminal sensory loss; a middle-fossa syndrome characterized by facial pain or numbness; a jugular foramen syndrome characterized by hoarseness and dysphagia; and an occipital condyle syndrome characterized by unilateral occipital pain and unilateral tongue paralysis. Patients with ipsilateral lung cancer may present with referred unilateral facial pain caused by invasion and compression of the vagus nerve [15].

In patients suffering from cancer, headache may also be the result of surgery, as well as chemotherapy or radiation therapy. Chemotherapy agents, such as all-trans-retinoic acid, procarbazine, and 5-FU as well as many others, have been implicated. Headaches can range from the aforementioned headache descriptions to a continuous hemicranial headache, including autonomic symptoms with exacerbations [16]. Most patients experience headache in the first few weeks after surgery for brain tumors, but this is usually short-lived, with less than 6% of patients having headaches that last more than 2 months [17].

Intrathecal (IT) administration of chemotherapeutic agents such as methotrexate (MTX) [18] and, less often, cytarabine (ara-C) [19] has been reported to cause a syndrome of aseptic meningitis characterized by headache, nuchal rigidity, fever, vomiting, and lethargy. Symptoms usually occur 2–4 h after the drug is injected and can last up to 72 h. The syndrome is typically self-limited, and no specific treatment is necessary. Coadministration of IT hydrocortisone and the use of a constant, rather than body surface area (BSA)-adjusted, IT dose [20] may decrease the incidence of arachnoiditis in these patients [21]. The posterior reversible encephalopathy syndrome (PRES) is another important consideration in the differential diagnosis of headache in patients with cancer. The most common cause is hypertensive encephalopathy, but PRES has also been described with the administration of several chemotherapeutic and immunomodulatory drugs. The clinical findings include headache, acute mental status changes, seizures, cortical blindness, or other visual disturbances [22] (further described below).

Acute radiation toxicity commonly manifests with severe headache, fever, nausea, vomiting, decreased level of consciousness, and worsening neurological deficits. These symptoms are generally more severe following the first radiation dose, with gradual improvement for subsequent treatments. This complication occurs mainly with "rapid-course," high-dose radiation therapy (>3 Gy) administered to a large brain volume [23], and it is considerably less common with current whole-brain radiation therapy (WBRT) techniques and the conventional use of low fractions (≤3 Gy). Proton beam radiation therapy can also precipitate headaches, but typically this is grade 1 and improves by 1-month follow-up [24].

The treatment of headache in patients with cancer depends on the etiology and should be aggressive in terms of pain and symptom control. Headache caused by raised intracranial pressure in patients with primary and metastatic brain tumors is primarily managed with corticosteroids, until more definitive therapy, such as surgical resection, stereotactic radiosurgery, or palliative radiation therapy, occurs. Analgesics, including acetaminophen and NSAIDS, opioid medications, and palliation of associated symptoms using a multimodality therapy approach, may be necessary when symptoms are not relieved by the treatment of the tumor. One randomized, controlled trial showed that postcraniotomy headache may be prevented with one preoperative dose of diclofenac, with results lasting for 5 days [25]. Somatostatin analogs improve headaches in about 54.6% of patients with pituitary tumors, compared with dopamine agonists which improve headaches in only 30% [26]. Several other agents have been studied in cancer-related breakthrough pain, including nociceptive and orofacial pain, including rapid-onset buccal fentanyl, anticonvulsants, cannabinoids, and ketamine [27, 28]. Unfortunately, the efficacy of many of these agents is generally low [29]. Non-pharmacologic therapies, such as acupuncture and massage, have also been studied with mixed results; these require further investigation [30, 31].

## Seizures

The onset of a new seizure disorder may represent a cardinal symptom of a serious or life-threatening disease, including malignant cerebral neoplasms or metastatic disease. In patients with known malignancies, however, the differential diagnosis is extensive, including toxic-metabolic as well as structural causes. For instance, patients may experience seizures in the setting of an acute metabolic disturbance, such as hypercalcemia secondary to osteolytic metastases or secretion of parathyroid-related hormone (PTHrP), hypomagnesemia associated with chemotherapy (cisplatin), hyponatremia secondary to dehydration or the syndrome of inappropriate antidiuretic hormone (SIADH) [32], hypo- or hyperglycemia (glucocorticoids), hepatic or renal failure, or hypoxia. Drug withdrawal states are another important consideration, particularly in patients who have been treated with long term with benzodiazepines, opioids, or muscle relaxants such as baclofen or dantrolene [33]. Several chemotherapeutic agents as well as radiation therapy

have also been reported to cause seizures, usually in the context of an acute (e.g., PRES) or chronic encephalopathy syndrome (further described below).

Structural causes of seizures include primary or metastatic brain tumors, meningeal carcinomatosis [13], ischemic and hemorrhagic strokes, or CNS infections (particularly in immunocompromised patients). The tumor type and location may influence the prevalence of seizures. Slower-growing meningiomas and low-grade gliomas are more likely to present with seizures than high-grade tumors, as illustrated in a review of 1028 patients with primary brain tumors. The prevalence of seizures was 49% in glioblastoma (GBM) patients, 69% in patients with anaplastic gliomas, and 85% among those with low-grade gliomas [34]. The incidence of seizures is lower in patients with metastatic brain lesions, compared to primary tumors. In a retrospective series of 195 patients with documented cerebral metastases, seizures were the presenting symptom in 18% and developed subsequently in an additional 10% of patients [35]. Similarly, tumors associated with a posterior fossa lesion are less likely to cause seizures, as opposed to hemispheric lesions [35].

Clinically, patients may present with either generalized tonic-clonic or partial seizures or even status epilepticus, depending on tumor type and location [36]. Drug-induced seizures are often generalized tonic-clonic, but partial-onset seizures have also been described [37]. A careful and comprehensive metabolic evaluation is essential in all patients who experience a seizure. Most cancer patients with a new-onset seizure disorder will need an imaging study of the brain (CT scan or MRI), and a lumbar puncture may also be required after brain imaging, particularly if meningeal carcinomatosis or an infectious etiology is suspected. The diagnosis of a drug-induced seizure is one of the exclusion and should be made only after all other potential etiologies have been ruled out.

Treatment should be directed at the correction of the underlying cause, if possible. Early surgical resection of brain tumors decreases rates of seizures [38]. Radiation therapy also may improve tumor-related epilepsy, and this effect is not strictly associated with tumor shrinkage [39]. Chemotherapy, including temozolomide and other agents, has also been shown to decrease seizure frequency, even in cases where patients have stable disease on MRI [40]. Patients who present with seizures due to a brain tumor should be treated with standard anticonvulsants, preferably those which do not affect cytochrome P450 enzymes, in order to avoid potential interactions with chemotherapeutic agents or other drug-drug interactions [41]. On the other hand, prophylactic therapy is not routinely recommended in patients with primary or metastatic brain tumors who have no history of epilepsy [42]. A meta-analysis of five randomized trials concluded that there is no evidence to support antiepileptic drug prophylaxis with phenobarbital, phenytoin, or valproic acid in patients with brain tumors and no history of seizures [43]. These findings were subsequently confirmed by a Cochrane database systematic review, which also found that the risk of an adverse event was higher in patients on prophylactic antiepileptic drugs [44]. However, there may be an exception with metastatic melanoma as one small, retrospective study suggested that prophylaxis with antiepileptic drug decreased seizure risk, especially in patients with multiple brain metastases and hemorrhage [45].

## Encephalopathy

### Acute Encephalopathy

The differential diagnosis of acute encephalopathy in patients with cancer is complex and includes both toxic-metabolic and structural causes. In patients with advanced malignancies, acute mental status changes can be caused by leptomeningeal carcinomatosis, the presence of CNS leukemia, rapid changes in intracranial pressure due to sudden changes in tumor size (e.g., bleeding into a brain metastasis), paraneoplastic syndromes, or cancer-associated coagulopathies resulting in either cerebral hemorrhage or symptomatic occlusion of cerebral arteries and veins [46]. More commonly, however, acute

encephalopathy in cancer patients is caused by electrolyte disturbances, hypo- or hyperglycemia, renal or hepatic dysfunction, hypoxia, narcotic medications, or sepsis.

In addition, acute central neurotoxicity can be caused by administration of various chemotherapeutic agents and by radiation therapy. Administration of high doses of intravenous methotrexate has been associated with the development of transient acute encephalopathy, characterized by confusion, somnolence, seizures, as well as focal neurological deficits which usually begin within 2 weeks of MTX administration [47]. Most patients have normal CSF and imaging studies [48] and recover fully. While retreatment is often possible, some patients suffer recurrences during subsequent courses of treatment. Although the exact mechanism of acute MTX-induced neurotoxicity is unknown, a number of studies have suggested that profound alterations in cerebral glucose metabolism may lead to decreased glucose utilization and protein synthesis [49, 50], and that this could be reversed by administration of intravenous folinic acid (leucovorin) [51]. Acute encephalopathy has also been described after intravenous administration of high doses of ifosfamide, occurring in up to 20% of patients in one study [52]. Agitation, confusion, hallucinations, and aphasia begin anywhere between 2 and 48 h after the administration of the drug and can progress rapidly to seizures, cerebellar or cranial nerve dysfunction, and even coma [53]. The syndrome is usually reversible, but in some patients, long-term CNS sequelae and even death have been reported [54]. Several risk factors have been associated with an increased risk of development of ifosfamide-induced acute neurotoxicity, such as low serum albumin concentration [52], renal insufficiency, pelvic disease [55], prior cisplatin treatment [56], or concurrent administration of drugs (e.g., phenobarbital) which can increase the breakdown of ifosfamide to active metabolites [53]. Several case reports and retrospective series suggest that methylene blue [57, 58] or thiamine [59] may be useful in both the treatment and prevention of ifosfamide toxicity, but this remains controversial, and a single-institution retrospective study has called this into question [60]. In most patients, symptoms resolve spontaneously and without any specific treatment [57]. The main neurotoxicity of 5-fluorouracil (5-FU) is a cerebellar syndrome, but continuous intravenous administration of high doses can rarely cause an acute encephalopathy manifested by an abrupt alteration in mental status with markedly elevated ammonium levels in the absence of organic liver disease [61, 62]. Symptoms include progressive confusion, agitation, ataxia, seizures, stupor, coma, and, at times, death; the median time of onset of encephalopathy was 2.6 +/−1.3 days from initiation of chemotherapy in one study [63]. Although no specific treatment is available, early recognition and measurement of plasma ammonium, followed by aggressive ammonia-trapping therapy (i.e., lactulose) and hemodialysis, appears to be critical [62]. Several cases of multifocal inflammatory leukoencephalopathy have been reported with the combined use of 5-FU and levamisole as adjuvant therapy for colon adenocarcinoma [64, 65]. Patients present with a subacute (weeks to months) progressive decline in mental status, ataxia, or transient focal neurological deficits. Characteristically, magnetic resonance imaging with gadolinium demonstrates prominent multifocal enhancing white matter lesions. Pathologically, these lesions are characterized by intense perivascular lymphocytic infiltration and myelin loss, with axonal sparing. The pathogenesis of this syndrome has not been completely elucidated, although levamisole can affect the blood-barrier function and is known to have an immune-modulating effect [66]. Complete recovery usually occurs within weeks after cessation of therapy; the role of corticosteroids and intravenous immunoglobulin treatment to accelerate improvement is unclear. Correct diagnosis of 5-FU-associated multifocal inflammatory leukoencephalopathy may require cerebral biopsy and may be important because the clinical presentation and MRI findings may be hard to distinguish from brain metastases. In patients with malignant CNS gliomas, administration of combination chemotherapy with procarbazine, lomustine, and vincristine may be associated with severe central neurotoxic effects with cognitive disturbances or

focal neurological deficits which may only be partially reversible with discontinuation of therapy. Of note, procarbazine-induced CNS toxicity worsens with the use of a phenothiazine to control emesis, possibly due to the weak monoamine oxidase inhibitor activity of procarbazine. Other cytotoxic agents known rarely to cause acute or subacute encephalopathy include L-asparaginase [67]; vincristine [68]; the purine analogs fludarabine, pentostatin, and cladribine [69]; and paclitaxel [70] especially when delivered at high doses (≥600 mg/m [2]) with stem cell support [71].

Biologic response modifiers such as interleukin-2 (IL-2) and the interferons are commonly associated with the development of central nervous system neurotoxicity, which is generally dose-dependent. Up to 50% of patients receiving high-dose IL-2 combined with autologous lymphokine-activated (LAK) cells may experience a transient encephalopathy or a neuropsychiatric syndrome with disorientation, severe cognitive and behavioral changes, delusions, hallucinations, and depression [72]. The vascular leak associated with systemic IL-2 administration may result in cerebral edema which can cause a sudden increase in brain metastases and in intracranial pressure. Less commonly, transient neurological deficits [73] or the development of multifocal acute leukoencephalopathy has been reported [74, 75]. The most common side effects associated with the use of interferons include flu-like symptoms (arthralgias, myalgias, fever, chills, headache), but at higher doses they can also cause significant neurotoxicity with confusion, somnolence, paresthesias, and extrapyramidal signs [76]. In children, the development of spastic paraplegia or quadriplegia syndrome has been reported 4–15 months after the onset of interferon therapy [77].

Immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab, have a variety of neurologic effects, mediated by their activation of the immune system [78]. A study which evaluated 752 patients who had received ipilimumab reported a total of 11 adverse events [79]. Patients frequently reported headache, dizziness, lethargy, and asthenia, but they also noted BGS, mening-radiculoneuritis, and cerebral edema precipitating seizures [79]. One series described two patients who developed autoimmune encephalitis within days after initiation of combination of nivolumab and ipilimumab; both significantly improved with steroids [80].

### Posterior Reversible Encephalopathy Syndrome (PRES)

The posterior reversible encephalopathy syndrome, otherwise referred to as the reversible posterior edema syndrome or the reversible posterior leukoencephalopathy syndrome (RPLS), was first described in 1996 by Hinchey and colleagues [22]. The name is a misnomer, as the syndrome is neither always reversible nor confined to the posterior white matter. The most common causes of PRES are hypertensive encephalopathy, eclampsia, and the use of immunosuppressive and chemotherapeutic drugs. The pathophysiology is not well understood, but proposed mechanisms include T-cell activation from oncogene-produced proteins and/or chemotherapeutic agents precipitating endothelial dysfunction and edema [81]. Elevated LDH is perhaps an early signal for PRES onset and may predict the degree of brain edema [82, 83]. The most common agents associated with the development of PRES include cyclosporine, sirolimus, tacrolimus, cytarabine, cisplatin, gemcitabine, and the monoclonal antibody bevacizumab [83–89]. New biologic and molecular therapy agents have also been linked to PRES, including rituximab, ipilimumab, imatinib, and sunitinib [90, 91]. Tumor lysis syndrome is likely a risk factor, as well [92]. In cases due to immunosuppressive or chemotherapeutic agents, the presence of toxic drug levels is not required for the development of neurotoxicity. Similarly, patients may be normotensive, although the blood pressure is usually elevated above their baseline. Affected patients commonly develop severe headache, visual disturbances which may progress to cortical blindness, seizures, and altered consciousness ranging from mild somnolence to agitation or stupor and even coma [22, 93]. One study of children with acute lymphoblastic leukemia undergoing

induction chemotherapy reported PRES between days 7 and 30 of chemotherapy, with another reporting an average of 11.1 days out from the last day of chemotherapy [83, 94]. The classic hallmark of this disorder is vasogenic edema in the territories of the posterior circulation, demonstrated on CT and MR brain imaging [95] (Fig. 33.1); but a new, large European study showed that about half of the patients have more atypical involvement, with edema involving the temporal or frontal lobes [96]. Prompt diagnosis and treatment of this commonly reversible syndrome is critical in preventing permanent neurotoxicity that can otherwise occur if the condition remains unrecognized. Dose reduction or immediate removal of the cytotoxic drug, as well as treatment of the associated seizure disorder, hypertension, and fluid overload may result in full recovery with no long-term sequelae. A study by Roth and colleagues reported long-term follow-up (mean 2250 days) of 25 patients with 27 episodes of PRES. Clinical recovery occurred, on average, after 7.5 days, and recurrence was observed in only 8% of patients, even though the causal factors for PRES were repeatedly experienced by the patients [97]. In a study of 31 patients who had experienced PRES, 47% were rechallenged with the original treatment regimen provided, and none had recurrent symptoms [98].

## Radiation-Induced Encephalopathy

Recent advances in radiotherapeutic techniques, such as the development of radiosurgery and brachytherapy, and the increased use of radiosensitizers have allowed local dose intensification for the treatment of brain tumors but have also resulted in increased radiation effects on the surrounding normal tissue. Moreover, improvement in life expectancy and the increasing number of long-term survivors in many cancer types where some form of brain irradiation is employed have uncovered a greater incidence of delayed, chronic radiation-induced neurotoxicity. It is therefore critical for the practicing oncologist and primary care provider to have a good understanding of the potential complications associated with brain and spinal cord irradiation in order to properly manage and counsel these patients and their families. The CNS neurotoxicity associated with radiation therapy can be divided into acute (occurring during the course of therapy), early-delayed (occurring weeks to up to 6 months postirradia-

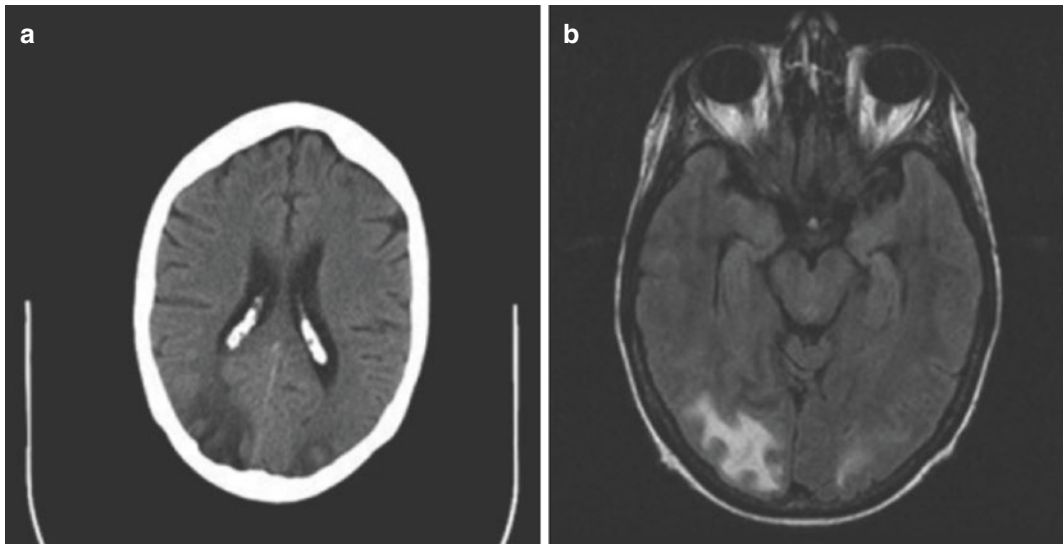


**Fig. 33.1** Computed tomography (**a**) and magnetic resonance imaging with gadolinium (**b**) demonstrating acute vasogenic edema of the posterior cerebral hemispheres in a patient with acute myelogenous leukemia and cytarabine-induced posterior leukoencephalopathy syndrome (PRES)

tion), and late-delayed (occurring more than 6 months to several years postirradiation) neurotoxicity [99]. The primary risk factors predictive for the development of radiation side effects include total radiation dose, fractionation schedule, volume and anatomical location of normal brain tissue treated, patient age (i.e., risk is greater in children less than 5 years old and the elderly), and the use of concurrent and sequential chemotherapy [100].

As previously mentioned, acute radiation toxicity is usually characterized by the development of an acute encephalopathy syndrome with severe headache, fever, nausea, vomiting, worsening neurological deficits, and a decreased level of consciousness. While most patients have complete recovery of neurological function, cerebral herniation and death have been rarely reported [23]. In a 1970 study, 6% of 54 patients with cerebral metastases treated with 10 Gy single-dose WBRT died in the first 48 h following treatment [101]. With current WBRT techniques and the conventional use of low fractions (≤3 Gy), the incidence of acute radiation neurotoxicity has substantially declined. The pathogenesis is thought to be the result of disruption of the blood-brain barrier with resultant worsening of cerebral edema. Steroids have been successfully used in the treatment and prevention of acute radiation-induced encephalopathy, and they should ideally be started 48–72 h before therapy [102], especially in patients with significant pretreatment brain edema.

Early-delayed radiation neurotoxicities include the somnolence syndrome, transient cognitive disturbances, transient focal neurological symptoms, and tumor pseudoprogression. The somnolence syndrome (SS) manifests with drowsiness, followed by anorexia, headache, fever, vomiting, ataxia, and excessive somnolence, which commonly develop in the first 4 weeks to 2 months after the completion of radiation treatment. This complication has primarily been described in children undergoing cranial irradiation for acute leukemia or lymphoma [103–105] but can also affect adult patients [106]. The incidence varies widely, with a reported incidence anywhere between 13% and 71% according to age, treatment modalities, and prophylactic steroid dose. Two studies have reported a significantly lower rate of SS in children receiving greater or equal than 15 mg/day of prednisone [103] or 4 mg/day of dexamethasone [104] during the entire course of cranial radiation therapy. Complete resolution is usually expected within 2–3 weeks; therefore, the patients and their families should be counseled about the transient nature of this syndrome.

The tumor pseudoprogression phenomenon is diagnosed mainly after combined radiochemotherapy for glioma and occurs 6 weeks to 3 months after the end of treatment and is thought to correspond to early-onset necrosis [107]. While the condition can mimic tumor recurrence both clinically and on standard imaging techniques (MRI) [108], it typically presents earlier than true tumor progression, with a median time to onset of 5 months with pseudoprogression and 7 months with true progression [109]. Pseudoprogression typically presents with larger and more symptomatic lesions, as well [109]. Many studies are investigating the role of additional testing, for example, apparent diffusion coefficient values calculated from MRI with diffusion-weighted imaging and IV ferumoxytol contrast, to predict risk for pseudoprogression vs. recurrence [110, 111]. Recent prospective studies indicate that the incidence of pseudoprogression may be as high as 50% in glioblastoma patients treated with concomitant radiotherapy and temozolomide [112, 113]. The lesions often remain asymptomatic and may stabilize or decrease in size without additional treatment. Steroids may be beneficial in some cases, and pilot trials support that bevacizumab may reverse the effects of radiation-induced necrosis and to assist in weaning off steroids [114, 115]. A randomized, double-blind, placebo-controlled clinical trial, coordinated by the Alliance Cooperative Clinical Trials Group, started accruing patients in 2016. In clinically symptomatic patients, surgery should be considered [108]. Failure to recognize this development can lead to premature abandonment of an effective adjuvant therapy.

## Chronic Encephalopathy and Memory Impairment

Chronic cognitive dysfunction associated with chemotherapy is an important and often underestimated long-term side effect of cancer treatment. The term "chemo brain" refers to persistent post-chemotherapy cognitive changes in cancer survivors that are independent of anxiety, depression, or fatigue [116]. It is a source of great anxiety and concern for patients and their families and a frequent topic of cancer support groups [117]. Although the true incidence of mild-to-moderate delayed cognitive impairment is difficult to assess, several prospective longitudinal studies have reported a definite decline in neuropsychological function after chemotherapy [118–120]. These changes are often subtle but can impact patients' ability to work and function. Frontal subcortical areas are most likely affected, resulting in difficulties with attention, processing speed, memory retrieval, and executive functions [116]. Magnetic resonance brain imaging may show reduced gray and white matter volumes of brain structures important for executive functions, attention, concentration, or visual memory [121–123]. A functional neuroimaging study by Silverman and colleagues showed that, during performance of a short-term recall task, modulation of cerebral blood flow in specific regions of frontal cortex and cerebellum was significantly altered in chemotherapy-treated subjects [124]. The mechanism for these effects remains unclear and may vary with cancer type, specific therapeutic regimen, age, preexisting conditions, and biological predisposition. The syndrome is often reversible.

Leukoencephalopathy, characterized by progressive cognitive slowing, dementia, gait disorder, and other motor dysfunction, usually results from treatment with chemotherapy and/or radiation therapy directed at the central nervous system. Severe chronic cognitive dysfunction is usually reported in children with acute leukemia treated with high-dose intravenous or intrathecal methotrexate [125–128] but has also been described in a significant percentage of adult patients treated with high-dose methotrexate and radiation therapy for primary CNS lymphomas [129]. In addition, cranial irradiation therapy, particularly when administered before chemotherapy, greatly increases the risk for development of late neurotoxicity [130]. Neurological deficits are often irreversible. There is no known effective treatment, and the syndrome may progress to severe dementia, coma, or even death. Brain imaging with CT or MRI generally shows diffuse atrophy, intracerebral calcifications, and widespread destruction of white matter [128]. Pathologically, the lesions consist of coalescing areas of coagulation necrosis, with demyelination and axonal loss; during later stages the white matter is reduced to a thin gliotic calcified layer [131]. A similar syndrome has also been reported with the use of intrathecal or high-dose intravenous ara-C and with intra-arterial cisplatin or carmustine (BCNU) treatment [1].

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# Neuromuscular Disease and Spinal Cord Compression

34

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## Peripheral Neuropathy

Peripheral nervous system (PNS) involvement in patients with cancer may result from cancer therapy, compression or infiltration by the tumor, nutritional deficiencies, metabolic processes, treatment toxicity, or paraneoplastic syndromes. Any level of the PNS can be involved, from the lower motor neuron to the neuromuscular junction [1].

Depending on the etiology, patients may present with nerve root syndromes (radiculopathy or polyradiculopathy), focal or diffuse plexopathy, mononeuropathy, multifocal neuropathy (mononeuritis multiplex), or more diffuse syndromes defined by distribution of weakness and type and distribution of changes in loss of sensory function.

Radiculopathies present with specific patterns of weakness defined by the root level, sensory loss in the same dermatomal distribution, loss of reflexes defined by the root level affected, and frequently, pain following readily identifiable patterns. The most common causes are leptomeningeal spread of lymphoma [2] and carcinoma [3], bone or dural metastasis, or infections (varicella zoster virus, cytomegalovirus).

Plexopathy can result from trauma, tumor infiltration [4], or radiation injury. Malignant plexus infiltration occurs in approximately 1% of patients with cancer [1], particularly head and neck tumors (cervical plexus), lung and breast cancer (brachial plexus) [5], and prostate, cervical, bladder, or colorectal cancer (lumbosacral plexus) [6]. Patients present with neuropathic pain, which is usually severe and progressive with varying combinations of pain, sensory loss, weakness, muscle atrophy, and areflexia [1]. Radiation-induced plexopathy typically occurs many months to years after completion of treatment, and it is often difficult to distinguish from local tumor recurrence. A syndrome of insidiously progressive paresthesias, weakness, and lymphedema without severe pain is more suggestive of radiation-induced plexopathy, while more rapidly evolving deficits with severe pain and, in cases of lower brachial plexus lesions, focal signs such as Horner's syndrome are more common with metastatic infiltration [5]. Electromyography (EMG) can suggest the diagnosis of radiation-related injury by demonstrating myokymic discharges [7]. Magnetic resonance imaging (MRI), sometimes in combination with positron emission tomography (PET), may be able to define tumor infiltration [8]. At times, surgical

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exploration with nerve fascicle biopsy may be needed to make an accurate diagnosis.

Mononeuropathy is defined as the involvement of a single nerve and is usually secondary to local causes, such as nerve compression or entrapment. Malignant tumors of the peripheral nerve sheath or metastases from local extension of solid tumors or non-Hodgkin lymphomas [4] are rare causes of mononeuropathy. Systemic amyloidosis is a rare cause of median nerve injury at the wrist (carpal tunnel syndrome). More common examples of mononeuropathy are carpal tunnel syndrome in patients already affected with more diffuse neuropathy syndromes such as those with diabetes and chemotherapy-associated neuropathy, or peroneal nerve palsy at the fibular head occurring in association with severe weight loss. Mononeuritis multiplex refers to the involvement of multiple nerve trunks and can be seen with multiple compressive neuropathies, vasculitic syndromes, or rarely, metastatic occlusion of the vasa nervorum, resulting in multiple nerve infarcts [1].

Polyneuropathy refers to more generalized, diffuse involvement of peripheral nerves. Although any variation in patterns of involvement is possible, most commonly, distal nerve segments are more severely affected. The clinical presentation depends on whether sensory or motor nerve fibers are affected, the subtype of sensory fiber injury, whether the primary pathology affects nerve myelin or the nerve (axonoaxonal versus demyelinating), and the rate of progression of nerve injury. In patients with cancer, polyneuropathy can be caused by a wide variety of factors, such as toxins (chemotherapy), metabolic or endocrine disturbances (cachexia; uremia; diabetes mellitus; hypothyroidism; vitamin B1, B6, or B12 deficiency), or critical illness. Malignancy-related syndromes include autoimmune paraneoplastic disorders, paraproteinemia of multiple myeloma and POEMS syndrome [9], amyloidosis, or cryoglobulinemia. In cancer patients, acute or subacute axonal neuropathies are most often seen as complications of certain chemotherapeutic agents such as platinum compounds, taxanes, vinca alkaloids, ixabepilone, bortezomib, and others [10–12]. Idiopathic acute (Guillain-Barré syndrome) or chronic inflammatory demyelinating neuropathies, thought to be immune-mediated, are rarely encountered in patients with cancer.

## Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy-induced peripheral neuropathy (CIPN) is a substantial oncologic clinical problem. It is one of the most common chemotherapy-induced complications of a number of cytotoxic agents. It can affect the majority of patients receiving these drugs and 30–40% of all patients receiving chemotherapy. Risk for CIPN increases with increasing age [13]. Recent data support that CIPN is more prominent in patients with higher body mass indices and patients who are more sedentary [13–15]. This brings into question whether patients with diabetes are at increased risk for chemotherapy-induced peripheral neuropathy. A 2010 retrospective, pooled analysis of three phase III studies did not suggest any difference in neuropathy between diabetics and nondiabetics [16]. This was supported by several studies, including a retrospective review of 62 patients treated with oxaliplatin between 2005 and 2009; the latter did note that diabetic patients experienced neuropathy at lower doses of oxaliplatin than other patients [17, 18]. However, recent data presented at ASCO 2016, as well as an article evaluating 102 patients treated with capecitabine and oxaliplatin, suggests diabetic patients experience a higher level of neuropathy [13, 19]. Interestingly, patients with autoimmune disease had a significantly lower risk for development of CIPN, suggesting potentially an immune and cytokine-release mechanism [13]. Additionally, the rate for chemotherapy-induced peripheral neuropathy varies depending on the type of chemotherapeutic agent (i.e., paclitaxel causes CIPN more frequently than docetaxel) and duration of exposure [13]. Gender, ethnicity, race, and other conditions like hypothyroidism have not consistently been shown to correlate with CIPN risk [13].

Symptoms, which are usually peripheral and start in a stocking glove distribution, include numbness, tingling, and neuropathic pain. These symptoms generally increase over time with repeated doses of chemotherapy. Chemotherapy-induced peripheral neuropathy limits cytotoxic chemotherapy doses, potentially inhibiting the efficacy of chemotherapy against malignant processes. While these symptoms are often times reversible upon chemotherapy cessation, it can take a long time for them to reverse, and some patients do not report resolution of their symptoms for years. Efforts have been ongoing in the past several years to try to prevent this condition from occurring, or when established, to alleviate symptoms of nerve injury.

## Prevention of Chemotherapy-Induced Peripheral Neuropathy

### Calcium/Magnesium Infusions

Calcium and magnesium infusions initially showed promise in the prevention for chemotherapy-induced peripheral neuropathy. Both an early retrospective trial and a later prospective, placebo-controlled clinical trial was encouraging [20, 21]. However, a recent double-blind, randomized trial showed no benefit of calcium and magnesium infusions in decreasing the incidence or severity of chemotherapy-induced peripheral neuropathy, which virtually completely stopped its use [22, 23].

### Acetyl-L-Carnitine

Acetyl-L-Carnitine provides an important component utilized in the Krebs cycle. It appears to prevent paclitaxel-induced peripheral neuropathy in animals, possibly through mitochondrial metabolism [24]. In humans, this relatively well-tolerated agent has been used with some success in diabetic- and HIV-associated neuropathy [25–28]. However, one double-blind, placebo-controlled trial of 409 patients showed that Acetyl-L-Carnitine performed no differently from placebo at 12 weeks and actually increased taxane-induced peripheral neuropathy at 24 weeks [29].

### Glutathione

Glutathione is a naturally occurring tripeptide that is generally well-tolerated and can be administered intravenously, intramuscularly, or by inhalation. It appeared to decrease the appearance of CIPN in several small randomized trials of patients treated with cisplatin or oxaliplatin [30–40]. However, a recent, double-blind, placebo-controlled clinical trial of 185 patients was completed in 2014 and did not support any benefit of glutathione in patients treated with carboplatin and paclitaxel [41]. While this trial shows that glutathione is not efficacious for preventing taxane-induced peripheral neuropathy, more trials are needed to determine whether glutathione may be helpful with peripheral neuropathy associated with oxaliplatin and cisplatin, which cause more severe neuropathy.

### Alpha-Lipoic Acid/Thiotic Acid

Alpha-lipoic acid has been effective in seven randomized trials and a meta-analysis involving patients with diabetic peripheral neuropathy [42]. The use of alpha-lipoic acid in the prevention of chemotherapy-induced peripheral neuropathy, however, did not show benefit in a randomized double-blind clinical trial of 243 patients. This trial had a high drop-out rate (71%), thought to be secondary to pill burden and three times daily administration [43].

### Pregabalin

Pregabalin is commonly used in the treatment of diabetic neuropathy. A phase II placebo-controlled clinical trial of 46 patients did not show any benefit in the prevention of paclitaxel-induced peripheral neuropathy [44].

### Venlafaxine

Venlafaxine has been utilized as an antidepressant and for several neuropathic pain-related conditions, including chronic pain syndrome. Its use in CIPN has been investigated, as well. While a small trial in 2012 suggested venlafaxine decreased acute and chronic oxaliplatin-induced neuropathy when compared with placebo, a second, randomized, placebo-controlled, phase II

trial with 50 patients randomized to each arm did not show any benefit [45, 46].

### Glutamine

Glutamine is an amino acid, a neurotransmitter precursor, and important in many neuronal and glial systems and pathways. Data on this agent in prevention of CIPN has been mixed. A randomized, but not placebo-controlled, clinical trial involving approximately 40 patients per arm evaluated this agent in patients receiving oxaliplatin and suggested it reduced incidence and severity of CIPN [47]. Another trial, however, did not show any benefit for prevention of paclitaxel-related peripheral neuropathy [48].

### Vitamin E

Vitamin E is another agent that has been proposed, based on its antioxidant properties, as being helpful for decreasing chemotherapy-induced peripheral neuropathy. Pilot data and an interim analysis of a placebo-controlled trial supported that this agent may decrease neuropathy in patients receiving cisplatin [49, 50]. However, a large double-blind, placebo-controlled clinical trial of approximately 200 patients getting neuropathy-inducing cytotoxic chemotherapy, mainly taxanes, did not provide any suggestion of benefit [51, 52].

### Omega-3 Fatty Acids

Omega-3 fatty acids have proposed benefits in restoring damaged nerves in diabetics. In supportive cancer care, they were studied in 1 small, placebo-controlled trial with 57 patients and were reported to significantly decrease the incidence of paclitaxel-induced neurotoxicity when compared to a placebo [53]. Further, larger studies are needed prior to widespread adoption of this agent for prevention of CIPN.

### Goshajinkigan

Goshajinkigan is a traditional Japanese herbal medicine, which has been used in patients with diabetic neuropathy. While early trials suggested possible benefits of this agent, a 2015 placebo-controlled, double-blinded study of 182 patients was closed early due to statistically significant worsening of neuropathy in the treatment arm [54].

Ganglioside-Monosialic Acid

Ganglioside-monosialic acid has also been studied for prevention of CIPN. A 2013 study randomized patients to IV ganglioside-monosialic acid or a control group without placebo. It was suggestive of benefit in prevention of oxaliplatin-induced peripheral neuropathy; however, additional studies comparing treatment to placebo are needed prior to recommending this agent [55].

### Cryotherapy

Cryotherapy has been effective in prevention of 5-FU-induced mucositis and taxane-induced nail toxicity. Two abstracts reported at the 2016 annual ASCO meeting provided randomized data to support that it was helpful for decreasing paclitaxel-related neuropathy [56]. Another randomized pilot clinical trial is currently underway to study the effects of cryotherapy (administered throughout as well as 15 min before and after chemotherapy infusion) for prevention of paclitaxel-induced neurotoxicity [57].

### Other Drugs

A number of drugs have been evaluated and have not shown any discernible benefit for preventing or reducing manifestations of neuropathy complicating chemotherapy. Zaliproden [58], amifostine [59], carbamazepine [60], oxcarbazepine [61], nimodipine [62], ORG-2766 (an adrenal corticotropic hormone analog) [63], and recombinant human leukemia inhibitory factor (RHU LIF) [64] have all failed in clinical trials.

## Treatment of Established Chemotherapy-Induced Peripheral Neuropathy

### Tricyclic Antidepressant Agents

Tricyclic antidepressants, such as nortriptyline and amitriptyline, have been utilized to treat neuropathic pain from a variety of insults. Based on this,

several trials have been conducted looking at nortriptyline and amitriptyline for treating established chemotherapy-induced peripheral neuropathy [65–67]. Two of these studies were double-blind, randomized, and placebo-controlled. They each involved 40–60 patients. Neither of them was able to demonstrate any evidence that the tested tricyclic antidepressant agent was any better than placebo. Given the relatively small numbers of patients on these clinical trials, it is possible that a small amount of efficacy might be seen with these agents if larger numbers of patients were studied.

### Gabapentin

Gabapentin was developed as an anticonvulsant but has proven to be helpful in patients with neuropathic pain syndromes, particularly related to herpes zoster and diabetic neuropathy. Based on positive clinical trial results in both of these situations, it has been utilized in clinical practice for patients with chemotherapy-induced peripheral neuropathy. This is despite results of a prospective randomized, double-blind crossover clinical trial in 115 patients where gabapentin, at a target dose of 2700 mg/day, showed no benefit in relieving numbness, tingling, or neuropathic pain compared to placebo [68].

A related compound, pregabalin, has also been utilized in practice for treating neuropathic pain from a variety of sources. It has been studied for prevention of chemotherapy-induced neurotoxicity (see above), without evidence of benefit. While further trials could help elucidate whether it is efficacious in the treatment setting, its lack of benefit in the preventive setting makes pursuing further trials less appealing. Both gabapentin and pregabalin are quite effective in other neuropathy conditions, and so clinicians might argue that pregabalin could be considered for treatment despite lack of prospective clinical trial data; ASCO CIPN guidelines, published in 2014, did conclude that it was reasonable to try in patients with CIPN, despite the lack of specific data to prove its efficacy in this situation.

### Lamotrigine

Lamotrigine, like gabapentin, was developed as an anticonvulsant. Based on results from trials suggesting that it might be helpful for neuropathic pain from a variety of sources, a randomized, double-blind crossover placebo-controlled trial was developed to test the utility of this agent in patients with established chemotherapy-induced peripheral neuropathy [69]. This trial, which involved 131 subjects, did not demonstrate any suggestion of benefit for this agent for established CIPN.

### Topical Baclofen, Amitriptyline, and Ketamine (BAK)

Based on suggestive evidence that a topical mixture of baclofen, amitriptyline, and ketamine (BAK) might help alleviate neuropathic pain, a clinical trial was conducted whereby these agents were given topically to patients with established chemotherapy-induced peripheral neuropathy [70]. This double-blinded and placebo-controlled clinical trial, while not strongly positive, did suggest that this topical preparation moderately decreased chemotherapy-induced peripheral neuropathy. It appeared to work better in the upper extremities as opposed to the lower extremities. While the above-noted trial was developed and conducted, another group independently developed a clinical trial evaluating topical amitriptyline and ketamine, based on similar background information. This double-blind, placebo-controlled, 6-week clinical trial of patients with established chemotherapy-induced neuropathy and pain of 4 out of 11 did not experience improvement in chemotherapy-induced pain, numbness, or tingling [71]. This could potentially be due to the lack of baclofen in the preparation; further studies are necessary.

### LC07

LCO7 is a Chinese herbal extract, composed of Herba Geranii, thought to act by promoting nerve growth factor and nerve fiber regeneration. One placebo-controlled trial of 102 patients showed that 75% of patients responded (compared to 33% in the placebo arm) in a median of 4.5 days, without side effects of the compound. This study is limited due to lack of blinding and the short duration of follow-up (7 days), and so more research is needed [72].

### Oral Mucosal Cannabinoid Extract

There has been increasing recent interest into studying the use of cannabinoids in the management of cancer and chemotherapy-related symptoms. There has been only one small, randomized, placebo-controlled trial of an oral mucosal cannabinoid spray for treatment of CIPN, which did not suggest any evidence of benefit and showed significant side effects, including fatigue, dry mouth, dizziness, and nausea [73].

### Scrambler Therapy

A potential non-pharmacologic for CIPN is scrambler therapy, which sends electrical impulses in damaged nerves. Initial pilot studies have been promising, including a 2014 trial in which 37 patients with CIPN were treated, with a 50% reduction in pain. Interestingly, patients treated during the second half of the study experienced more benefit than patients in the earlier group, thought to be due to improved skills of the scrambler operator. It was limited by the lack of a placebo arm [74]. There is a current clinical trial underway evaluating the efficacy of scrambler therapy versus TENS unit therapy as placebo [75].

### Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Pilot data suggest that two different SNRIs, venlafaxine and duloxetine, might be helpful agents for treating established chemotherapy-induced peripheral neuropathy. A Cochrane report, along with other manuscripts, concluded that venlafaxine can be helpful for patients who have neuropathy from a variety of causes [76–78]. Additionally, data in animals also suggest that this drug can decrease hyperalgesia [79]. More specifically, with regards to chemotherapy-induced peripheral neuropathy, there are four reports suggesting that venlafaxine can treat and/or prevent chemotherapy-induced peripheral neuropathy [80–83]. Results of a small, placebo-controlled, randomized clinical trial presented at the 2009 American Society of Clinical Oncology meeting supported that venlafaxine was helpful for the treatment and prevention of oxaliplatin-caused neuropathy [84]. A larger prospective clinical trial, however, failed to support the utility of venlafaxine for treating chemotherapy-induced peripheral neuropathy [46].

Duloxetine has been established to be helpful for patients with diabetic peripheral neuropathy and is well-tolerated [85]. Duloxetine is currently the only medication for treatment of CIPN that has consistently been shown to be effective in robust clinical trials. It was initially studied in a randomized, placebo-controlled, crossover trial of 231 patients for treatment of oxaliplatin-induced neuropathy. Patients in the duloxetine treatment arm had a decrease in neuropathic pain, as well as numbness and tingling [86]. A smaller crossover trial involving 34 patients randomized to duloxetine versus vitamin B12 (placebo arm) also showed a significant improvement in numbness and pain compared to vitamin B12. Side effects of duloxetine include drowsiness and malaise [87].

## The Taxane Acute Pain Syndrome

Paclitaxel and docetaxel cause acute toxicities which are not seen with most other cytotoxic agents. This consists of pain occurring 1–3 days after the drug has been given and lasting for up to a week or longer. In the past, this has been termed paclitaxel-induced arthralgias/myalgias [88–91]; they are most common in the lower extremities but also affect the back, shoulders, and other areas. The pain is generally noted to be a deep aching pain. Patients describe it as radiating, shooting, stabbing, and/or pulsating. Incidence with docetaxel ranges anywhere from 14 to 46% depending on dose, frequency, and stage [92]. Additionally, its presence and severity correlates with development of chemotherapy-induced peripheral neuropathy, supporting a neurogenic mechanism for pain [93, 94]. Interestingly, this toxicity has not been demonstrated in patients receiving cabazitaxel [95]. Small pilot reports or trials have investigated gabapentin [96, 97], pregabalin [44], glutamine [98], antihistamines [99], corticosteroids [100], opioid analgesics [101], amifostine [102], and Shakuyaku-Kanzo-To (a Japanese herb), none of which have consistently shown significant benefit [103]. None of these can be recommended for clinical practice at this time.

## Summary

Chemotherapy-induced peripheral neuropathy is a prominent clinical problem. Multiple agents have been studied in the prevention and treatment of this condition; however, few have been consistently shown to be effective. There are no agents known to prevent the development of CIPN, and only duloxetine has been shown to provide a benefit in treatment. There are promising results from cryotherapy and topical preparations (baclofen, amitriptyline, and ketamine and LCO7), but trials have been small and/or with likely sources of bias. Therefore, efforts should be undertaken to decrease the incidence and severity of CIPN through careful chemotherapy medication choices, dose modifications, and reevaluation of therapy after consideration of side effects.

## Paraneoplastic Syndromes

Although the exact incidence of paraneoplastic neurologic autoimmunity is difficult to assess, these conditions are rare, affecting less than 1% of patients with cancer [1, 104]. In the majority of cases, the neurological disorder occurs months or years before the primary malignancy is diagnosed [104], and it often follows a subacute course, leading to severe and disabling symptoms [104]. The discovery of cancer-related antibodies that react with both the tumor and the nervous system (onconeural antibodies) in the serum and/or cerebrospinal fluid of many patients with paraneoplastic syndromes suggest that many of these syndromes are immune-mediated. However, many paraneoplastic syndromes are not associated with known marker antibodies [105]. Conversely, several marker antibodies, known to be associated with a variety of neurological disorders, may occur simultaneously in the same patient. Moreover, some well-defined onconeural antibodies may occur in patients with or without identifiable cancer and without a neurological illness. Therefore, the identification of these antibodies alone is neither sufficient nor necessary for defining a neurological condition as being paraneoplastic [106]. The antibodies do not predict the neurological disorder, as more than one syndrome can be associated with any given antibody marker. For instance, voltage-gated calcium channel antibodies, which are classically thought to be related to small-cell lung cancer, are also associated with breast cancer, lymphoma, and tonsillar adenoma and can precipitate a myriad of symptoms, including encephalopathy, ataxia, myelopathy, neuropathy, myopathy, and neuromuscular junction disorders [107]. However, the identification of one or more antibodies often helps to predict the associated cancer and directs the search for occult disease. Paraneoplastic neurological autoimmunity can affect any level of the nervous system. For the purpose of this discussion, several well-known syndromes are discussed, which manifest as spinal cord or neuromuscular disease. Subacute or chronic myelopathy, associated with CRMP-5, and acute transverse myelopathy associated with ANNA-1 are predictors of small-cell lung cancer (SCLC). ANNA-1 and ANNA-2 have been associated with subacute motor neuropathy and are also highly predictive of an underlying small-cell cancer. ANNA-1 has been associated with sensory neuronopathy and CRMP-5 with polyradiculopathy and plexopathy. An array of antibodies and paraproteinemias has been associated with sensory-motor neuropathy of varying severity, but some of the antibodies are clearly predictive of the associated neoplasm. Myasthenia gravis is associated with antibodies to muscle acetyl choline receptors, muscle-associated proteins (striational antibodies), voltage-gated potassium channels, neuronal acetyl choline receptors, and glutamic acid decarboxylase. When seen in some combinations, these antibodies may often predict thymoma. While approximately 75% of patients with MG have thymic disease (most commonly thymic hyperplasia), thymic carcinoma is present in only about 10% of patients. Conversely, approximately 30–40% of patients with thymoma have associated MG [108, 109]. Occasionally, MG is diagnosed in patients with tumors other than thymomas, especially lung cancer or non-Hodgkin lymphomas [110,

111]. Another disorder of neuromuscular transmission, Lambert-Eaton syndrome, directly related to the presence of antibodies to P-/Q-type voltage-gated calcium channels [112], predicts the presence of an occult SCLC in 50–60% of patients but, when found with additional onconeural antigens such as AGNA-1, is 80–90% predictive of SCLC [113]. Disorders of neuromuscular hyperexcitability (acquired neuromyotonia) may be associated with voltage-gated potassium channel antibodies. When found in high titer, the presence of these antibodies has a low, but not insignificant, predictive value for determining the presence of an underlying cancer.

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the presynaptic nerve terminal at the neuromuscular junction. Autoantibodies accelerate internalization and degradation of P/Q-type voltage-gated calcium channels and impair acetylcholine release in response to action potentials. The dominant neurological features include proximal limb muscle weakness, which is most prominent in the legs, worse at rest, and improved with activity. Additionally, patients may experience autonomic dysfunction with mouth or eye dryness, blurred vision, constipation, impotence, and orthostatic hypotension [113]. Characteristically, an EMG shows a significant increment in the compound muscle action potential (CMAP) following high-frequency repetitive stimulation or brief maximal isometrical muscle activation. Successful treatment of cancer leads to improvement in many patients. In addition, therapy with 3,4-diaminopyridine (3,4 DAP) is recommended. 3,4-DAP increases the effects of acetylcholine at the postsynaptic membrane and effectively improves muscular strength per a Cochrane review [114]. Common side effects of 3,4-DAP include perioral tingling and digital paresthesias. A treatment algorithm has been proposed; depending on severity of symptoms despite the aforementioned interventions, one can also consider adding pyridostigmine, a combination of prednisone and azathioprine, and even immunotherapy with plasma exchange and IVIG [115–117]. Rituximab has been proposed as a treatment but has only been studied in a few case reports [118, 119]. Myasthenia gravis (MG) is a postsynaptic disorder of the neuromuscular junction, caused by autoantibodies that accelerate acetylcholine receptor degradation [120]. Weakness that often worsens with sustained muscle activity may present with disorders of ocular motor function, dysphagia, and dysarthria. Some patients present with more generalized weakness, while others evolve to a more generalized, proximal weakness after a period with a more restricted pattern of ocular muscle or bulbar muscle weakness. This generalization may progress subacutely and can prominently affect the muscles of ventilation leading to respiratory failure. As with LEMS, treatment includes symptomatic therapies to increase the availability of acetylcholine at the postsynaptic membrane, immunotherapy, and thymectomy, even in patients who do not have thymomas [121]. In patients with severe generalized weakness, plasma exchange or IVIG can lead to rapid improvement over days to weeks.

Paraneoplastic neuromyotonia (Isaac syndrome) produces continuous motor unit activity with muscle stiffness, cramps, twitching, or weakness [122]. It is most frequently associated with thymoma, small-cell lung cancer, and Hodgkin lymphoma, and diagnosis is typically made by electromyography. Treatment is primarily symptomatic, focusing on agents used to stabilize neuronal hyperexcitability, such as anticonvulsants like valproic acid, carbamazepine, and phenytoin. In more severe cases, immunotherapy is considered [123].

In general, the approach to paraneoplastic autoimmunity is mainly directed at removing the source of antigen by treatment of the underlying cancer or plasma exchange and/or suppression of the immune system [104]. Those syndromes associated with antibodies to cell surface antigens or cation channels have the greatest potential for reversibility, while those associated with antibodies to cytoplasmic or nuclear antigens fair most poorly, with often irreversible neurological disability by the time the cancer is identified, treatment initiated, and immune-mediated injury arrested. Some physicians have used the combination of intravenous immune globulin, corticosteroids, and other immune modulators [117, 124].

## Muscle Disease

In patients with cancer, myopathy is often a consequence of treatment but may also be secondary to metabolic/electrolyte disturbances, endocrine disorders, infections, rhabdomyolysis (e.g., seizures), or paraneoplastic syndromes. Many patients with advanced malignancies complain of generalized weakness. It is important to distinguish between true myopathy and cancer asthenia secondary to cachexia, anemia, or depression. This is often possible by formal assessment of muscle strength on physical examination, given that strength is often preserved in patients with asthenia. In addition, history and physical examination is useful in localizing the site of the lesion causing muscle weakness to the upper or lower motor neuron, peripheral nerve, or muscle.

Corticosteroid treatment is a well-known cause of myopathy. Weakness is proximal, affecting neck flexors, the muscles of the shoulder, and pelvic regions. Creatine kinase is normal. Chemotherapy drugs rarely cause isolated myopathy, but cases have been described with the use of paclitaxel [88], vincristine, or interferon [125]. Anthracyclines have been shown to induce skeletal muscle dysfunction in mouse models and may contribute to myopathy in children with acute lymphocytic leukemia treated with multidrug regimens [126]. In addition, certain chemotherapy drugs can cause significant electrolyte abnormalities resulting in muscle weakness, such as hypomagnesemia seen with cisplatin administration [127], or hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone produced by vincristine [128].

Inflammatory myopathies, such as dermatomyositis and polymyositis, may also have a cancer association. Whether the mechanisms of this association are immune-mediated is unclear. Approximately 15% of patients with dermatomyositis and 9% of patients with polymyositis develop a neoplasm [129]; the most common tumors are breast, ovarian, lung, and gastrointestinal carcinomas, as well as non-Hodgkin lymphomas [130]. The clinical presentation of paraneoplastic poly- and dermatomyositis is similar to that of patients without cancer [105]. Treatment is directed primarily at controlling the underlying cancer and suppression of the immune system (steroids, intravenous immune globulins [131], azathioprine [132]).

Acute necrotizing myopathy is a rare disorder that may be associated with certain connective tissue diseases; and in some circumstances there is serological evidence of autoimmunity. It can be seen in patients with cancer, primarily with gastrointestinal, genitourinary, and lung carcinoma. It is characterized by severe painless muscle weakness, with a markedly elevated creatine kinase and histological evidence of muscle necrosis [133].

## Spinal Cord Compression

Malignant epidural spinal cord compression (ESCC) is one of the most feared complications of metastatic cancer and a true oncological emergency. Left untreated, ESCC will result in permanent loss of neurological function in the vast majority of affected patients. The incidence is difficult to estimate accurately, as some patients with advanced cancer may have subclinical spinal cord involvement, while others may decline further invasive diagnostic testing or therapy late in the course of their illness. In one large Canadian population-based study, the cumulative probability of experiencing ESCC in the 5 years before death from a known malignancy was 2.5% overall, ranging from 0.2% in pancreatic cancer to almost 8% in multiple myeloma [134]. Similarly, the frequency of ESCC in autopsy studies has been found to be approximately 5% in patients dying with cancer [135]. However, with improved imaging modalities and recent advances in therapy, it is likely that the incidence of metastatic spinal disease will increase as overall survival improves for many cancers. It is therefore important that medical and radiation oncologists, neurologists, and all other physicians caring for patients with cancer understand the pathophysiology, clinical presentation, diagnostic workup, and management of this complex oncological problem.

The most accepted definition of ESCC encompasses both clinical and radiographic criteria. As a general rule, any radiologic evidence of thecal sac indentation causing clinical symptoms (local or radicular pain, motor weakness, sensory disturbance, and/or sphincter disturbance) is considered evidence of ESCC [136]. Subclinical cord compression, on the other hand, is defined by the presence of radiographic abnormalities of spinal cord compression in the absence of clinical symptoms [136]. Therefore, in adults, the spinal cord ends at L1, and below this level compression of the thecal sac causes impingement of the lumbosacral nerve roots only, commonly referred to as cauda equina syndrome. Nonetheless, since the pathophysiology of this syndrome is similar to that of spinal cord compression, most authors include compression of cauda equina in the syndrome of ESCC.

Malignant tumors reach the epidural space and compress the dural sac and its contents (spinal cord and/or cauda equina) via three main mechanisms. The most common mechanism is hematogenous spread to the vertebral body [137]. Therefore, the initial anatomic location of the metastasis is in the posterior portion of the vertebral body in the vast majority cases [138]. This gives rise to a vertebral mass that progressively enlarges and eventually causes secondary compression of the spinal cord or an acute vertebral body collapse with dislocation of bony fragments into the epidural space. Less common mechanisms of ESCC include growth of a paraspinal mass through the vertebral neural foramen (lymphomas, neuroblastomas [139]), or direct metastasis to the epidural space without involvement of the vertebral body or a paraspinal mass component. The most common site of metastasis is the thoracic spine, proportional with the relative bone mass and the blood flow (approximately 60% of cases), followed by the lumbosacral (30%) and cervical spine (10%) [140]. Thirty to 40% of patients with ESCC have multiple epidural metastases resulting in multiple sites of spinal cord compression [141, 142].

ESCC is often a late event in the clinical course of patients with advanced systemic malignancies. Most cases are due to tumors with a high tendency to metastasize to the spinal column, such as carcinoma of prostate, breast, and lung, which account for 15–20% of cases each. Other common causes of ESCC are renal cell carcinoma, multiple myeloma, and non-Hodgkin lymphoma, with the remaining cases being caused by metastatic colorectal cancers, sarcomas, cancers of unknown primary, and, less commonly, other tumors [134, 141, 143, 144]. However, up to 20% of patients can present with spinal epidural metastases as the initial manifestation of cancer. The great majority of neoplasms presenting with ESCC in a Mayo Clinic study were carcinoma of the lung, cancers of unknown primary, multiple myeloma, and non-Hodgkin lymphoma [145].

## Clinical Presentation

The most common symptom of ESCC is back pain, which is present in 80–95% of patients at diagnosis [139, 143, 146]. Initially, the pain is localized to the spine, is confined to the affected region, and is caused by extension of metastasis from the vertebral bone marrow to the periosteum or surrounding soft tissues [140]. The pain is usually worse at night and with recumbency (possibly due to distension of the epidural venous plexus [140]) and is often exacerbated by movement and Valsalva-type maneuvers. Mechanical back pain in a patient with ESCC may also be caused by a pathological fracture or vertebral body collapse and may result in spinal cord instability and impending cord compression. Radicular pain results from compression or invasion of the nerve roots and is most common in patients with lumbosacral spine metastases [146]. In patients with thoracic spine involvement, the pain is often bilateral and wraps around anteriorly, in a "girdle-like" fashion.

Approximately 60–70% of patients with ESCC exhibit some degree of motor weakness and/or gait abnormalities at diagnosis [143, 146]. The pattern and magnitude of the motor deficit depends on the location of the spinal cord lesion and the involvement of upper versus lower motor neuron tracts. Upper motor neuron deficits usually result in fairly symmetrical weakness of the

upper or lower extremities, whereas lower motor neuron weakness is commonly asymmetrical [140]. The progression of motor weakness is followed by loss of gait function and ultimately paralysis; in large series, up to two-thirds of patients were non-ambulatory at diagnosis [143, 147]. Isolated sensory deficits are uncommon, but sensory deficits are present at diagnosis in up to 70% of patients, often in association with back pain or weakness [139, 146]. Patients may report ascending paresthesias but tend to be less aware of radicular sensory deficits. Cauda equina lesions usually result in sensory loss in a saddle-type distribution, in contrast to lesions located above this level which commonly spare sacral dermatomes. When a sensory level is present, the anatomic localization of the spinal lesion is typically one to five segments above the level of the sensory deficit. Lhermitte's phenomenon, described as brief electric-like shock sensations down the spine with neck flexion, can be seen in patients with cervical or thoracic ESCC [148]; it also has been described in patients suffering from chemotherapy or radiation therapy associated myelopathy. Other clinical findings, such as bowel or bladder dysfunction or autonomic symptoms tend to occur late in the clinical course of ESCC [140]. However, up to 50% of patients have some degree of bowel or bladder dysfunction at diagnosis [143], and they are generally a poor prognostic sign for preservation of ambulatory status [140].

## Diagnosis

Early recognition of ESCC is crucial since the main determinant of clinical outcome and post-treatment ambulatory function is the patient's pretreatment functional status [149, 150]. Unfortunately, delays in diagnosis and referral are common and are associated with loss of motor and bladder function which may be irreversible [147]. In a prospective study of 301 patients with ESCC [147], the median delay to treatment was 73.5 days from the onset of back pain, 13.5 days from onset of weakness, and 4 days from loss of ambulation. While 3–4 day delays were due to lack of patients seeking attention, the majority were attributable to diagnostic delays at general practitioner (3 days) and general hospital level (4 days). Because the outcome can be devastating, a high index of suspicion is vital especially in a patient with known cancer and new onset of back pain or neurological complaints. Magnetic resonance imaging (MRI) is the method of choice for the diagnosis of ESCC and can provide an accurate evaluation of the vertebral bones, paraspinal soft tissues, and the spinal cord. MRI has an overall accuracy of 95% (sensitivity 93%, specificity 97%) [151]. The importance of imaging the entire spine was illustrated in a retrospective Mayo Clinic study in which failure to image the thoracic or lumbar spine would have missed secondary epidural deposits in 21% of patients [141]. Myelography, often used in combination with computed tomography (CT), was the imaging modality of choice prior to the widespread use of MRI, and it is still used when MRI is not feasible or is contraindicated (e.g., severe claustrophobia, metallic implants). However, myelography is more invasive and requires a lumbar or cervical puncture and the use of intrathecal contrast agents. Positron emission tomography (PET) scans are not used in the diagnosis or treatment planning of ESCC as their anatomic resolution is suboptimal comparative to MRI and are not informative enough about thecal sac compression [140]. Although plain films are often obtained, they have a 10–17% false-negative rate [152]; additionally, paraspinal masses may not be visualized on plain roentgenograms of the spine if there is no bone erosion.

## Treatment

Treatment of ESCC includes administration of corticosteroids followed by surgery and/or radiation therapy (RT). Studies in animals have shown that spinal cord compression by tumor causes occlusion of the epidural venous plexus with breakdown of the blood-brain barrier and vasogenic edema, which can be partially or completely reversed by the administration of dexamethasone [153]. In the late stages of cord

compression, the arterial supply to the spinal cord is impaired resulting in infarction and irreversible cord damage.

While bracing and specific positioning is frequently employed in cord compression and has been extensively studied, there is no consensus regarding efficacy or how and when to brace [154].

## Corticosteroids

To date, three randomized controlled trials (RCTs) [155, 156], one phase II trial [157], and one case-control study [158] addressed the efficacy and optimal dose of corticosteroids in ESCC. In a study by Sorensen and colleagues [156], 57 patients undergoing RT for ESCC were randomized to high-dose corticosteroids (96 mg bolus intravenously, followed by 96 mg orally for 3 days and a 10-day taper) or no steroid treatment. A statistically significantly higher percentage of patients in the dexamethasone arm remained ambulatory at the end of therapy (81% versus 63%) and at 6 months (59% versus 33%) compared to patients in the control group. Significant side effects associated with steroid treatment were reported in three patients (11%), two of whom discontinued treatment. The optimal loading dose of dexamethasone was addressed in the study by Vecht et al., in which 37 patients with complete myelographic obstruction were randomized to high-dose (100 mg) versus moderate-dose intravenous bolus dexamethasone (10 mg), followed by 16 mg per day orally. The average pain score improved significantly with steroid therapy in all patients, but there were no significant differences between the two groups in pain reduction or neurological outcome. Although the study was small and insufficiently powered, the authors concluded that a lower loading dose could be used, given similar results. Moreover, for selected patients, steroid therapy may not be required. A small study by Maranzano et al. [157], suggested that selected patients with subclinical cord compression, no neurologic deficit, and limited involvement of adjacent spinal elements on MRI or CT imaging can be treated successfully with RT alone, therefore avoiding the effects of steroid treatment. A recent Cochrane meta-analysis concluded that there is insufficient evidence about the role of corticosteroids in ESCC and that serious adverse events were most frequently seen in patients treated with high dexamethasone doses [159]. Currently, there is no consensus in regards to the best loading dose and maintenance corticosteroid regimen in patients with ESCC. Some authors recommend reserving the high-dose regimen for patients with paraparesis/paraplegia or rapidly progressive neurological symptoms, while ambulatory patients with minimal or nonprogressive motor symptoms could be treated with moderate doses (10 mg bolus followed by 16 mg daily) [141].

## Surgery

In the past, surgical management of ESCC in patients with neurological compromise consisted mainly of posterior decompression of the spinal cord using a laminectomy. However, the bulk of the tumor is usually located in the vertebral body, anterior to the thecal sac, and laminectomy is therefore unsuccessful in removing the tumor from the epidural space in many cases. Given that the results of laminectomy did not differ from that of RT alone [140, 159–161], surgical treatment was largely abandoned until recently, when new techniques of tumor resection, circumferential decompression, and spine reconstruction were developed. A randomized trial compared the role of aggressive tumor debulking by circumferential decompression within 24 h of study entry followed by RT (30 Gy over 10 days within 14 days of surgery) with the same RT alone in 101 patients with a known diagnosis of cancer and metastatic ESCC. Both groups were started on 100 mg dexamethasone loading dose followed by 24 mg every 6 h until they began treatment, followed by a taper until completion of RT. The study was stopped after a planned interim analysis showed a significantly better outcome in the group who had surgery followed by radiation compared to those who had RT alone. Patients treated with surgery had a higher ambulatory rate (84% versus 57%; $p = 0.001$) and were able to

walk for a significantly longer period (median 122 versus 13 days; $p = 0.003$). In addition, a higher number of patients regained the ability to walk (10 of 16 patients) compared to those treated with RT alone (3 of 16 patients). Median survival was also longer in the surgery group (126 versus 100 days, respectively; $p = 0.003$). While the results of this trial indicate that radical resection followed by RT is effective in regaining the ability to walk and maintain ambulation, careful interpretation of the conclusion and adequate selection of patients who qualify for this aggressive approach is required. For instance, the trial excluded patients with more than one site of ESCC or certain radiosensitive tumors (multiple myeloma, lymphomas, leukemias, germ-cell tumors). In addition, a later unplanned subgroup analysis suggested that preservation of ambulation was significantly prolonged in patients under the age of 65 years, but not in older individuals [162]. Additionally, surgery and radiation therapy combined conveys a benefit in ambulatory status and overall survival compared with radiation therapy alone [163]. A recent prospective trial evaluated the effects of surgical intervention and found that, following surgery, there was a significant improvement in ambulatory status, lower extremity motor scores, pain, disability, and quality of life [164]. However, as with any medical decision, risks versus benefits should be carefully considered as high-risk surgery may worsen quality of life in patients with aggressive tumors and poor prognoses [165].

## Radiation Therapy

External beam RT is used in the treatment of ESCC in patients who are not surgical candidates or in association with surgery (see above). RT results in preservation or improvement of function, particularly in patients who have tumors that are radiosensitive and who are ambulatory at presentation [141]. The optimum dose and treatment regimen are still controversial, and a variety of radiation schedules have been used. A prospective nonrandomized trial compared 30 Gy in 10 fractions versus 40 Gy in 40 fractions in 231 patients with ESCC; although both regimens resulted in similar functional outcomes and overall survival, the long-course RT was associated with significantly better local control (77% versus 61%; $p = 0.032$) and 12 months progression-free survival (72% versus 55%; $p = 0.034$) [112]. In a retrospective analysis of 1304 patients, Rades et al. looked at 5 radiotherapy schedules: 1 8 Gy dose in 1 day ($n = 261$), 5 doses of 4 Gy in 1 week ($n = 279$), 10 doses of 3 Gy in 2 weeks ($n = 274$), 15 doses of 2.5 Gy in 3 weeks ($n = 233$), and 20 doses of 2 Gy in 4 weeks ($n = 257$). Once again, the five RT schedules provided similar functional outcomes, but the protracted regimens seemed to result in fewer in-field recurrences. Also, high daily doses may be more toxic resulting in acute necrotizing injury to the spinal cord [166]. One recent systematic review, including two randomized controlled trials as well as other prospective studies, recommends that patients with poor prognosis receive 8 Gy, whereas those with more favorable prognosis should receive 30 Gy in ten fractions [167].

## Chemotherapy

Chemotherapy is rarely used in the acute management of ESCC, even in patients with chemosensitive tumors, as the response is generally too slow and unpredictable [103]. However, chemotherapy is sometimes used in combination with radiation therapy where dictated by the circumstances of the systemic malignancy. For those who have a recurrence in a previously irradiated field precluding further treatment, and no surgical options, chemotherapy may be the only appropriate treatment choice.

## Bisphosphonates

Bisphosphonates have a proven benefit in reducing bone pain and pathological fractures [168, 169] as well as the risk of bone metastases [170] in patients with cancer. In a recent meta-analysis by Ross and colleagues [171], the use of bisphosphonates significantly decreased skeletal

morbidity but did not significantly decrease the risk of ESCC despite a positive trend (OR 0.71; 95% CI 0.47–1.08; $p = 0.113$).

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# Eye Symptoms and Toxicities of Systemic Chemotherapy

35

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## Introduction

Many malignancies have become chronic in nature due to advances in treatments and development of new therapies that target cancer-cell-specific pathways on a molecular level. Patients are living longer, often with exposure to multiple treatment regimens, each with their own toxicities. Attributing a toxicity to a specific agent is often difficult when drugs are administered in combination, even with the preclinical identification of a potential toxicity. Some toxicities are dose-dependent and may be unique to high doses (e.g., cytosine arabinoside, methotrexate) or to cumulative doses of the drug. Toxicity may vary by route of administration (oral, intravenous, intrathecal, intra-arterial) and by inadvertent prolonged exposure to the drug due to coexistent renal or hepatic insufficiency. Visual complications may come to light as part of a questionnaire or as a result of a complaint or as an observed manifestation of toxicity. Most ophthalmic complications are mild to moderate in nature and are readily reversible with dose modification or cessation of the drug, if the toxicity is recognized early; others are more severe and may be irreversible despite discontinuation of the medication.

Descriptions of ocular effects in this chapter are limited to oral, intravenous, or intrathecal administration of chemotherapy agents. Ocular effects from intracarotid administration, instillation in the eye, or those due to opportunistic infection, such as reactivation of latent viral infections as a consequence of chemotherapy-related immunosuppression, are not included in this review.

Common chemotherapy-related ocular effects include development of blepharitis (inflammation of the eyelids including meibomian gland dysfunction), cataracts, glaucoma, conjunctivitis, dry eye (keratoconjunctivitis sicca), epiphora (tearing due to increased lacrimation or decreased drainage), and keratitis (corneal infection or inflammation). Common symptoms of the above conditions may include photophobia, blurry vision, foreign body sensation (itchy, gritty, irritated eyes), or even eye pain. Retinal and optic nerve damage are more serious potential consequences of some chemotherapy drugs and if unrecognized can result in visual loss which may be irreversible [1, 2]. Effects may persist even when ocular effects appear to have resolved. Corneas from donors recently treated with systemic chemotherapy are susceptible to

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I. Olver (ed.), *The MASCC Textbook of Cancer Supportive Care and Survivorship*,
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development of ocular surface disease and central corneal opacification that is a direct consequence of the effect of the chemotherapy on the corneal epithelium. It is estimated that up to 4% of recipients from chemotherapy-treated patients may be affected [3].

Individual drugs and their associated ocular toxicities are reviewed by categories as defined by the mechanism of action of the agent.

## Alkylating Agents

### Non-platinum Alkylating Agents: Chlorambucil, Cyclophosphamide, Ifosfamide, Busulfan, and Nitrosoureas

Ocular effects of *chlorambucil* are likely due to cumulative exposure to the drug. The most frequently reported effect is keratitis, with a single case of diplopia with bilateral papilledema and retinal hemorrhages reported [4] as well as visual failure and optic atrophy after several years of chlorambucil [5].

Because *cyclophosphamide* is rarely administered as a single agent, it is often difficult to determine if ocular side effects are due to the drug alone or to combination therapy. Transitory blurred vision is common and can occur anywhere from minutes to 24 h after administration, especially with high doses, and generally resolves after 1–14 days [2]. Up to 50% of patients treated with cyclophosphamide develop dry eye (keratoconjunctivitis sicca). Blepharitis and conjunctivitis are also common side effects of this medication. The ocular surface side effects have been attributed to an irritative and a direct toxic effect of drug accumulation in tears [6]. Pinpoint pupils and recurrent transitory myopia have been reported following intravenous bolus administration of the drug [2]. A case of irreversible lacrimal duct stenosis and epiphora in a patient undergoing combination cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy led to a retrospective study over 2.5 years of 128 women undergoing the same treatment regimen. In that review, 18% of women reported ocular side effects, including 4 additional cases of epiphora that resolved completely in all but 1 patient when chemotherapy ended [7]. Lacrimal outflow obstruction from sclerosing canaliculitis following CMF has been documented, with histology showing changes of chronic inflammation and fibrosis of the lacrimal apparatus [8].

A case report describes reversible blurred vision and conjunctivitis, similar to that observed with cyclophosphamide, during the third day of *ifosfamide* infusion, with resolution of symptoms after the infusion ended [9].

The most common and characteristic ocular side effect of *busulfan* is development of posterior subcapsular cataract with a polychromatic sheen, although nonspecific blurred vision and dry eye syndromes may occur also [2]. Busulfan is secreted in tears and may have a direct irritative effect on the ocular surface, and as such could potentially aggravate preexisting dry eyes. The incidence and severity of cataract formation are proportionate to the total cumulative dose and duration of treatment. Imperia et al. reported that patients who developed a posterior subcapsular cataract had a mean duration of therapy of 113.5 months [10], although cataract development after only 4 days of high-dose treatment (212 mg/day) has been reported [11]. Al-Tweigeri et al. [4] suggested that busulfan-induced cataracts are mechanistically related to decreased DNA synthesis in proliferating lens epithelial cells. The incidence of cataract formation increases when busulfan is combined with corticosteroids, which are cataractogenic in their own right.

The *nitrosoureas* (*carmustine, CCNU, methyl CCNU*) cross the blood–brain barrier and, as such, penetrate the blood–retinal barrier and can be associated with increased neuro-retinal toxicity [6]. Nonspecific and transient blurred vision, loss of depth perception, acute conjunctival hyperemia, and retinopathy have been reported [2, 12]. Toxicity is usually worse with higher doses such as those used with autologous bone marrow rescue, often with delayed onset. Shingleton et al. [13] described delayed bilateral ocular toxicity in 2 of 50 patients treated with high-dose intravenous BCNU with autologous

bone marrow rescue. Segmental perivascular staining, retinal artery destruction, widespread late capillary leakage, and optic nerve head hyperfluorescence were evident with fluorescein angiography [13], and others have reported focal optic nerve demyelination [14]. Johnson et al. described ten cases of ocular toxicities with varying degrees of vision loss and ischemic microvascular lesions of the retina and optic disc that developed around the same time as pulmonary toxicity after high-dose BCNU, cyclophosphamide, and cisplatin followed by autologous hematopoietic progenitor cell support. Cotton-wool spots were noted at 1–4 months post-transplant and three patients developed optic disc edema and variable vision loss associated with the onset of BCNU-induced pulmonary toxicity [15]. All of the ocular toxicities resolved and the cotton-wool patches and hemorrhages faded away within 2–3 months.

## Platinum Agents (Cisplatin, Carboplatin, Oxaliplatin)

*Cisplatin*-associated neurotoxicity is dose-limiting and when administered intravenously, neuroretinal side effects, including blurred vision, color vision defects, and electroretinographic (ERG) changes, may occur [2, 6]. Optic nerve changes including edema, neuritis, and retrobulbar neuritis have been reported for high dose as well as cumulative lower doses of the drug [2]. Higher doses are associated with transient cortical blindness and temporary homonymous hemianopsia, as well as macular pigmentary changes which may persist after discontinuation of treatment [2]. All but the pigmentary changes are reversible. Wilding et al. reported on 13 women treated with high cumulative doses of platinum (400–800 mg/m$^2$) over 2–4 cycles for ovarian cancer, noting that 8 patients experienced blurred vision, 3 experienced decreased color vision (blue–yellow axis), 6 developed irregular pigmentation in the macula, and nine patients developed color vision testing or ERG abnormalities consistent with cone dysfunction [16]. Blurred vision improved after discontinuing the drug, but color defects persisted for up to 16 months. Katz described a patient who developed bilateral irreversible visual loss after four cycles of cisplatin; fundoscopic exam was normal, but there were coexistent ERG changes and bilateral central scotomas on visual field exam [17]. A single case of monocular vision loss after the fifth cycle of combination cisplatin and gemcitabine has been reported [18]. Reversible segmented nerve demyelination similar to that seen with heavy metal CNS toxicity may occur with cisplatin, and nystagmus secondary to cisplatin-induced vestibular pathology may occur and may be of greater severity in those with darker irises since cisplatin is sequestered in melanocytes [19].

Maculopathy, optic neuropathy, cortical blindness, ocular surface discomfort, blurred vision, and choroidoretinitis and optic neuritis have been reported with intravenous *carboplatin*.

Fischer et al. reported the case of a patient with carboplatin dosed by AUC who developed bilateral papilledema and only partially reversible visual impairment [20]. After the fourth cycle, the patient complained of lack of focus and scattered blind spots in the right eye. Slightly reduced visual acuity was present in both eyes, and bilateral papilledema was noted on fundoscopy, with a more prominent optic nerve head in the right eye and some hemorrhages in the nerve fiber layer. After the fifth cycle, visual acuity decreased, and new visual field losses in the left eye had developed. Increased papilledema was noted bilaterally, particularly in the left eye, the hemorrhages in the right eye had almost disappeared, and some signs of ischemia were noted. Visual acuity in the left eye worsened, and there was a left relative afferent pupillary defect. With tapering doses of oral prednisolone over 10 weeks, visual acuity in the right eye was stable, and the left eye improved over 2 years although residual optic atrophy persisted. Varying degrees of papilledema and blindness have been reported following high-dose (AUC 12) [21] and fixed-dose (400 mg/m$^2$) carboplatin [22] and after simultaneous carboplatin and cisplatin administration [23].

Vision abnormalities, in particular transient vision loss which is reversible following discontinuation of treatment, have been reported with

*oxaliplatin*. Episodes of transient blindness lasting for seconds or minutes may recur repeatedly and last for hours to days. Cranial nerve dysfunction may occur by itself or along with ptosis [24] or diplopia, eye pain, decrease of visual acuity, visual field disorders, and/or transient blindness [25]. Tunnel vision, visual loss with postural changes, and papilledema have been reported at various times following treatment with oxaliplatin [26].

## Antimetabolites

### Pyrimidine Analogs (5-Fluorouracil, Capecitabine, Cytosine Arabinoside [Cytarabine])

*5-Fluorouracil* (*5-FU*) is sometimes administered as a single agent, often as a continuous infusion, or in combination with other agents. Because therapeutic doses of 5-FU are often close to its toxic level, almost one-third of patients develop some type of ocular side effect manifested by blurred vision, ocular pain, photophobia, epiphora, ocular irritation, and conjunctivitis out of proportion to clinical findings, periorbital edema, ectropion (turning out of the lower eyelid), and/or keratitis. Effects may occur early in the course of treatment or after long-term exposure [27]. Rapidly proliferating cells such as the epithelial cells on the eye surface are especially susceptible to 5-FU, which has been isolated in tears at levels comparable to plasma levels of patients with excessive tearing but not in patients without eye symptoms. With long-term therapy and if left undetected, lacrimal duct stenosis and excessive tearing may occur [28], sometimes with severe squamous metaplasia of the lacrimal canaliculi [29]. Toxic effects to the cornea, including corneal opacities, can also occur. Neuroophthalmologic effects, including nystagmus and diplopia, may occur as a result of drug-related neurotoxicity [28]. Severe ocular and systemic toxicity has been reported in patients with complete or partial deficiency of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in 5-FU catabolism [30].

Ocular symptoms can be managed by use of frequent artificial tears or topical steroids during peak serum levels of 5-FU and with use of cold compresses to the periorbital area [31].

*Capecitabine* is ultimately metabolized enzymatically to 5-FU and essentially mimics continuous infusion 5-FU. Ocular irritation similar to that observed with 5-FU has been reported in at least 10% of capecitabine-treated patients. Superficial white corneal deposits in a whorl pattern have been reported in two patients with antecedent keratoconjunctivitis sicca prior to initiation of capecitabine [32]. In one case there were two positive rechallenges with complete clearing in between reexposures. Figure 35.1 demonstrates the corneal deposits observed with use of capecitabine [32]. Signs and symptoms may develop in 4–6 weeks, with resolution after a similar period of time has elapsed without reexposure. Decreasing the dose may lessen the degree of toxicity.

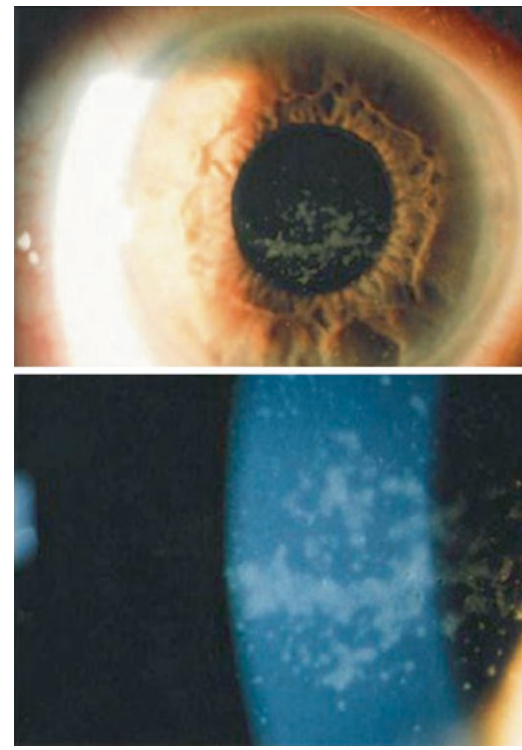

**Fig. 35.1** Corneal deposits due to capecitabine (From [32]. Copyright © 2000 Massachusetts Medical Society. All rights reserved)

The most frequent side effect of *cytosine arabinoside* (also known as cytarabine) is time- and dose-dependent ocular toxicity. Blurred vision and keratoconjunctivitis are the most frequent ocular effects noted, and lateral gaze nystagmus, diplopia, and lateral rectus nerve palsy often occur with drug-related cerebellar dysfunction. While little ocular toxicity is noted with low doses [33], most patients experience ocular effects with prolonged exposure and with high doses of the drug. High-dose cytarabine penetrates the blood–brain barrier, and the drug is found in tears, in part explaining the high prevalence of keratitis. Ocular effects usually occur after 5–7 days of exposure and are characterized by eye pain, excess lacrimation, a foreign body sensation, photophobia, and blurred vision with bilateral conjunctival hyperemia. Central punctate corneal opacities, subepithelial granular deposits, refractile epithelial microcysts due to profound degeneration of rapidly dividing basal epithelial cells, superficial punctuate keratitis, and, rarely, mild corneal edema with stria may be seen with high doses [34]. Symptoms improve after a few days once the drug is discontinued, vision improves in 1–2 weeks, and corneal opacities resolve within 4 weeks after cessation of the drug. Prophylactic use of topical steroids or topical 2-deoxycytidine, a competitive inhibitor of cytarabine, is effective in the management of cytarabine-associated corneal toxicity [34]. Individual case reports of transient visual loss and anterior uveitis following high-dose cytarabine describe the clinical course of these events [35, 36]. Optic nerve atrophy and blindness may occur with either intravenous high-dose cytarabine or with intrathecal administration.

Ocular side effects are also noted with a liposomal formulation of cytarabine for intrathecal administration, as noted in the DEPOCYT package insert [37]. A similar incidence of blurred vision was noted in a head-to-head trial comparing DEPOCYT (12%) with intravenous Ara-C (14%), and across all Phase I–IV clinical trials in adults, 11% reported blurred vision.

## Folic Acid Analogs (Methotrexate, Pemetrexed)

*Methotrexate* is dispensed in multiple dosing regimens and via different routes of administration (low-dose oral, low-dose intravenous, high-dose intravenous {which crosses the blood–brain barrier}, and intrathecal). Approximately 25% of patients treated with high-dose methotrexate develop ocular toxicity within 2–7 days after starting therapy. Periorbital edema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis, conjunctival hyperemia, and both decreased and increased lacrimation have been reported [2, 4]. Symptoms usually resolve within 10 days of discontinuing the drug and are ameliorated with the use of artificial tears. Methotrexate levels in tears mirror serum levels, but without correlation between tear concentration and ocular effects. Ocular symptoms are likely related to the anti-mitotic effect of the drug in the rapidly dividing cells of the corneal and conjunctival epithelium [2].

Ocular muscle weakness and palsy, usually transient in nature, may occur with intrathecal or low-dose oral methotrexate dosing schedules [38]. Exaggerated effects, especially transient ophthalmoplegia, may occur when intrathecal methotrexate is administered with concomitant radiotherapy and even with lower-than-routine doses [6]. Retinal and optic nerve effects of methotrexate may occur with low-dose therapy, and effects may not be fully reversible. Only partial improvement of vision and persistent abnormal ERG findings were documented as late as 3 years after discontinuation of long-term (8.5 years) weekly low-dose methotrexate [6, 39, 40].

*Pemetrexed* is often administered in combination with cisplatin as well as alone as monotherapy. An additive effect of the two drugs on ocular toxicity is evident from a clinical trial comparing pemetrexed monotherapy to pemetrexed in combination with cisplatin. With pemetrexed monotherapy, 1% of patients developed conjunctivitis, while 5% reported conjunctivitis when the two drugs were administered concomitantly [41].

## Purine Analogs (Fludarabine, Deoxycoformycin)

*Fludarabine*-related ocular effects are infrequent but may be rapidly progressive, sight-threatening, and are largely irreversible. Fludarabine development was almost discontinued due to serious toxicities, including neurotoxicities and blindness, in Phase I trials. Early reports of diplopia, photophobia, and decreased visual acuity probably secondary to optic neuritis with or without disc edema, and/or cortical blindness occurred in patients treated with doses that are higher than those used in current clinical practice. In a comprehensive review of fludarabine-related ocular effects, Ding et al. [42] noted that ocular susceptibility to fludarabine toxicity is not limited to high-dose therapy. At the 5-year follow-up of a National Cancer Institute study of patients with chronic lymphocytic leukemia treated with fludarabine, 1% of the 705 evaluable patients had developed grade 3 (generalized symptomatic subtotal loss of vision) visual toxicity, while grade 4 (blindness) toxicity had occurred in 0.3% of patients [43].

With standard doses of fludarabine, visual loss may be hallmarked by the onset of visual hallucinations, floaters, and diminished visual acuity. Dramatic loss of retinal ganglion cells, bipolar cell damage, and extensive optic nerve atrophy has been noted at postmortem exam. The etiology of the ocular damage is not clear and could be due to direct neuronal toxicity from fludarabine and/or retrograde neuronal atrophy. Fludarabine-related neurotoxicity and ocular toxicity appear to be largely irreversible, although visual recovery has been reported in some cases with immediate cessation of the drug at the first signs of neurotoxicity [42].

Bilateral conjunctivitis and keratitis have been reported rarely with *deoxycoformycin* and generally occur after long-term use. Symptoms generally resolve within a week after discontinuation of the drug, although the corneal involvement may take up to 3 weeks to resolve [43].

## Antibiotics (Doxorubicin, Epirubicin, Mitoxantrone, Mitomycin C)

Increased tearing and conjunctivitis are the most frequently reported ocular effects of *doxorubicin* and the liposomal formulation of the drug. Up to 25% of patients treated with doxorubicin develop conjunctivitis during the course of treatment, and conjunctivitis is noted in roughly 15% of patients treated with epirubicin [2].

*Mitoxantrone* in aqueous solution for intravenous injection is dark blue in color, and blue-tinged eyelid, sclera, and conjunctiva have been reported. Conjunctival discoloration is self-limiting and resolves within 24 h after infusion. Pigmentation of the sclera and eyelids is transitory, due to deposition of the dark blue drug, and regresses over time [44].

*Mitomycin C* may cause blurred vision [2], and damage to the corneal epithelium may occur as a result of tear film changes [45].

## Mitotic Inhibitors (Taxanes and Vinca Alkaloids)

### Taxanes

*Paclitaxel*-related neurotoxicity can be dose-limiting. Transient scintillating scotoma (a localized area of diminished vision edged by shimmering colored lights, most often associated with the aura that precedes the onset of migraine headaches), visual impairment, photopsia (flashing lights), and possible ischemic optic neuritis have been reported. Photopsia usually lasts from 15 min to 3 h after infusion and was noted in 6 of 25 patients treated with paclitaxel (250–275 mg/m$^2$) as a 3-h infusion [46]. Patients described seeing flashing lights across the entire visual field, usually beginning during the last 30 min of the drug infusion. Photopsia recurred on rechallenge at the same or slightly reduced dose without any apparent chronic sequelae. Ophthalmologic examination was normal in three of these patients, and visual acuity was not affected. Photopsia was not

observed with doses less than 250 mg/m$^2$ and did not correlate to peak plasma levels. Capri et al. reported similar ocular toxicities in 9 of 47 patients (19%) treated with paclitaxel at doses of 175–225 mg/m$^2$ as a 3-h infusion [47]. These individuals described small luminous dots (or flies) in the visual fields of both eyes at about the time of the end of the infusion. The events always resolved spontaneously and did not necessarily recur with subsequent cycles. Three of the nine patients also reported a subjective reduction in vision. One of the patients had an abnormal visual evoked potential (VEP), suggesting an effect on the optic nerve, and a normal ERG. Fundoscopic and ERG exams were normal in the other two, but abnormal VEP was noted. These abnormalities did not worsen and recovered somewhat. Scaioli et al. evaluated 30 patients with breast cancer treated with either paclitaxel alone or in combination with doxorubicin and found electrophysiological changes involved both the retina and anterior optic pathway, with only a weak correlation between visual symptoms and electrophysiologic changes suggestive of retinal hypoxia due to vascular dysregulation and ischemia in the optic pathways [48].

Ocular/visual changes are also associated with the administration of an albumin-bound formulation of paclitaxel (*Abraxane*). Ocular toxicity (superficial keratopathy and blurred vision) was a dose-limiting toxicity in the Phase I trial but has not been evident in subsequent studies at doses at or below the MTD [49, 50].

A rare but reported association has also been reported between taxane medications and cystoid macular edema (CME). In these cases, CME was found in the absence of angiographic leakage with fluorescein. Specific reports have been linked to docetaxel and paclitaxel [51–53].

## Docetaxel

Canalicular and nasolacrimal duct obstruction, leading to excessive tearing, and conjunctivitis are the most commonly reported ocular side effects of treatment with docetaxel and have been noted with every 3 week and, more commonly, with weekly dosing schedules [54]. Nasolacrimal duct obstruction may be due, at least in part, to stromal fibrosis in the mucosal lining of the lacrimal drainage apparatus. Tsalic et al. [55] prospectively evaluated the incidence of excessive tearing in 21 consecutive patients with different malignancies undergoing weekly docetaxel (35 mg/m$^2$/week iv for 6 weeks, with cycles repeated every 49 days), including a standard baseline questionnaire before each dose of docetaxel. In their study, 7 of 21 (33%) patients developed excessive tearing related to canalicular stenosis at a cumulative docetaxel dose of 208–645 mg/m$^2$ (median: 400 mg/m$^2$). In all patients, the tears overflowed onto the face, causing significant interference with normal activities. Patients continuously rubbed the eyes, causing additional irritation and lower eyelid ectropion (turning out of the lower eyelid). Fundoscopy was normal. Two patients developed complete canalicular stenosis requiring surgery. Madarosis (loss of eyelashes) was often present, and keratinization of the cornea and conjunctiva further exacerbated ocular irritation. The excess tearing resolved completely in three patients 4–6 weeks after cessation of docetaxel but persisted for 5–12 months after discontinuing therapy in four patients [55]. Because of the severity of the excessive tearing, some patients undergoing treatment with docetaxel may benefit from prophylactic temporary placement of silicone or similar tubes to maintain the patency of the lacrimal apparatus [55].

There is one report in the literature of possible taxane-induced open-angle glaucoma that developed in a woman with metastatic breast cancer treated initially with docetaxel 100 mg/m$^2$ at 3-week intervals along with routine steroid premedication [56]. She developed progressively diffuse fluid retention after the first cycle and complained of loss of vision after the fifth cycle. Open-angle glaucoma was diagnosed with elevated intraocular pressure (44 mm Hg) in both eyes. Docetaxel was discontinued, and the increased intraocular pressures normalized with treatment. She was then treated with vinorelbine for 9 months and went without any specific treat-

ment and without recurrence of the glaucoma for eight additional months. When treatment with paclitaxel 135 mg/m$^2$ q 21 days was initiated, fluid retention occurred after the second cycle, and open-angle glaucoma (intraocular pressures of 35 mm Hg and 40 mm Hg) recurred after the third cycle. Paclitaxel was continued along with treatment for the glaucoma, which did not improve. Fundal exam showed typical cupping and bilateral scotoma [56].

## Vinca Alkaloids

### Vincristine, Vinblastine, Vindesine, and Vinorelbine

The most common ocular side effects of treatment with vinca alkaloids are related to the neurotoxicity of the drugs and are dose-related. Cranial nerve palsies (ptosis, extraocular muscle palsies, and internuclear ophthalmoplegia, corneal anesthesia or hypoesthesia, and lagophthalmos) may occur in one form or another in up to 50% of patients treated with vinca alkaloids [2, 6]. Other effects are optic neuropathy, including optic nerve atrophy, cortical blindness, or night blindness [2, 6]. Effects may be noted as soon as 2 weeks after the initial dose, and most will experience at least partial resolution with cessation of the drug. Individual reports of reversible vincristine-related nerve palsy describe the clinical course of events [57–59]. Amelioration of vincristine-related neuropathy and cranial nerve effects may be achieved with pyridoxine or pyridostigmine [60]. Vincristine-associated optic neuropathy and bilateral optic atrophy have been documented, with improvement and sometimes complete recovery after discontinuation of the drug [61], and retinal damage has been observed at autopsy [6]. Irreversible blindness, transient cortical blindness (lasting from 24 h to 14 days) with recovery in 1–14 days [62], and development of night blindness after vincristine have been reported [63].

*Vinblastine*-associated ocular effects are less frequent than with those observed with vincristine, possibly due to incorporation of vincristine rather than vinblastine in many childhood malignancy treatment regimens. Nonetheless, there is a report of vinblastine-associated ptosis 6 weeks after starting vinblastine in a 2-year-old [64]. Inadvertent drug exposure, such as that which can occur by accidental splashing of vinblastine into the eye, can have especially serious consequences. A characteristic keratopathy, including microcystic edema, superficial punctuate keratitis, and corneal erosion with or without low-grade anterior uveitis has been described [6]. Decreased vision and damage to the cornea are noted in the first few days after exposure, and the keratitis can take weeks to months to resolve and may be permanent. There is one report of increased astigmatism developing after inadvertent exposure to vinblastine [6].

## Hormonal Agents (Selective Estrogen Receptor Modulators, Aromatase Inhibitors, Anti-androgens)

### Tamoxifen

Visual problems associated with tamoxifen have been reported for over 30 years, and comprehensive profiles of tamoxifen-associated ocular toxicity have been published [65–67].

An increased risk of posterior subcapsular cataracts, color vision changes, optic neuritis, and intra-retinal crystals are the most commonly noted ocular effects associated with tamoxifen. While some reports suggest no increased risk of cataract formation compared to women with other malignancies not treated with tamoxifen [68], the vast majority of studies cite an increased incidence of cataracts with tamoxifen therapy [65–67]. A small relative risk of developing cataracts and, more specifically, a higher risk of undergoing cataract surgery were reported from the NSABP breast cancer prevention trial [69]. The longer the duration of exposure, the higher is the likelihood of cataract development. Women exposed to tamoxifen for 4–5 years were at slightly elevated risk of cataracts compared to nonusers, whereas women exposed for 6+ years were at greater risk. Cataract pathogenesis may

in part be due to interference by tamoxifen of chloride channels essential for maintaining lens hydration [70]. In a study that included patient questionnaires, Gallichio et al. reported that 13% of tamoxifen users noted an adverse ocular side effect and found that the presence of visual complaints correlated with high serum levels of tamoxifen and its N-desmethyltamoxifen metabolite [71]. While tamoxifen can affect vision, serious side effects are not common and, if present, generally occur at doses >10 g (standard dose is 20 mg daily). Compared with non-treated participants, tamoxifen-treated women had no limitation or differences in vision-dependent daily activities, visual acuity measurements, or other tests of visual function except for subclinical changes in color discrimination, especially with long-term tamoxifen use [67].

Effects on the retina can be acute and not well-defined, consisting of loss of vision, localized edema, optic disc swelling, and hemorrhage after even only a few weeks of therapy. These acute effects are likely due to the estrogenic effect of tamoxifen and associated thrombotic phenomena of the retinal vein and are reversible when the drug is discontinued [72, 73].

Tamoxifen is secreted in tears, which may be a factor in symptoms of reduced vision, photophobia, and ocular irritation. Penetration of the drug to at least the basal surface of retinal pigmented epithelium is suggested by case reports of stabilization of optic nerve head metastases and reduction in size of retinal metastases after starting treatment with tamoxifen [74]. Typical tamoxifen retinopathy consists of small refractile or crystalline dot-like yellowish deposits in the peri-macular area and may be the products of axonal degeneration [72]. These changes are more likely to occur after a year of more of tamoxifen [75], although retinopathy may be present in their absence [73]. Goren et al. reported that any retinal occlusive disease in their study was consistent with chance occurrence rather than due to tamoxifen [73], while a twofold higher incidence of deep-vein thrombosis, pulmonary embolism, or retinal vein thrombosis during the active treatment period, relative to placebo, was reported in long-term follow-up in the International Breast Cancer Intervention Study (IBIS-I), although specifics isolating retinal vein thrombosis from other thromboembolic events were not reported [76].

Characteristic white, whorl-like subepithelial corneal deposits have been reported, may be dose-related, and when present are of no visual significance [34].

Because of the potential for the development of ocular effects due to tamoxifen, a baseline ophthalmologic exam within the first year of treatment is warranted, with periodic follow-up, especially if ocular symptoms occur [6]. However, even if cataracts develop, they are likely to progress even after the drug is discontinued.

## Raloxifene and Anastrozole

Both *raloxifene* and *anastrozole* are associated with an increased risk of cataract development, although perhaps slightly less so than with tamoxifen [77, 78].

## Leuprolide

Ocular toxicities are also likely to some extent with *leuprolide*. Transitory blurred vision may occur shortly after each injection or after multiple injections and usually lasts for 1–2 h, although in rare instances, the duration may be as long as 2–3 weeks. Other effects that have been reported include pseudotumor cerebri and papilledema, ocular vascular accidents, eye pain, and lid edema [79].

## Nilutamide

The most frequent ocular effect of *nilutamide* is delayed adaption to darkness after exposure to bright light, which is dose-dependent and occurs in up to 90% of patients. Photostress recovery time is prolonged to 10–30 min (normal is roughly 1 min). No retinal changes are found on examination. Adaptation to darkness may nor-

malize while continuing on the drug or with dose reduction or discontinuation of the drug, in which case recovery may take up to a year, likely due to delayed regeneration of visual pigments [80].

## Steroids

Corticosteroids such as prednisone and dexamethasone are often included in treatment regimens for hematologic malignancies and are often administered just prior to chemotherapy as an adjunct to antiemetic therapy. The cataractogenic properties of long-term steroid usage have been identified in patients with rheumatologic diseases as well as malignancies [12]. Increased intraocular pressure and subsequent glaucoma is another potential ocular effect of long-term steroid usage [72].

## Molecular Targets

*Imatinib mesylate* was the first molecularly targeted agent in clinical practice, and the ocular effects of the drug have been documented extensively [81, 82]. The most commonly reported findings are blurred vision, periorbital edema as well as edema of the eyelid and conjunctiva, and excessive tearing. Mild-to-moderate periorbital edema occurs in approximately 70% of patients treated with imatinib [81, 82]. Results of a chart review reported by Fraunfelder et al. [82] noted that 73 of 104 imatinib-treated patients (70%) with chronic myelogenous leukemia (CML) developed periorbital edema (29% of whom also had concomitant peripheral edema), and 18% reported increased tearing. Demetri et al. [83] reported a similar incidence of periorbital edema (74.1%) in imatinib-treated patients with gastrointestinal stromal tumor. The periorbital edema can become apparent early (as soon as 24 h) or late (after 1 year) after initiation of imatinib, although it is most frequently noted after 2 or 3 months of treatment. The reaction appears to be dose-dependent, with a higher incidence with doses higher than the usual 400 mg/day. In a case report of a patient with periorbital edema causing visual obstruction that required surgical debulking, Esmaeli et al. noted that imatinib-related inhibition of PDGFR (platelet-derived growth factor receptor) in dermal dendrocytes of periorbital skin may cause decreased interstitial fluid pressure that results in localized edema [84]. Figure 35.2 is a very dramatic instance of periorbital edema that occurred as a result of treatment with imatinib [84]. Other ocular problems reported in Fraunfelder's review included abnormal vision

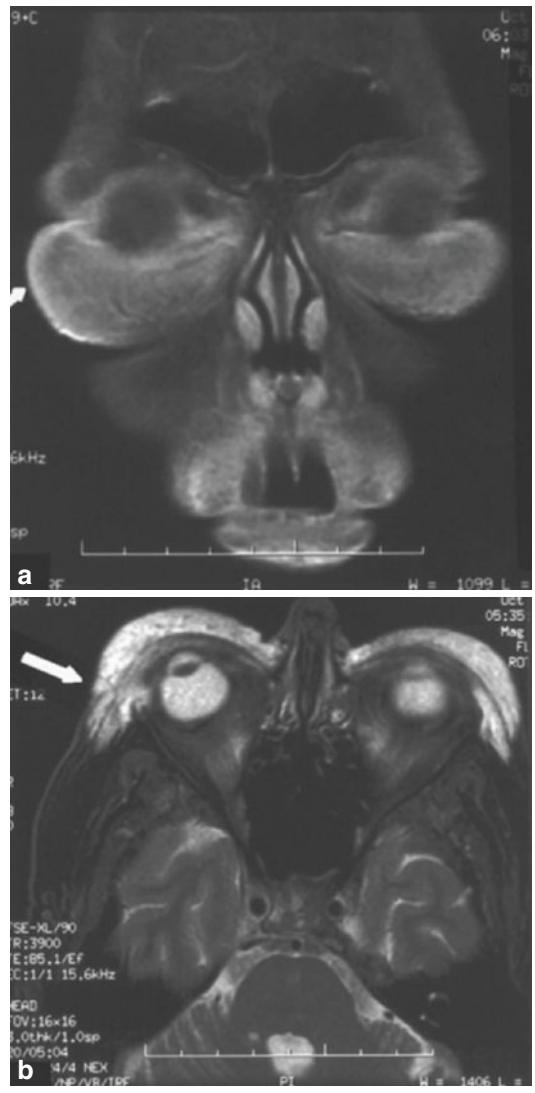


**Fig. 35.2** Imatinib-related periorbital edema (From [84]. Reprinted with permission from John Wiley & Sons, Inc.)

(ten patients), blepharoconjunctivitis (nine patients), and increased intraocular pressure, ptosis, photosensitivity, and an isolated retinal hemorrhage, each occurred in one patient [82]. Rare instances of retinal hemorrhage, usually reversible, in the first few months after starting treatment has been reported [82]. Increased tearing was the primary ocular complaint in some patients who also had periorbital edema and were treated with mean daily doses of 540 mg [85]. Retinal macula edema has been reported after 2 months of treatment with imatinib 600 mg daily, with resolution 2 weeks after discontinuation of the drug [86]. Individual cases of macular ischemia, optic neuritis, and optic disc edema with photopsia have been reported with standard (400 mg/day) doses of imatinib [87–89]. Glaucoma and conjunctival hemorrhage have been reported infrequently [81, 90]. For the most part, ocular effects of imatinib resolve with discontinuation of the drug and side effects can be managed conservatively and with low doses of diuretics and topical steroids, without discontinuation of the drug. Concomitant oral short-term steroid therapy without discontinuation of imatinib may also be of benefit, especially when doses greater than 400 mg are needed [91].

Visual disturbances (dry eye, blurred vision, conjunctivitis, and reduced visual acuity) have been reported in patients treated with *dasatinib* after failure of imatinib. Bajel et al. reported a case of safe treatment of a patient with CML who has previously developed retinal edema while on treatment with imatinib [92, 93].

## Targeted Monoclonal Antibodies

### Epidermal Growth Factor Receptor Inhibitors (Gefitinib, Cetuximab, Erlotinib, Panitumumab)

Ocular toxicities associated with EGFR inhibitors include trichomegaly (excess growth of eyelashes or brow) or madarosis (loss of eyelashes), meibomian gland dysfunction and blepharitis, dry eye, and miscellaneous changes such as iridiocyclitis and punctate epithelial erosions of the cornea [94]. The Skin and Eye Reactions to Inhibitors of EGFR and Kinases Clinic at the Northwestern University and the Robert H. Lurie Comprehensive Cancer Center report that in their experience, approximately one-third of patients treated with EGFR inhibitors experience adverse ocular effects [94]. See references [94, 95] for an example of the eyelash changes that frequently occur in patients treated with an EGFR inhibitor.

*Gefitinib*-related conjunctivitis (mostly grade 1 or 2) was reported in 15.6% of patients in one Phase I clinical trial, and in another Phase I study, one patient was reported to have a grade 3 epithelial defect in the cornea caused by abnormal eyelash growth [96, 97]. Marked lengthening of both the eyebrows and eyelashes has been reported after 7 weeks of treatment with gefitinib [98].

*Cetuximab*-related ocular toxicities include conjunctival hyperemia, conjunctivitis, and blepharitis, as well as photophobia, excessive tearing, and itching. Tonini reported a case of blepharitis and associated ocular discomfort that began after 3 weeks of cetuximab treatment [95]. The patient reported discomfort in both eyes characterized as periocular pruritis, photophobia, foreign body sensation, tearing, excoriation of the periocular skin, and blepharitis. Fundoscopic examinations, visual acuity, and intraocular pressure were normal, although mild conjunctival hyperemia was noted. Recovery was evident within 1 week after cessation of the drug but recurred 2 weeks after cetuximab was restarted. Tonini et al. [95] postulated that ocular symptoms were related to the altered composition of the tear film due to the drug's targeting of the EGFR-expressing cells of the meibomian glands. The clinical spectrum of ocular side effects related to cetuximab monotherapy is illustrated in Fig. 35.3 [95]. Cetuximab-related trichomegaly may develop within a few months of starting treatment. Excess hair growth does not usually occur in other sites, and the eyelash lengthening may be very bothersome and has the potential to cause significant eye irritation [99]. Eyelash epilation may be necessary for ocular comfort. Eyelash effects resolve within 1 month after stopping the drug.

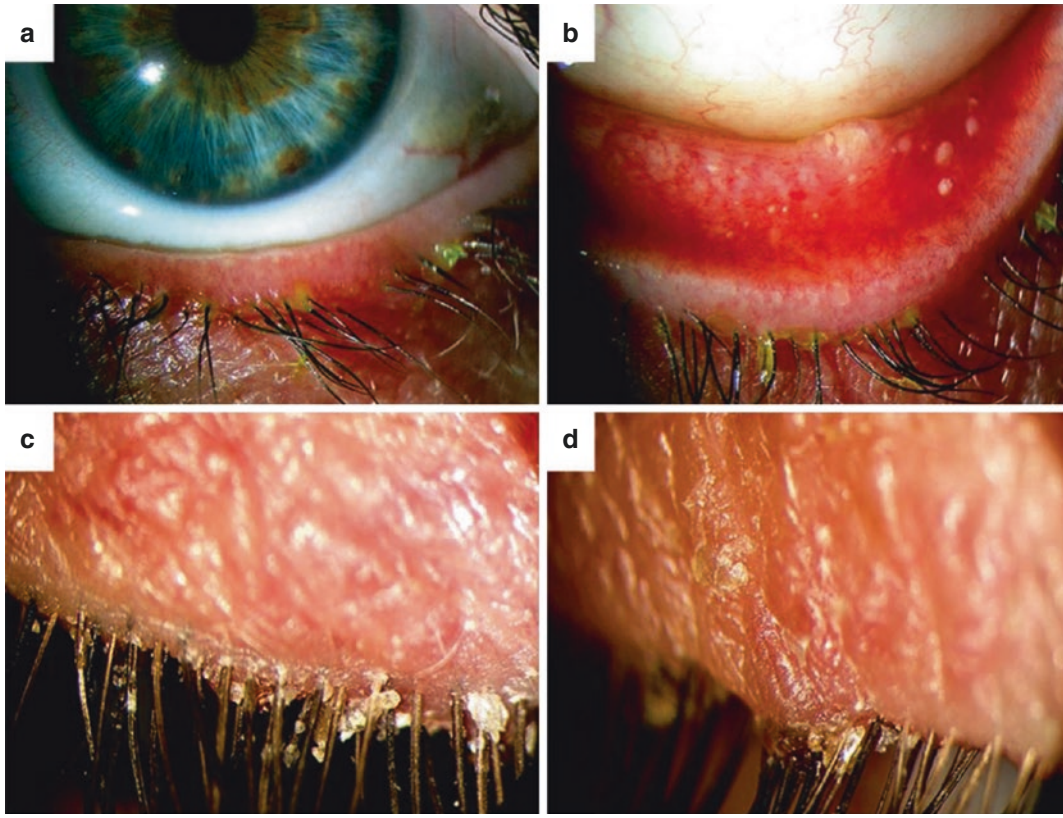


**Fig. 35.3** Clinical spectrum of ocular side effects of cetuximab monotherapy (From [96], with permission of the Oxford University Press)

*Erlotinib* use is associated with mild ocular toxicity [100]. The prescribing information notes that conjunctivitis and keratoconjunctivitis sicca each occurred in 12% of patients with non-small-cell lung cancer [101].

Another EGFR antagonist, *panitumumab*, is also associated with ocular effects. In clinical trials, ocular toxicities occurred in 15% of patients and included, but were not limited to, conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation (1%), all predominantly grade 1 or 2. Growth of eyelashes was reported in 6%. The median time to the development of ocular toxicity was 14 days after the first dose [102]. Human epidermal growth factor receptor 2 inhibitor (HER2) inhibitors trastuzumab has been associated with conjunctivitis and rarely with macular edema, macular ischemia, and serous retinal detachment [103] and Ado-trastuzumab emtansine has been associated with dry eyes and symptoms of tearing, blurred vision, and conjunctival injection.

## Protein Kinase Inhibitors (Trametinib, Cobimetinib, Binimetinib, Selumetinib, Vemurafenib, Dabrafenib. Crizotinib)

Newer agents that affect the mitogen-activated protein kinase enzymes (MEK1 and MEK2) in the MAPK/ERK pathway show a growing role in the treatment of metastatic melanoma. Current clinical trials are also investigating other targets such as ovarian and small-cell lung cancer. Widely reported case series have demonstrated a characteristic pattern of reversible time-dependent retinopathy comprising multifocal serous retinal and retinal pigment epithelial (RPE) detachments associated with MEK inhibitor use. Up to 77% of patients being

treated with binimetinib for melanoma exhibited this pattern of retinopathy [104]. While the exact mechanism for this toxicity is not known, electro-oculography was found to be abnormal in nearly all cases of binimetinib toxicity, suggesting RPE dysfunction. These lesions are often mildly symptomatic and resolve with decreasing or discontinuing the use of medications. Similar to MEK inhibitors, a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, erdafitinib, is currently in clinical trials for treatment of metastatic urothelial cancer. This medication targets receptors that also function in the MAPK pathway. Early case reports are emerging which show a similar pattern of reversible retinopathy, including during the Phase I clinical trial [105]. The BRAF inhibitors vemurafenib and dabrafenib are approved for treatment of metastatic melanoma with a BRAFV600 mutation. Treatment with vemurafenib has been associated with dry eyes (in 2%)and conjunctivitis (on 2.8%), usually mild in nature and usually with no need for discontinuation of therapy [106] Mild-to-moderate uveitis (in around 4%) was diagnosed at a median of 117 days after starting treatment; treated with corticosteroids was successful, and while dose reduction was needed in some patients, all were able to continue therapy [107]. Anaplastic lymphoma kinase (ALK) inhibitors such as crizotinib have been associated with visual disturbances that have been reported as flashes of light, image persistence especially when moving from dark light to light-lit areas, blurred vision, decreased visual acuity, and photophobia. Onset of symptoms is usually within the first week of starting treatment and in general do not have an effect on usual daily activity [108]. Optic neuropathy and blindness have been reported although confounded by prior whoile-brain irradiation [109]. It is possibe thatretinal ganglion cells may be affected and the cause of visual disturbances [110].

## Biological Response Modifiers (Interferons, Interleukins)

Most reports of ocular effects of *interferons* have been due to treatment with interferon alpha, although similar side effects have been reported to a lesser degree with beta and gamma interferon as well as with consensus interferon and pegylated interferon. Changes in vision, nonspecific conjunctivitis, and ocular pain are the most frequently reported ocular side effects, and cotton-wool spots and retinopathy may occur as well [6]. Ocular effects are more likely with higher doses and with coexistent diabetes or hypertension. The onset of effects may be as rapid as 15 min after the initial exposure to interferon, or ocular effects may not be noted for many months. Decreased vision is usually transitory, may occur after each injection, and is rarely permanent. Visual changes may include transient bright afterimages. The presence of the drug in tears likely contributes to the development of conjunctivitis, subconjunctival hemorrhages, and transient corneal microcysts [111]. Deng-Huang et al. reported a case of Graves' ophthalmology that developed in a patient with chronic hepatitis after 6 months of treatment with interferon. Reversible impaired tear dynamics and squamous metaplastic changes on the ocular surface were noted and persisted for up to 6 months after interferon was discontinued [112]. Interferon-associated overgrowth of eyelashes has been reported [6]. Retinal effects usually develop as early as 2 weeks and generally before 3 months of treatment with interferon and are more common with high doses. Less than 1% of interferon-treated patients develop these changes. Spontaneous regression may occur while continuing on the drug or when it is discontinued, although the changes are not always self-limiting and may be progressive. Retinal ischemic changes of large vessels and capillaries may be noted with fluorescein angiography. Retinal changes and cotton-wool spots due to vascular occlusion can occur even with an absence of ocular complaints or without any apparent impairment in visual acuity. Retinopathy is likely due to immune complex deposition in the retinal vasculature and leukocyte infiltration, resulting in retinal ischemia and nerve fiber layer infarcts [113].

*Interleukin-2* may cause ocular effects, usually of a neuro-ophthalmic nature. Scotomas and palinopsia (afterimages) are dose-related [114].

Diplopia, blurred vision, and conjunctival irritation have been reported also.

Conjunctival injection and disc edema, especially in children, are reported ocular effects of *interleukin-11*. Conjunctival injection was noted in 13% of patients in *oprelvekin* clinical trials, but the most serious effect is disc edema (1% in adults but 16% in children), which prompted a cautionary letter to health-care professionals [115]. Disc edema resolves with discontinuation of the drug.

## Miscellaneous Agents (Bortezomib, All-trans retinoic acid, Denileukin Diftitox)

Only rarely have ocular side effects been noted with treatment with some of the newer agents introduced into clinical practice, such as the immunomodulatory drugs thalidomide and lenalidomide, the epothilone ixabepilone, the mammalian target of rapamycin (mTOR) inhibitor temsirolimus, or the proteasome inhibitor bortezomib. When noted, ocular effects are reported as mild in nature and are usually as a result of adverse event reporting in a clinical trial. Bortezomib is associated with case reports of severe meibomian gland disease and development of chalazia [116]. All-trans retinoic acid is associated with rare instances of increased intracranial pressure with papilledema and splinter and flame hemorrhages. Blind spots are observed on visual field exam. Treatment of increased intracranial pressure with acetazolamide results in resolution of papilledema and related symptoms [117]. More serious ocular effects are noted with *Denileukin diftitox (ONTAK)*, such that the FDA mandated a change in the prescribing information: "Loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling has been reported following administration of ONTAK. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment" [118]. This addition was based on post-marketing reports of ophthalmic toxicity, and the incidence of such events was not specified. It is possible that the vascular leak syndrome that can be caused by this drug may be a contributory factor to the development of these ocular toxicities.

Immunotherapy: Prognosis of several malignancies, including urothelial cancer and NSCLC, has improved with introduction of immunotherapy as an approved treatment for malignancies. Checkpoint inhibitors include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agents (ipilimumab)and programmed cell death-1 (PD-1) {nivolumab and pembrolizumab} and programmed cell death-1 ligand (PD-L1) receptors {atezolizumab, avelumab, and durvalumab}. Ipilimumab has been associated with conjunctivitis, episcleritis, uveitis (which can be severe and may occur along with other immune-mediated adverse events and systemic autoimmune toxicity), and Graves-like ophthalmopathy, which is not usually related to immune-mediated thyroiditis. Corticosteroid eye drops is beneficial and is often administered along with systemic steroids added for treatment of systemic immunemediated toxicities [119]. Graves-like opthalmopathy, including proptosis, diplopia, exposure keratopathy and ophthalmoplegia and enlargement of extraocular muscles, with potential for optic nerve compression, has been reported. This may occur with or without elevation of lab values such as anti-thyroid peroxidase that are generally associated with immune-mediated endocrinopathy and has been reported in euthyroid patients [120]. Uveitis during treatment with all checkpoint inhibitors is rare and is likely to be more frequent when combinations of these agents are used [121]. Ocular toxicity may occur along with other immune-mediated adverse events; [122]. Early recognition and prompt referral for thorough ophthalmologic evaluation and management is key to prevention of long-lasting visual sequelae. An overview of the key ocular effects of chemotherapy agents is provided in Table 35.1.

**Table 35.1** Summary of the ocular effects of selected chemotherapy agents

| Drug | Cornea | Conjunctiva | Retina | Optic nerve | Glaucoma | Excessive tearing | Cataract | Neurotoxicity | Other/comment |
|---|---|---|---|---|---|---|---|---|---|
| Chlorambucil | Keratitis | | | Rare papilledema, optic nerve atrophy after several years | | | | | Cumulative effect of drug |
| Cyclophosphamide | Keratitis | Conjunctivitis | | | | With CMF | | | Lacrimal outflow obstruction from sclerosing canaliculitis with CMF → excessive tearing |
| Ifosfamide | | Conjunctivitis | | | | | | | |
| Busulfan | Keratitis | Conjunctivitis | | | | | Yes | | |
| Nitrosoureas | | Conjunctival hyperemia | Retinal damage | Optic nerve damage | | | | | With high-dose BCNU and ASCT |
| Cisplatin | | | ERG changes | Neuritis; transient cortical blindness | | | | Nystagmus | Decreased color vision |
| Carboplatin | | | Macular changes | Neuritis, transient cortical blindness | | | | | |
| Oxaliplatin | | | | Transient loss of vision, papilledema | | | | Ptosis | |
| 5-FU | Keratitis; corneal opacities | Keratoconjunctivitis | | Optic neuropathy | | With CMF | | Nystagmus, diplopia | Photophobia; prophylactic topical steroids, ocular ice packs |
| Capecitabine | Keratitis; corneal opacities | | | | | | | | |

(continued)

**Table 35.1** (continued)

| Drug | Cornea | Conjunctiva | Retina | Optic nerve | Glaucoma | Excessive tearing | Cataract | Neurotoxicity | Other/comment |
|---|---|---|---|---|---|---|---|---|---|
| Cytosine arabinoside (cytarabine) | Keratitis; corneal opacities | Keratoconjunctivitis | | | | Yes, esp. with high doses | | Nystagmus, diplopia | Photophobia; prophylactic topical steroids |
| Methotrexate | | Conjunctivitis | ERG changes possible | | | | | | |
| Fludarabine | | | | Optic neuritis, cortical blindness | | | | Diplopia | Visual hallucinations |
| Doxorubicin | | Conjunctivitis | | | | Yes | | | |
| Mitoxantrone | | Blue-tinged conjunctiva | | | | | | | |
| Paclitaxel | | | Non-leaking CME | Ischemic optic neuritis | Rare | | | | Photopsia |
| Docetaxel | | Conjunctivitis | Non-leaking CME | | Rare | Yes | | | Lacrimal outflow obstruction from sclerosing canaliculitis → excessive tearing |
| Vincas | | | | Optic neuropathy, cortical blindness | | | | Cranial nerve palsies | Night blindness |
| Tamoxifen | Subepithelial corneal deposits | | Intra-retinal crystals | Optic neuritis | | Yes | | | Color vision changes |
| Raloxifene | | | | | | | Yes | | |
| Anastrozole | | | | | | | Yes | | |
| Leuprolide | | | | Rare papilledema | | | | | Transitory blurred vision after injection |
| Nilutamide | | | | | | | | | Delayed adaptation to dark |
| Steroids | | | | | Yes | | Yes | | |
| Imatinib | | Conjunctivitis | Retinal macula edema | | Rare | Yes | | Periorbital edema | |

| Drug | Cornea | Conjunctiva | Retina | Optic nerve | Glaucoma | Excessive tearing | Cataract | Neurotoxicity | Other/comment |
|---|---|---|---|---|---|---|---|---|---|
| EGFRs | Rare keratopathy | Conjunctivitis | | | | | | | Trichomegaly; severe meibomian gland inflammation/ blepharitis |
| Interferons | Corneal microcysts | Conjunctivitis | Retinopathy | | | | | | Trichomegaly |
| IL-2 | | Conjunctivitis | | | | | | | Palinopsia |
| IL-11 | | Conjunctivitis | | Disc edema, esp. in children | | | | | |
| Denileukin diftitox | | | Retinal pigment mottling | | | | | | Loss of visual acuity; color vision loss |
| MEK inhibitors | | | Multifocal serous retinal detachments, pigment epithelial detachments | | | | | | Mild, reversible |

## Conclusion

Ophthalmologic effects of chemotherapy drugs occur less frequently than other chemotherapy-related toxicities, and ocular complications tend to be less severe than other toxicities. Most ocular effects improve or resolve completely upon discontinuation of the offending drug; sequelae are often minimized by early recognition.

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# Part XI

# Skin

# Extravasation

# 36

Ian Olver

Extravasation of cancer drugs refers to the accidental leakage of the drugs into the perivenous or subcutaneous tissue during their administration [1].

It is worth speculating as to whether we will need separate chapters on extravasation in future textbooks on the toxicity of cancer treatment. The incidence is decreasing with better administration procedures and greater awareness of early detection and treatment [2]. One hospital reported a tenfold decrease in incidence over the 15 years up to 2002 [3]. Vesicant cytotoxics such as the anthracyclines and vinca alkaloids are giving way to more targeted therapies. Some of the newer small molecules are given orally, and although immunological therapies come with a range of skin toxicities, most are not vesicants [3, 4].

Implantable venous access devices have made it safer to administer cytotoxics, particularly in patients with fragile peripheral veins [5]. Reformulating vesicant drugs like anthracyclines into liposomal preparations changes their potential for tissue destruction if extravasation occurs [6].

There have been few randomised studies to guide treatment, and early treatment recommendations in review articles when traced to their source were based on very few patients (instilling sodium bicarbonate,) or limited animal studies (heat after vinca alkaloid extravasation) and were either ineffective or may have even caused more damage [7, 8].

## Incidence

In reported studies, the incidence estimated for extravasation injuries varies between 0.01% and 7% [2]. If a central venous access device is inserted, this should result in less extravasations, but rates of extravasation of up to 4.7% have been reported [10].

## Classification of the Potential for Tissue Damage of Intravenous Drugs

Intravenous anticancer drugs are often classified under five categories according to the damage that they cause. It is the vesicants that have the potential to cause the greatest tissue damage and therefore have been the major targets for extravasation prevention and treatment strategies [11].

### Vesicants

Drugs that cause irreversible tissue damage including necrosis, pain, blistering and inflammation can lead to loss of mobility. Examples are

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the anthracyclines, vinca alkaloids, mitomycin C and actinomycin D.

### Exfoliants

These drugs cause more superficial damage with inflammation and peeling of skin but no necrosis. They include cisplatin, oxaliplatin, taxanes and mitoxantrone.

### Irritants

These drugs cause inflammation and pain at the site of extravasation, or burning along the vein while being administered, but no blistering or irreversible damage. Examples include epipodophyllotoxins, carboplatin, bleomycin and bendamustine. Monoclonal antibodies seem to fit into this category as do checkpoint inhibitors, such as ipilimumab which can cause thrombophlebitis.

### Inflammatory Agents

These agents cause painless redness or flare at the extravasation site. They include 5-fluorouracil, methotrexate, bortezomib and raltitrexed.

### Neutrals

These are drugs which cause no inflammation when extravasated. Many of the targeted therapies are in this category, including bevacizumab, cetuximab, rituximab and trastuzumab as well as cytotoxics such as cyclophosphamide, cytarabine, gemcitabine and melphalan.

There are several possible mechanisms for tissue damage. For example, the vesicant doxorubicin binds to the DNA and inhibits cell division. When the cell dies, the free radical can be released to bind to surrounding cells [12]. Alternatively, hyperosmolar solutions will result in fluid shifting from the intracellular to the extracellular space resulting in oedema which can increase mechanical pressure resulting in ischaemia and tissue death [13].

These mechanisms highlight the factors which will determine the extent of the tissue damage. The pH and osmolality of the fluid extravasated is important, as is its potential to cause vasoconstriction. The length of time that the extravasated drug remains in the tissue is important. Anthracyclines which bind to DNA will cause immediate and prolonged tissue damage, and there can be a further flare of damage at a previous site of extravasation with subsequent dosing. Drugs like the vinca alkaloids and taxanes, however, do not bind to DNA and are metabolised and therefore are not retained in the tissue to cause ongoing damage [14]. Concomitant medications can influence infusion site adverse events. The antiemetic fosaprepitant when infused causes infusion site reactions but more so when given with anthracycline-containing regimens [15].

## Risk Factors

Risk factors can be characterised by those associated with the drugs being infused, characteristics of the patients and the experience and technique of the staff [2].

Drugs

- Vesicants
- Concentration
- pH
- Osmolality
- Duration of exposure

Patients

- Small fragile veins [16]
- Sclerosed veins from previous infusions
- Multiple prior venepunctures
- Predisposed to bleeding disorders
- Prior lymph node surgery in the limb and lymphoedema
- Concomitant illness compromising the circulation like peripheral vascular disease, neuropathy and diabetes [16, 17]

- Obesity
- Age (children and geriatrics)

Staff

- Inexperienced staff selecting poor venous access sites (dorsum of hand, antecubital fossa, joints) [13]
- Multiple punctures [18]
- Poorly secured cannulas
- Bolus or continuous infusion pump into a peripheral vein [13, 19, 20]

## Prevention

Prevention of extravasation is multifaceted. It involves education of the staff in techniques and patients to alert them to the symptoms so that they can report an extravasation as early as possible. The choice of equipment and veins for access is also vital.

- Training of staff in intravenous administration of drugs and in preventing, detecting and treating drug extravasations.
- Education of patients about the possibility of extravasation and symptoms to report immediately, as well as reinforcing the need for the limb to be immobile during the infusion.
- Choosing the correct venous access device including the correct diameter of flexible polyethylene or Teflon cannulas, avoiding metal cannulas. A central venous access device may be required if there are poor peripheral veins or the need for prolonged infusions. The device should be secured and a clear dressing used to allow early detection of extravasations.
- Selection of veins on the arm that are not fragile, or around joints where immobilisation will be difficult, is required. Arms with oedema or neuropathy should be avoided. If multiple attempts to access a vein are made, each attempt should be proximal to the last.
- The patient should be able to be monitored during the infusion.

## Symptoms

The symptoms have been most thoroughly studied for doxorubicin extravasation. Although some cases are asymptomatic, the initial symptom of extravasation is a burning sensation at the infusion site. This is due to a chemical cellulitis and may be accompanied by erythema and swelling [13, 21]. Hours later with vasodilatation, the initial swelling may subside, but the pain can increase, and oedema proximal to the infiltration can occur, which over days can become indurated [22, 23]. Early induration can be associated with later ulceration [22, 23].

The painful erythematous induration persists as capillaries thrombose, collagen breaks down and red cells extravasate [24]. Over weeks, ulceration can occur in the brown discoloured skin, and necrosis of the skin can be so severe that underlying tendons, vessels and nerves are exposed. These ulcers do not tend to spontaneously heal and can be a site for infection [25]. The ulcers can appear over 3–5 months. If there is no ulceration, the pain, skin discolouration and swelling subside over several months. However, pain and contractures can persist, and if the injury was close to a joint, permanent impairment of movement can result [21].

If extravasation occurs from central venous access devices, it may be more difficult to diagnose. Fluid may leak around the exit site along the subcutaneous tunnel, and this could cause pain and swelling of the chest wall. However, extravasation may just manifest itself as an ache in the neck or shoulder region on the side of the implanted device [26].

The National Cancer Institute of the National Institutes of Health in the United States has published the Common Terminology Criteria for Adverse Events which has a scale for grading extravasation injury from 1 to 5, where 1 and 2 are the erythema, pain and oedema, 3 introduces ulceration and the need for surgery and 4 is a life-threatening complication with 5 being death [27]. The severity of the damage depends on how far from physiological the pH and osmolality of the drug is; how much it irritates and vasoconstricts the

veins, thereby making cell death more likely; and of course how long it remains in the tissue [11].

## Differential Diagnosis

A flare reaction can occur with drugs including anthracyclines, cisplatin, fludarabine, asparaginase, bleomycin, trimetrexate and melphalan and is a hypersensitivity reaction with local urticaria or pain and redness along the vein which resolve within 1–2 h. This must be distinguished from an extravasation of these drugs [28, 29].

There is also a thrombophlebitic type of hypersensitivity reaction of the vessel if small amounts of drug infiltrate the cell wall during injection. It causes immediate pain and vasospasm and then swelling at the injection site. Subsequently the vein becomes hard and thrombosed with discolouration of the skin. However, no ulceration occurs [30].

Further, rarely, there is an allergic type of reaction with doxorubicin where only a small extravasation with initially few signs or symptoms progresses to cause extensive tissue damage [30].

## Management

Decisions about how to best treat extravasation injuries have come predominantly from animal studies, single case reports and multi-institutional case series rather than randomised clinical trials. However, some of the major oncological societies have published guidelines which should help standardise the approach.

### Guidelines

The American Society of Clinical Oncology (ASCO) published procedures for extravasation management in safety standards documents [31]. This was in collaboration with the Oncology Nursing Society (ONS) who also published a book on the prevention and management of extravasations [31]. ASCO in subsequent audits of compliance with its Quality Oncology Practice Initiative Certification Program highlighted the importance of following up-to-date extravasation guidelines [32]. Likewise, the European Society of Medical Oncology (ESMO) and the European Oncology Nursing Society (EONS) have published joint guidelines [2]. In addition, there are many institutional and health district guidelines such as the National Health Service north of England Cancer Network's Guidelines for the Management of Extravasation [33].

### General Measures for Managing Extravasations

There are specific antidotes recommended to deal with extravasations of particular agents, but there are also some general measures that apply to most situations.

- If an extravasation is suspected, the infusion should be stopped [34].
- A 5 mL syringe should be attached to the cannula, which is left in place so that an attempt can be made to slowly aspirate any of the extravasated drug that is present in the tissues [16].
- It is worthwhile to document the extent of the extravasation by marking the outline with a pen or photographing the site.
- Most recommend elevating and immobilising the limb [35] (e.g. in outpatients use a sling [16]).
- Apply the appropriate general or specific measure to limit the damage from the extravasated agent [36].

Here the literature has changed over the years. Historically injection of sodium chloride 0.9% into the area was recommended in an attempt to dilute the extravasated drug; however, this was based on little evidence, and there were concerns that this may spread the vesicant, and so this is no longer recommended [24, 37]. Similarly, the use of corticosteroids such as hydrocortisone was suggested for their anti-inflammatory effects. However, there may be little inflammation associated with extravasations; steroids can irritate the skin, and in animal models they worsened the damage if administered with vinca alkaloids; and any clinical benefits with doxorubicin extravasation were marginal at best [9, 37].

The two general measures that are important to discuss are the application of cold and heat.

## Cooling

One of the early interventions suggested for extravasation of vesicants such as anthracyclines was the application of ice to cool the areas of extravasation [38]. The rationale was to cause vasoconstriction so that the vesicant did not spread. The cellular uptake of doxorubicin was found to be reduced in mice as were cisplatin, carmustine and bleomycin [39, 40]. The efficacy of cooling when used as the only treatment of extravasation is limited, but it appeared to be synergistic with dimethyl sulphoxide [41–43]. Administration schedules varied widely, but they intermittently used ice packs for between 1 and 3 days [44]. The big advantage of this approach was its ready availability and lacked adverse effects.

In a series of 175 patients with extravasation injuries, initially treated without surgery, 34 subsequently required surgery, and 87% of those treated with ice needed no further treatment in comparison with 54% who had other mainly nonspecific antidotes instilled. However, 28% on the anthracycline extravasations required surgery [45].

However, a murine study suggested that cooling the skin may worsen the effects of vincristine extravasation [9]. For this agent, it appeared that heat and hyaluronidase to disperse the vincristine were a better strategy but with very little animal or human evidence of efficacy [9].

What has evolved in many guidelines is the application of ice for vesicants except the vinca alkaloids and heat for the vinca alkaloids [11]. Heat is also recommended for the non-vesicant drugs which are better treated by reducing the concentration locally.

Specific Antidotes

There are some agents that have been found to be useful for specific cytotoxic extravasations in addition to the general measures.

## DMSO

DMSO (dimethyl sulphoxide) is a solvent which penetrates tissues and acts as a free radical scavenger to remove anthracycline and mitomycin radicals from the tissues. DMSO also has anti-inflammatory and analgesic properties [46, 47].

In pig and rat models, DMSO had been shown to decrease doxorubicin skin ulcers [48–50]. Max Schwarz and I described the initial case of the use of DMSO in a patient who had had an extensive anthracycline extravasation into the antecubital fossa [51]. I then followed this with a prospective study in 20 patients with anthracycline extravasation injuries, and none of them progressed to ulceration [52]. We applied DMSO 99% solution to twice the area of redness from the extravasation and left the skin to dry without dressing. This was repeated every 6 h for 14 days, although subsequently 7 days have been used. Given that it had been estimated from previous observations that around 30% of anthracycline extravasation will ulcerate, this was considered an impressive result [45].

Subsequently, a large series of 144 patients was reported as being treated with DMSO for a range of extravasation injuries (doxorubicin or epirubicin [56], mitomycin [5], mitoxantrone [13], cisplatin [44], ifosfamide [14] and fluorouracil [5]), and only one patient, who had received epirubicin, ulcerated [43].

Side effects were a burning sensation on application and redness and mild scaling of the skin. Some patients reported a mild garlic breath odour [52].

DMSO is effective, but there was no commercial benefit promoting it in this situation, as it is low cost. However, it is effective and inexpensive and could at least be quite useful in extravasation kits in developing nations or elsewhere if available.

## Dexrazoxane

Dexrazoxane is a bisdioxopiperazine initially intravenously administered to reduce anthracycline cardiotoxicity [53]. It is thought to work both by chelating iron and reducing the oxidative stress of anthracycline/metal ion complexes and is a topoisomerase II inhibitor and a free radical scavenger [54, 55].

Preclinical studies showed that dexrazoxane administered systemically 3 h after anthracycline

extravasation in a mouse prevented wound formation [56]. The efficacy in the murine model was initially demonstrated for extravasations of doxorubicin, daunorubicin and idarubicin and more recently for related anthracyclines, amrubicin, mitoxantrone and liposomal pegylated doxorubicin [57].

In addition to case reports, there are two prospective single-arm clinical studies of dexrazoxane used for anthracycline extravasation. Only one patient from 54 in the trials required subsequent surgery, a success rate of over 98% [58]. The dexrazoxane was administered intravenously daily over 1–2 h for 3 days (1000, 1000 and 500 mg/m$^2$) and was started no later than 6 h after a histologically verified extravasation.

One impressive case report of the successful use of dexrazoxane was following a massive anthracycline chest wall extravasation from a port-a-cath. There was pain relief and slowing of necrosis, and it was combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) infiltrations along the borders [59]. There have also been retrospective practice reviews published [60].

Dexrazoxane is tolerated well. There can be local discomfort at the dexrazoxane infusion site, nausea, transient elevation of liver transaminases and neutropenia, but these latter can overlap with anthracycline toxicities. It is suggested that the dose be reduced in patients with renal impairment [61]. There was concern about a risk of longer-term toxicity when repeated doses (required for cardiotoxicity) were given to paediatric patients, and a higher incidence of second primary cancers was seen versus controls in two randomised studies. But this has not been a consistent observation in other series [62, 63].

For anthracycline extravasation, dexrazoxane has been recommended by the major guidelines, EONS (European Oncology Nursing Society), ONS (Oncology Nursing Society) ASCO (American Society of Clinical Oncology) and NCCN (National Comprehensive Cancer Network).

## Hyaluronidase

Hyaluronidase is an enzyme which by degrading the hyaluronic acid in connective tissue allows better absorption of an extravasated drug [64]. After animal studies that showed decreased ulcer size by up to 50%, a small study of seven patients with vinca alkaloid extravasation showed no ulceration [64, 65]. The difficulty is that hyaluronidase has to be injected either through the existing intravenous line or subcutaneously with 150–100 IU given as 0.2 mL injections [66]. It has been recommended to be used with extravasations of vinca alkaloids and taxanes but mainly on low-level qualitative evidence [67].

## Sodium Thiosulphate

This is an antidote generally recommended for use after mechlorethamine extravasation, although animal studies suggest it could also inactivate cisplatin [11, 68, 69]. It inactivates these drugs through nucleophilic reactions and is a free radical scavenger [70]. In murine studies, it was protective when injected intradermally after the extravasation, and this has been the method used for humans [69]. A study in 63 patients showed improved healing after extravasation of other drugs including anthracyclines, vincas and mitomycin C, but other antidotes which don't require intradermal administration are at least as effective [14]. So, it is recommended following mechlorethamine extravasation but with a low level of evidence [67].

## Newer Experimental Techniques

The growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), has been reported as accelerating wound healing after doxorubicin extravasation. It is postulated to work by stimulating cells such as endothelial cells [59, 71]. Corticosteroids have also been used clinically, but the variable benefit seems to relate to the degree of inflammatory response at the site of the extravasation [71].

There has been a case report of the use of allogeneic platelet gel applied topically to a skin flap necrosis every 5 days for 60 days following an extravasation injury after induction chemotherapy pre-transplant for myeloma. It was well tolerated and resulted in complete wound healing [72].

Advances in the formulation of chemotherapeutic agents have reduced the chance of extrava-

sation injury. Using nanoparticles as carriers using liposomes, micelles or polymers with vesicants such as anthracyclines, platinums, vinca alkaloids and taxanes reduces the ability for the drugs to diffuse into tissues [73, 74].

There are non-pharmacological approaches which have been tried for extravasation injuries. One is negative-pressure wound healing where a vacuum-assisted wound dressing applies a negative pressure which helps to aspirate some of the vesicant [75].

Using a hyperbaric oxygen chamber has been postulated to promote extravasation wound healing by the production of oxygen free radicals, and there is evidence in rats of improved healing after doxorubicin extravasation, compared to controls [76, 77].

## Surgery

In early recommendations for the management of extravasation injuries, early referral to a plastic surgeon for consideration of debriding the affected area was suggested [78]. However, because it was estimated that only one third of vesicant extravasations would progress to ulceration, currently referral occurs upon failure of conservative measures where the indications for surgery include persisting pain (for 10 days), full-thickness skin damage or chronic ulceration [79]. The procedure is to widely excise all of the damaged tissue and temporarily cover with a biological dressing. Once it is clear that there is a clean site, a split skin graft can be applied immediately but more often is delayed by a few days [79].

Attempts are being explored to image the extent of damage and to determine whether imaging can predict the extent of extravasation damage [10]. For example, indocyanine green angiography has been used to study blood flow in the extravasated area, and differences in perfusion have been correlated with those patients who required surgery and those in whom the damage was reversible, which were those showing hyperaemia [80].

Measuring extravasated tissue platinum concentrations by laser ablation inductively coupled mass spectroscopy revealed that the risk of tissue damage increased with increasing concentrations [81]. An emerging method for predicting extravasation is thermographic imaging during chemotherapy administration, where a fanlike pattern at the puncture site predicted subsequent induration [82]. Even simpler, when administering cytotoxics to children, an observation window at the peripheral intravenous catheter site has proven effective for early recognition of an extravasation [83].

## Central Extravasations

Central venous access devices reduced the rate of extravasation injury. In a series of 815 patients, this complication occurred in 0.24% patients [84]. Extravasation is usually into the neck or chest wall but can occur into the mediastinum or pleural spaces, and the risk is higher with a higher body mass index. Management is only guided by case reports. If detected early, a subcutaneous washout procedure (SWOP) can be useful to remove some of the extravasated drug and reduce the complication rate [85]. Cases have been reported of surgical washout being helpful for extravasations into the pleural space and video-assisted thoracoscopy being useful [86, 87]. Specific antidotes can be used, such as dexrazoxane for anthracycline extravasations, and analgesics or antibiotics may be required.

Another site where extravasation has been reported is with intravesical chemotherapy. In a case series, six of nine patients who presented with symptomatic extravasations required surgery following the extravasation [88].

## Extravasation Policy

Centres that deliver chemotherapy should create extravasation kits so that the antidotes, hot and cold packs, needles and cannulas, gauze and gloves are readily available for use as soon as the extravasation is detected [55]. Local extravasation procedures should be based on the evidence-based guidelines of societies like ASCO and ONS and ESMO and EONS [2, 31]. Continuous monitoring of cytotoxic infusions should occur, at least every 5–10 min.

It is important that all aspects of extravasation injuries are well documented with patient demographics, the drug being infused and the time of

the incident, a description of the site, the type of intravenous access, the signs and symptoms and a record of the extent of the injury (with photographs if practical) or at least drawing a line around the area involved. The steps taken to manage the extravasation injury should be carefully recorded. Given that randomised studies in this field are uncommon, these records will help refine policy.

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# Dermatologic Adverse Events

# 37

Azael Freites-Martinez and Mario E. Lacouture

## Introduction

Chemotherapy and radiation can potentially lead to numerous adverse events, affecting the skin and its adnexa (i.e., hair and nails) and mucous membranes. Frequent adverse events such as alopecia and mucositis associated with cytotoxic agents are well known to health-care providers. In addition, novel targeted chemotherapy agents may lead to dermatologic AEs that occur in the majority of patients and have been described only recently. This chapter will address skin and nail AEs induced by both conventional cytotoxic and recently introduced agents, as well as radiation-induced skin AEs. Underlying mechanisms and clinical presentation will be delineated, and management strategies will be emphasized. Anticancer therapy-induced alopecia is reviewed in greater detail separately in Chap. 38.

## Grading of Dermatologic Adverse Events

Accurate grading is critical to assess response to antitoxicity interventions and impact on patients [1]. The most widely used system is the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, published by the US Department of Health and Human Services on June 14, 2010 (Refer to Table 37.1). The most recent version takes into consideration the degree to which activities of daily living (ADLs) may be affected (e.g., instrumental and self-care for grades 2 and 3 of severity, respectively). It also modifies the percentages of body surface area (BSA) affected by acneiform (papulopustular) and maculopapular rash. In the 4.0 version, hand and foot skin reaction (HFSR) has been renamed to palmar-plantar erythrodysesthesia syndrome and takes into consideration hyperkeratotic lesions typically seen in HFSR to multikinase inhibitors. In addition, the actual version segregated nail toxicity into separate categories of nail discoloration, ridging, and loss. An updated version (CTCAE V5) is under review.

## Adverse Events of the Skin

### Acneiform (Papulopustular) Rash

Acneiform (also referred to as papulopustular) rash is the most common cutaneous adverse event of epidermal growth factor receptor inhibitors (EGFRIs) and can be seen in more than two-thirds of patients receiving any of these agents (although severe in only 5–10%) [2, 3]. Several EGFRIs are currently being used in the treatment

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**Table 37.1** Common terminology criteria for adverse events (CTCAE) version 4.03

| Skin and subcutaneous tissue disorders | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| Adverse events | 1 | 2 | 3 | 4 | 5 |
| Dry skin | Covering <10% BSA and no associated erythema or pruritus | Covering 10–30% BSA and associated with erythema or pruritus; limiting instrumental ADL | Covering >30% BSA and associated with pruritus; limiting self-care ADL | – | – |
| **Definition: A disorder characterized by flaky and dull skin; the pores are generally fine; the texture is a papery thin texture** | | | | | |
| Nail discoloration | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | – | – | – | – |
| **Definition: A disorder characterized by a change in the color of the nail plate** | | | | | |
| Nail loss | Asymptomatic separation of the nail bed from the nail plate or nail loss | Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL | – | – | – |
| **Definition: A disorder characterized by loss of all or a portion of the nail** | | | | | |
| Nail ridging | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | – | – | – | – |
| **Definition: A disorder characterized by vertical or horizontal ridges on the nails** | | | | | |
| Palmar-plantar erythrodysesthesia syndrome | Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain | Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL | Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL | – | – |
| **Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet** | | | | | |
| Photosensitivity | Painless erythema and erythema covering <10% BSA | Tender erythema covering 10–30% BSA | Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs) | Life-threatening consequences; urgent intervention indicated | Death |
| **Definition: A disorder characterized by an increase in sensitivity of the skin to light** | | | | | |

| Skin and subcutaneous tissue disorders | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| Adverse events | 1 | 2 | 3 | 4 | 5 |
| Pruritus | Mild or localized; topical intervention indicated | Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL | Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated | – | – |
| **Definition: A disorder characterized by an intense itching sensation** | | | | | |
| Rash acneiform | Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness | Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL | Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated | Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences | Death |
| **Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest, and back** | | | | | |
| Rash maculopapular | Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness) | Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL | Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL | – | – |
| **Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus** | | | | | |
| Skin hyperpigmentation | Hyperpigmentation covering <10% BSA; no psychosocial impact | Hyperpigmentation covering >10% BSA; associated psychosocial impact | – | – | – |
| **Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition** | | | | | |
| Skin hypopigmentation | Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact | Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact | – | – | – |

(continued)

**Table 37.1** (continued)

| Skin and subcutaneous tissue disorders | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| Adverse events | 1 | 2 | 3 | 4 | 5 |
| **Definition: A disorder characterized by loss of skin pigment** | | | | | |
| Skin induration | Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up) | Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL | Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self-care ADL | Generalized; associated with signs or symptoms of impaired breathing or feeding | Death |
| **Definition: A disorder characterized by an area of hardness in the skin** | | | | | |

*ADL* activities of daily living, *BSA* body surface area, *NSAIDs* nonsteroidal anti-inflammatory drugs
Source: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 10.06.16

of cancer, including the small molecule tyrosine kinase inhibitors (e.g., gefitinib, erlotinib, lapatinib, afatinib, osimertinib) and the monoclonal antibodies cetuximab, necitumumab, and panitumumab. Lapatinib is a dual inhibitor of the epidermal growth factor receptor (EGFR) and Her2, which has a lower incidence of dermatologic adverse events. In addition to EGFRIs, the MEK inhibitors (MEKIs) trametinib and cobimetinib are also associated with acneiform rash [4].

Epidermal growth factor receptors (EGFRs) play a critical role in normal skin physiology, development, and integrity, by regulating keratinocyte proliferation, differentiation, and survival. Direct inhibition of EGFRs is believed to underlie the pathophysiology of rash. Exposure of epithelial cells to these drugs leads to increased synthesis of a variety of chemokines which recruit inflammatory cells such as leukocytes and neutrophils, generating an inflammatory response. The UV radiation may be related to the development or severity of acneiform rash, especially for the frequent localization in sun-exposed areas such as the face, scalp, "V" area of the neck, and upper chest [5]. The acneiform rash is characterized by papules and pustules which are associated with pruritus and pain and are usually distributed in the seborrheic areas, such as the scalp and face (Fig. 37.1). The onset of the rash is during the first 2 weeks of treatment [6]. It is noteworthy that this acneiform rash is not acne but a separate entity, since no comedones are seen and the histopathology differs [3]. There is a correlation between both the occurrence and severity of the rash with the tumor response and overall survival, underscoring the need to treat patients who develop rash so that they can continue receiving EGFRI therapy [1].

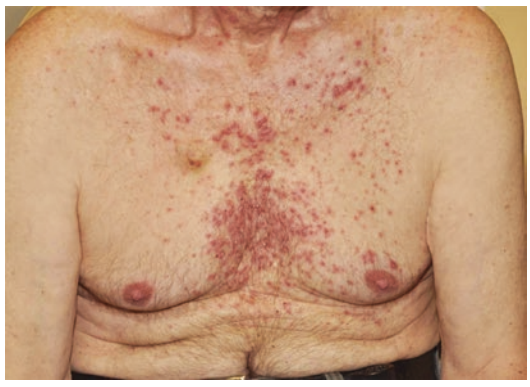

**Fig. 37.1** Acneiform rash

Although most of the cases are mild to moderate, up to 32% of providers discontinue and up to 76% hold treatment, which may affect clinical outcome [7]. It is important to notify patients about the potential adverse event and their signs and symptoms prior to initiation of therapy. Lifestyle modifications such as taking baths in tepid water as opposed to hot showers, using emollients that are alcohol-free to avoid skin dryness, avoidance of sun, and using other sun-protective methods such as sunscreen are recommended to reduce skin AEs [6]. There have been several randomized controlled trials (RCTs) to evaluate prophylactic management of EGFRI-induced skin AEs. The Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) compared preemptive treatment with a skin moisturizer, sunscreen, 1% hydrocortisone cream, and doxycycline 100 mg twice daily versus reactive treatment which was decided by each separate investigator involved in the study. Not only did preemptive treatment diminish the occurrence of grade 2 or greater rash by more than 50%, but it also significantly delayed the time period to the first manifestation of any grade 2 or greater skin toxicity. In addition, a similar effect was seen with severe (grade 3) skin toxicity, where the time to onset was significantly delayed [8]. Another study examined the benefits of prophylactic oral minocycline as opposed to placebo in patients with metastatic colon cancer prior to cetuximab therapy [9], showing a decrease in both the total facial lesion count and occurrence of moderate to severe pruritus in the treatment arm. A similar study used oral tetracycline 500 mg bid as a prophylactic agent in patients prior to EGFRI treatment. Tetracycline did not possess the ability to prevent the rash. However, it decreased grade 2 rash from 55% to 17% [10]. A recent study showed that topical dapsone 5% applied twice daily in conjunction with oral antibiotics was able to reduce rash by >87% [11].

Whereas prophylactic treatment is recommended, given the high incidence of rash, reactive management may be necessary in some cases and is superior to no treatment [12]. Multiple treatment algorithms have been designed over the years in an attempt to reduce and/or eliminate the rash and improve quality of life (QOL) (see Fig. 37.2 for treatment algorithm).

The pathophysiology of skin toxicity induced by EGFRI does not appear to involve an underlying bacterial infection but an apparent benefit from oral semisynthetic tetracycline antibiotics may be secondary to their anti-inflammatory properties [7]. Nevertheless, superinfection can occur in up to 38% of patients and should be recognized and treated. For example, signs like a sudden change in the appearance of the lesions, oozing of fluid, and yellow and/or brown crusting may suggest an underlying superinfection, which is of bacterial origin in the majority of cases.

## Maculopapular Rash (Morbilliform Eruption)

A rash characterized by pink to red macules and/or papules that blanch with pressure, the so-called morbilliform rash, is one of the most common skin AEs associated with oral or systemic agents [13]. Some of the agents that can trigger this type of skin rash include taxanes, asparaginase, gemcitabine, pemetrexed, liposomal doxorubicin, topotecan, vemurafenib, imatinib, dasatinib, and the monoclonal antibodies directed against CTLA-4 and the programmed cell death protein 1 (PD-1) or its ligand (PD-L1) [13, 14]. The rash typically presents with erythematous macules, papules, and rarely bullae that predominantly involve the trunk and proximal extremities. Acral sites are most often spared, although the face, palms, and soles may be involved. The treatment typically includes topical and/or oral corticosteroids and antihistamines which could

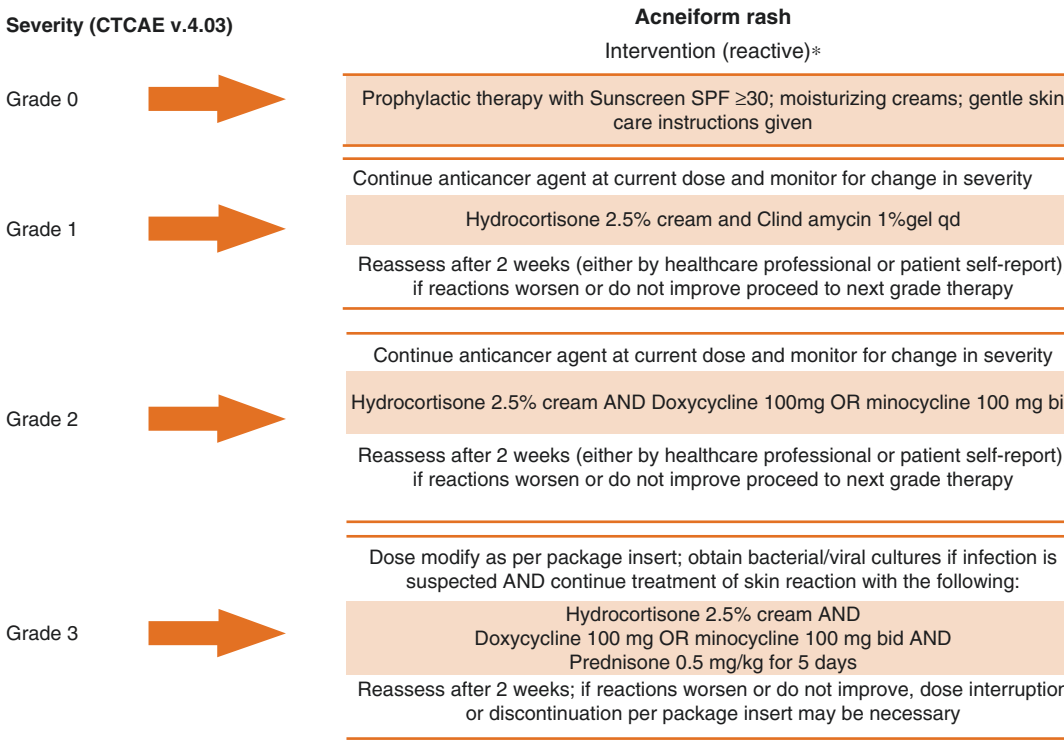


**Fig. 37.2** Treatment algorithm for acneiform rash. *It is recommended that patients treated with EGFR inhibitors begin prophylactic rash therapy with doxycycline 100 mg bid or minocycline 100 mg daily and a low potency topical steroid bid for first 6 weeks of therapy

be used as premedication in some cases [13]. It is important to note that this type of rash needs to be carefully observed for progression to severe reactions such as DRESS or SJS/TEN [15]. In cancer patients, multiple other medicines are usually being administered, therefore the culprit should be carefully investigated and attribution established. NSAIDs, antibiotics, and anticonvulsants are other frequent culprits. Treatment algorithms can be found in Fig. 37.3.

## Hand–Foot Skin Reaction

Despite striking similarities to hand and foot syndrome (HFS) as seen with multiple conventional cytotoxic chemotherapy agents such as 5-fluorouracil, cytarabine, capecitabine, and doxorubicin, a distinction should be made between HFS to cytotoxic agents and hand–foot skin reaction (HFSR) to multitargeted kinase inhibitors (MKIs). They share qualities such as a palmoplantar distribution, dose dependency, and pain, but they differ in clinical as well as histopathological features [16]. HFSR usually manifests itself within the first 2–4 weeks after therapy initiation. Clinically, HFSR presents with erythema, paresthesias, or dysesthesias, involving the palms and soles with blisters followed by thick hyperkeratotic, tender lesions. Lesions commonly occur in the regions of friction and/or trauma, arising on the flexural surface of interphalangeal joints, distal phalanges, or heels and can significantly influence weight-bearing ability and mobility (Fig. 37.4). This is in contrast to diffuse regions of erythema and edema seen in HFS [16–18].

MKIs, such as sunitinib, sorafenib, axitinib, regorafenib, and pazopanib, have been found to be associated with HFSR along with multiple other cutaneous adverse event including a rash, xerosis, alopecia, and pigmentary changes [18]. All of these agents have been found to be associated with significantly increased risk of HFSR in patients with multiple solid tumors. In addition to MKIs, cabozantinib, which targets multiple

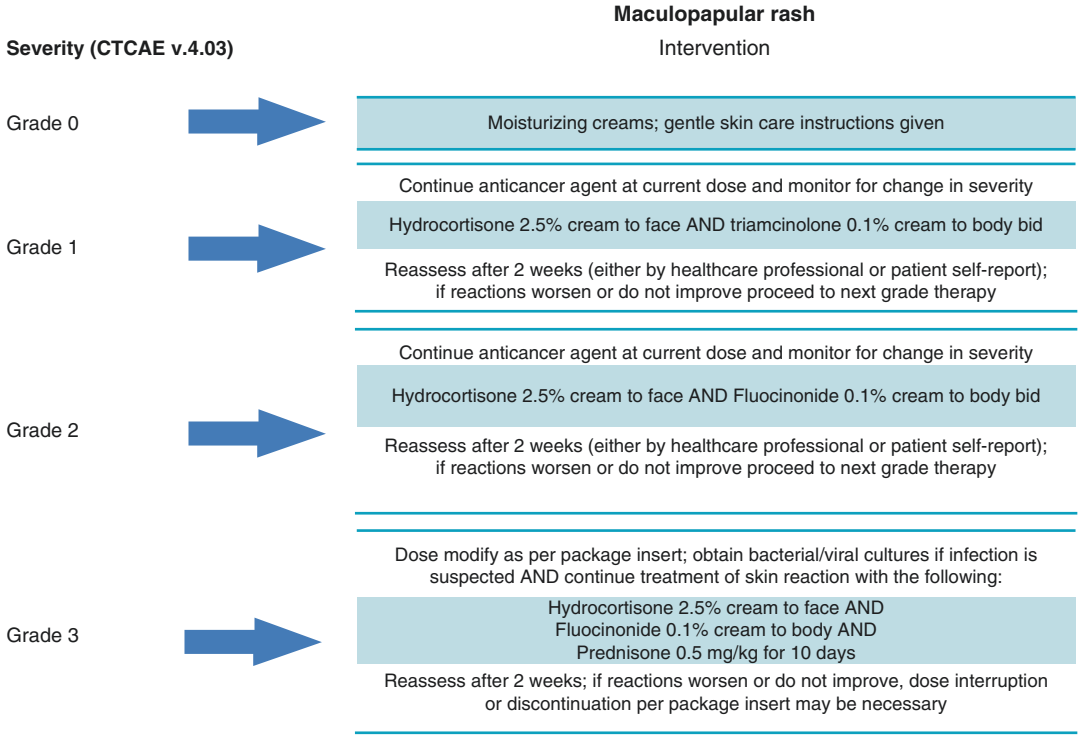


**Fig. 37.3** Treatment algorithm for maculopapular rash

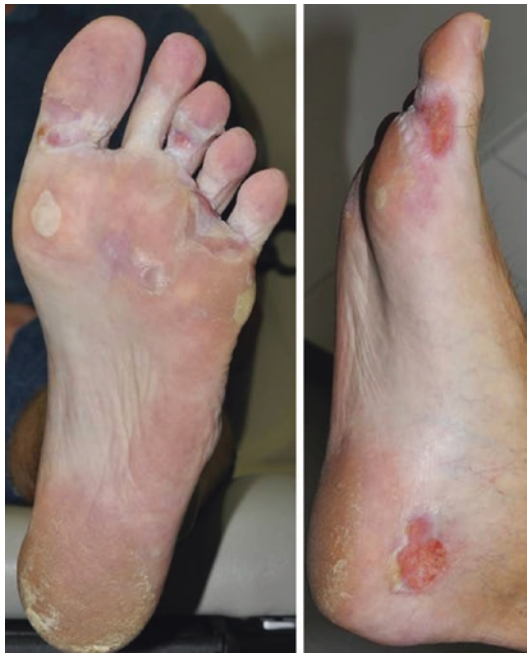

**Fig. 37.4** Hand–foot skin reaction

receptors (e.g., vascular endothelial growth factor receptor and tyrosine kinase), has an overall incidence of 35.3% for all grades of HFSR [19].

The peripheral vasoconstriction in combination with repeated subclinical daily friction and trauma can result in the characteristic palmoplantar affectation [16]. HFSR by itself is not life-threatening, but by leading to either reduction or interruption of treatment, it can potentially compromise the efficacy of the agent. Certain recommendations for treatment have been proposed. Preemptive strategy is a crucial part of the management of HFSR (Table 37.2). Certain prophylactic measures such as removing calluses and orthotics where indicated have been shown to avert the first and recurring episodes of HFSR [18, 20]. Once HFSR develops, therapy is given based on the degree of the severity. These proposed guidelines arise from expert opinions of clinicians commonly treating this type of skin AE [17] (Fig. 37.5). To diminish trauma to lesions of HFSR, cotton socks or gloves, gel inserts, and soft shoes or memory foam slippers can be used [20]. Urea is a keratolytic agent able to loosen up the horny layer of the skin, thereby softening the

**Table 37.2** Preemptive strategies for HFSR

| |
|---|
| • Full-body exam to look for hyperkeratotic regions on palms and soles and removal of calluses |
| • Avoiding hot water when taking shower, bath, or dishwashing |
| • Avoidance of trauma and friction during the first 2–4 weeks |
| • Avoidance of vigorous exercise, especially during the first month of therapy |
| • Avoidance of tight-fitting shoes and evaluation by orthotist if necessary |
| • Avoiding excessive pressure when applying lotions |
| • Utilization of moisturizing creams containing keratolytics such as ammonium lactate (both prior and during therapy) or urea |
| • Wear thick cotton gloves and/or socks and slippers |

Data from Lacouture et al. [17]

areas of thickening. Tazarotene, used in psoriasis patients, also has an effect of decreasing epidermal thickness. These agents can be used to treat hyperkeratotic lesions and should be applied to affected areas only in order to avoid irritation to normal surrounding skin [16, 17].

## Hand–Foot Syndrome (Palmoplantar Erythrodysesthesia)

Hand–foot syndrome (HFS), also known as palmar–plantar erythrodysesthesia, is a skin AE associated with several cytotoxic chemotherapeutic agents. However, common culprits include 5-flourouracil, its prodrug capecitabine, doxorubicin, liposomal doxorubicin, docetaxel, and cytarabine [21]. The incidence of HFS varies depending on the offending agent [21, 22]. Pegylated liposomal doxorubicin (PLD) has an improved adverse events profile as compared to its predecessor, with the exception of HFS, which appears with higher frequency [23]. It should be noted that even a single drug can lead to different frequencies of HFS depending on the modality of administration. Such a case is with 5-flourouracil, whereby continuous infusion (CI) gives rise to a higher incidence as compared to a bolus infusion. A meta-analysis revealed that 34% of patients developed HFS if the drug was administered by CI versus 13% if treated by 5-flourouracil bolus [24]. In the case of PLD, it was shown

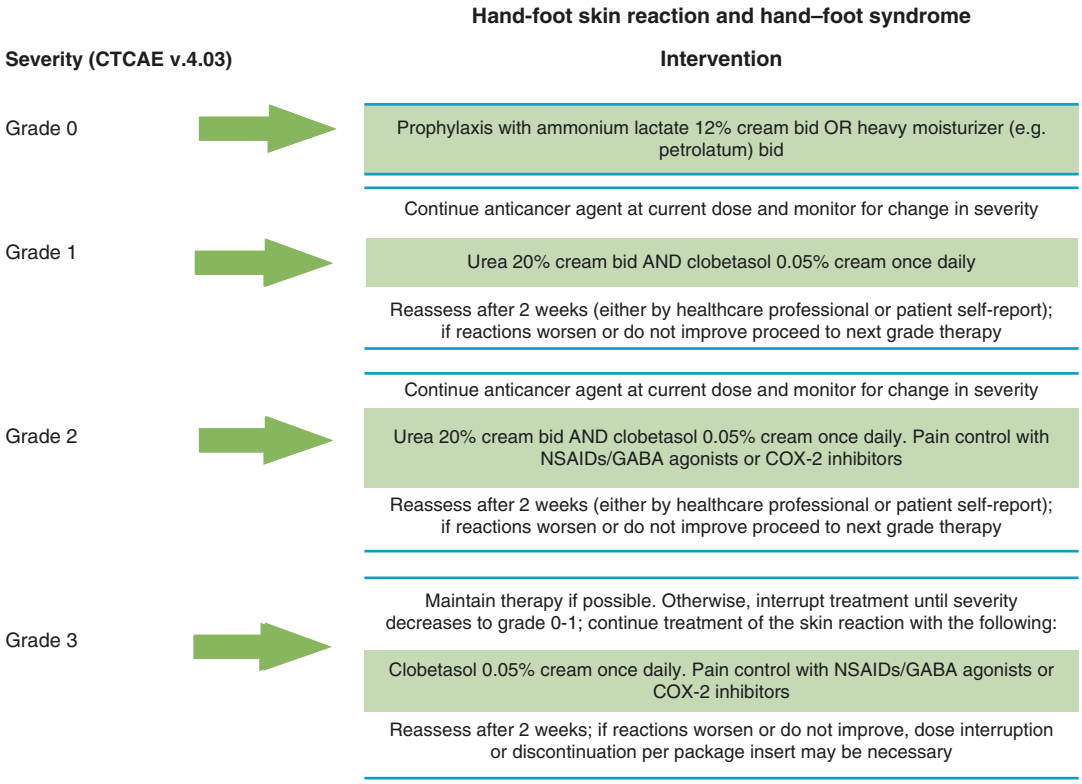


**Fig. 37.5** Treatment algorithm for hand–foot skin reaction and hand–foot syndrome

that the reaction is more likely to occur after repeated administrations of the drug. While most of the HFS cases are mild, it is the most prevalent cumulative AE in patients treated with PLD and is seen in up to 45% of the patients [16]. In addition to 5-flourouracil and PLD, a pooled analysis that included various molecularly targeted therapies (e.g., alemtuzumab, rituximab, imatinib, dasatinib, erlotinib, vandetanib, sorafenib, and cabozantinib) showed an overall incidence of 7% for all grades of HFS in pediatric patients [25].

The onset of symptoms is variable and ranges anywhere from a few days to up to 10 months after the initiation of therapy [26]. The characteristic initial manifestation is with paresthesias, followed by the appearance of symmetrical painful erythema and edema involving the palms and soles after 3–4 days (Fig. 37.6). Without appropriate interventions the lesions can blister, desquamate, form crusts, ulcerate, or even progress to epidermal necrosis [23].

The histologic findings of HFS are nonspecific, and its pathophysiology is not fully understood. Extravasation with accumulation of the drug in the stratum corneum has been hypothesized as a potential mechanism of toxicity [23, 26].

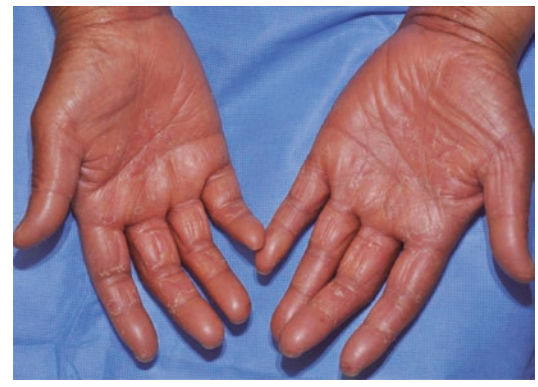

**Fig. 37.6** Hand–foot syndrome

One of the most important aspects in the management of these patients is their education and surveillance to assist in early detection of signs and symptoms. Certain lifestyle modifications have been recommended including avoiding hot showers and baths that lead to vasodilatation, tight-fitting clothing, and significant friction or pressure. In addition, avoidance of vigorous exercise, and keeping lower extremities elevated when appropriate, is recommended as well [26]. Topical therapy using emollients and moisturizing creams can be used to alleviate the symptoms of HFS [23].

Studies suggesting symptomatic improvement from pyridoxine led to interest in the use of this vitamin as a preventive agent. However, due to the lack of adequate clinical data and a recent negative trial, pyridoxine is not recommended for routine clinical use in cases of capecitabine-induced HFS [27]. Similar to oral pyridoxine, the use of corticosteroids in the management of HFS is not straightforward, and no large RCTs were conducted so far to examine its use. The effectiveness of oral dexamethasone for HFS prevention was evaluated in a prospective case study conducted in patients receiving PLD. None of the patients treated with dexamethasone required PLD dosage adjustment for grade 2 or higher HFS, while each of the three patients who did not receive dexamethasone required treatment delay or dose reduction for grade 2 or higher HFS [26]. In addition, successful use of oral prednisone in alleviating patient's pain and swelling in the setting of HFS induced by cytarabine has been described [28]. Local cooling of extremities during therapy by applying ice packs to the wrists and ankles may help by decreasing blood flow to the hands and feet. Unfortunately, similar to the use of pyridoxine and steroids, the lack of adequate evidence prevents this method from being recommended for wide use [26]. There is a hypothesis that HFS is a type of inflammation limited to the hands and feet and can be prevented with a COX-2 inhibitor (celecoxib). An RCT have shown that celecoxib can be used effectively and safely to prevent capecitabine-related HFS. All patients received celecoxib 200 mg twice a day for 14 days per cycle. This therapy should be used on patients with no important history of cardiovascular disease [29].

In the case of PLD, RCTs have been conducted in order to investigate the potential benefit of dose intensity modification to reduce the associated AE. The available evidence suggests that PLD treatment schedule with 40 mg/m$^2$ every 4 weeks reduces HFS incidence without compromising efficacy [6, 26].

Overall, due to the lack of adequate supporting evidence, the recommendation for management of HFS heavily relies on working closely with the patients and educating them about the importance of recognizing early signs and symptoms in order to implement individualized interventions on time. In addition, prevention and supportive measures are an integral component as well [26]. For treatment approaches and prophylactic measures, refer to Fig. 37.5.

## Stevens–Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)

SJS and TEN represent rare, severe, and potentially fatal mucocutaneous blistering reactions that form a spectrum sharing the same underlying disease process [30]. These two adverse events are categorized according to the degree of epidermal detachment, expressed as the percentage of the total body surface area (TBSA) affected [31]. With the involvement of less than 10% of TBSA, it falls into the category of SJS; greater than 30% of TBSA, TEN is used, whereas SJS/TEN overlap affects between 10% and 30% of TBSA. It should be noted that SJS/TEN are commonly recognized as separate diseases from erythema multiforme [30]. An overwhelming majority of TEN cases are associated with drug exposure. In cases of SJS, drugs are still the predominant cause, with other triggers including infections, vaccinations, and GVHD [30, 32]. Overall, allopurinol is the most common drug to trigger SJS/TEN followed by sulfonamide antibiotics, NSAIDs, and anticonvulsants [30]. Several different families of chemotherapy agents such as monoclonal antibodies, antimetabolites, and alkylating agents can be associated with both SJS and TEN [33].

Depending on the degree of epidermal detachment, the mortality ranges between 1% and 5% in SJS and up to 35% in cases of TEN [32]. The pathophysiology underlying the development of SJS/TEN is thought to involve an immune response to drugs or drug metabolites that may be the initial trigger in the cascade of events with a variety of immune cells (cytotoxic CD8+T, CD4+T cells, and macrophages) that may play a role. Fas ligand and perforin/granzyme B pathways may account for keratinocyte necrosis that is seen in SJS/TEN [30]. In addition, other suggested immune pathways include HLA-B susceptibility, especially in Asian patients [34].

SJS/TEN are characterized by the epidermal detachment which distinguishes them from the previously described morbilliform drug eruption. The typical skin lesions in SJS/TEN are diffuse, flat, atypical target lesions or purpuric macules, often with a necrotic center [30, 32]. There is epidermal detachment from the underlying dermis resulting in flaccid blisters and superficial erosions [32]. Different mucosal sites can be affected to a variable degree including the eyes, oral mucosa, tracheobronchial tree, and genitalia. Although the diagnosis heavily relies on the clinical presentation, it should be confirmed with the biopsy that typically shows diffuse keratinocyte apoptosis and full-thickness epidermal necrosis [30].

There are several aspects that need to be considered for optimal management of SJS/TEN. Since a variety of medications appear to be a culprit, early recognition of these entities is essential for timely removal of the offending drug which has been shown to improve the prognosis [35]. Furthermore, patients with these conditions require immediate in-hospital assessment for diagnosis confirmation and evaluation of severity and referral to the most appropriate health-care setting (e.g., intensive care unit, burn unit), to initiate supportive care and specific treatments [36].

Corticosteroid use is contraindicated in patients with extensive skin detachment. Theoretically, corticosteroids increase the risk of sepsis, prolonged the period of disease progression and protein catabolism, and decrease the rate of epithelialization [36, 37]. There is no high quality evidence supporting the use of IVIG in SJS/TEN. However, it is often considered for treatment due to available data, clinical experience, and relatively minimal AEs. Overall, decreased mortality is seen when the total dose of IVIG is greater than 2 g/kg [32]. According to a recent European guideline, IVIG should be administered as soon as possible after confirming the diagnosis of TEN at a recommended total dose of 3 g/kg of the body weight over the period of 2–5 days [38].

## Seborrheic Dermatitis-Like Rash

Multikinase inhibitors (MKIs), such as sorafenib and sunitinib, have been associated with a rash closely resembling seborrheic dermatitis [17]. Scalp dysesthesia may occur simultaneously or prior to the onset of the rash. The rash affecting the scalp and the medial aspect of the face is usually seen a couple weeks after initiation of treatment. For symptomatic patients, treatment with 2% ketoconazole or topical steroids (hydrocortisone 2.5% cream) can be attempted [39].

## Intertrigo-Like Rash

An intertriginous (intertrigo-like) eruption, characterized by erythematous patches that may be painful or pruritic and involves areas of skin folds such as an axillae and groin or regions that are exposed to, can be seen with pegylated doxorubicin (PDL). Topical corticosteroids such as triamcinolone and hydrocortisone cream in combination with silver sulfadiazine 1% cream may be useful in diminishing the rash and frequently occurring secondary infections. Maintaining good hygiene and keeping the involved areas dry may be of benefit. Thick barrier creams (zinc oxide 20–30%) can be used to diminish the friction [15, 40].

## Eccrine Squamous Syringometaplasia

A variety of agents including but not limited to cytarabine, anthracyclines, cisplatin, cyclophosphamide, carmustine, methotrexate, melphalan, busulphan, and the tyrosine kinase inhibitors imatinib and sunitinib have been associated with the condition, eccrine squamous syringometaplasia (ESS) [41]. The manifestation of the ESS may be characterized by the erythematous macules, papules, vesicles, or plaques that are either generalized or localized in distribution [41, 42]. The onset of the lesions may occur several days to 5 weeks following the initiation of therapy, and the resolution is spontaneous within approximately 4 weeks without scarring [41, 42]. It is hypothesized to be due to a direct toxicity of a chemotherapeutic agent on the eccrine (sweat) glands [42].

## Neutrophilic Eccrine Hidradenitis

Neutrophilic eccrine hidradenitis (NEH) may present similar to ESS with erythematous maculopapules or plaques involving the head, neck, trunk, and extremities with the usual onset approximately within 1–2 weeks after initiation of the chemotherapy. Pustules may be seen as well. Fever usually accompanies the rash [42]. The periorbital area or the ear may be potentially affected, clinically resembling cellulitis [41]. Similar to ESS, disappearance of the rash is expected without a specific treatment or subsequent hyperpigmentation and scarring. The drugs most commonly associated with NEH include chlorambucil, lomustine, daunorubicin, doxorubicin, cytarabine, cisplatin, vincristine, bleomycin, and mitoxantrone. The removal of the offending drug will result in self-resolution. To alleviate the pain that may accompany the rash, corticosteroids may be attempted. Reexposure to the drug may induce the same rash [41, 42].

## Cutaneous Eruption of Lymphocyte Recovery

Eruption of lymphocyte recovery (ELR) is thought to occur in response to autologous hematopoietic stem cell transplants (HSCT) and is limited to skin. It is also considered a variant of autologous graft-versus-host disease (GVHD) that lacks involvement of other system organs which may not have been reported or recognized [43]. The typical manifestation of the lesions takes place approximately within 3 weeks posttransplant. It presents with an erythematous maculopapular rash which may lead to erythroderma. Patients may commonly complain of pruritus with occasional eczematous lesions. Fever may follow the eruption of the rash [41].

## Graft-Versus-Host Disease

Multiple organ systems can be affected by graft-versus-host disease (GVHD), but the skin is typically the first and most commonly involved organ [44]. As opposed to a previously used scheme of categorizing GVHD into acute (<100 days) and chronic (>100 days) diseases, the US National Institutes of Health (NIH) modified the classification by adding a late-onset acute GVHD in which symptoms appear after 100 days posttransplant. Similarly, a category of an overlap syndrome was created with features of both acute and chronic GVHD regardless of time of onset [44]. The underlying pathophysiology of acute GVHD is believed to result from activation of antigen-presenting cells (APC) by pre-transplant treatments such as total body irradiation, followed by activation of donor T cells with their proliferation and migration resulting in subsequent organ tissue damage [44, 45]. The etiology of chronic GVHD is less understood but appears to be related to an immune-mediated process [45].

A maculopapular rash accompanied by fever and occurring within 2 weeks of transplant is referred by some authorities as a hyperacute stage of acute GVHD [45]. The typical acute GVHD manifests between the second and sixth

week, with an abrupt onset of pruritic, symmetric morbilliform rash that can become diffuse. With progression, bullae and desquamation can occur, mimicking TEN [45]. Chronic GVHD has various manifestations and can result in dyspigmentation, new onset alopecia, poikiloderma, lichen planus-like lesions, or sclerodermoid changes [44]. Prevention of GVHD focused on immunosuppression of the donor cells, either pharmacologically (such as calcineurin inhibitors, cyclosporine, methotrexate, or tacrolimus) or via T cell depletion. However, there is no agreed upon standard regimen, and clinical practice varies by institution [46].

Topical emollients should be used in both acute and chronic xerotic GVHD. With acute GVHD affecting less than 50% of BSA, topical potent corticosteroids or tacrolimus should be employed. With more severe skin and other organ involvement, high doses of systemic corticosteroids and other immunosuppressives are the primary therapy [45]. Steroid-resistant acute GVHD is challenging to treat. Extracorporeal photopheresis has been shown in a phase II study to enhance the recovery from a steroid-refractory GVHD [44].

Chronic GVHD is also more difficult to manage, and a combination of systemic corticosteroids with or without calcineurin inhibitors (e.g., cyclosporin, tacrolimus) remains the primary strategy. The use of topical steroids and tacrolimus in chronic GVHD is not well-established [45]. Utilization of extracorporeal photopheresis, especially in cutaneous GVHD, has been found to be beneficial in chronic GVHD. Resistant chronic GVHD limited to skin can be attempted to be managed with PUVA therapy [45]. A review suggests that rituximab, a monoclonal antibody targeting the CD20 molecule on B cells, may be a useful alternative option in the treatment of steroid-refractory chronic GVHD, by targeting various antibodies thought to play a role in pathogenesis of chronic GVHD [47]. Ruxolitinib, a selective Janus Kinase (JAK) 1/2 inhibitor, was used to treat six patients with steroid-refractory GVHD. All patients responded positively with respect to clinical GVHD symptoms and serum levels of proinflammatory cytokines [48].

## Sclerodermiform Dermatitis

A sclerodermiform dermatitis predominately involving the lower extremities is a rare adverse event in which the taxanes (docetaxel, paclitaxel) appear to be the main culprit, with some reported cases induced by gemcitabine. The rash manifests as flesh-colored to brown plaques that may have a shiny appearance. Swelling and edema of the lower extremities precedes the onset of the skin induration and fibrosis. Usually, the serologies are negative for connective tissue disease [41, 49]. Skin induration is seen after several cycles of chemotherapy, but the reversal of the fibrosis can be expected after the discontinuation of the offending drug or use of high-potency topical corticosteroids [15, 21].

## Dermatomyositis-Like Rash

Hydroxyurea has been associated with the dermatomyositis-like rash which is characterized by the erythematous to violaceous periorbital plaques. Additionally, scaly plaques involving the chest, arms, metacarpophalangeal, and interphalangeal joints are seen. No involvement of the muscles and no markers of muscle damage are present. The removal of the offending agent is followed by resolution in anywhere between 10 and 18 months. Sun avoidance and sunscreen use are recommended, along with topical or oral corticosteroids [15].

## Radiation Recall

Radiation recall is characterized by a rash that is caused by chemotherapy and manifests itself in the areas of previous radiotherapy. The underlying etiology is unclear, and some propose that it may be the result of the combination of chemotherapy-induced free radicals and the genetic defects induced by prior radiation treatments [19, 29]. A variety of drugs have been associated with these reactions (Table 37.3). The latency period for the radiation recall is wide and ranges any-

**Table 37.3** Chemotherapeutic agents associated with radiation recall

| | |
|---|---|
| Methotrexate | Hydroxyurea |
| Etoposide | Melphalan |
| Doxorubicin | Capecitabine |
| Cytarabine | Cyclophosphamide |
| Dactinomycin | Gemcitabine |
| Bleomycin | Pemetrexed |
| Etoposide | Oxaliplatin |
| Paclitaxel | Vinblastine |
| 5-fluorouracil | Docetaxel |
| Lomustine | Idarubicin |

Payne et al. [49] and Heidary et al. [21]

where from a period of several months to years [15, 42].

Conversely, EGFRI-induced rash may be absent in the areas of previous irradiation, which may be explained by the lack of cells that express EGFRs as a result of prior radiation treatment. On the other hand, EGFRI can behave as sensitizers, leading to a more pronounced skin reaction in cases where radiation treatment is administered simultaneously [50]. Topical corticosteroids may be used to diminish the inflammation. Overall, termination of therapy and wound care is helpful in healing the area of involvement [15].

## Radiation Dermatitis and Enhancement

One of the most prevalent adverse events of radiotherapy is an acute skin reaction, which occurs within hours to weeks after radiation exposure [51] and results from immediate structural tissue damage and generation of short-lived free radicals, due to direct tissue toxicity and involvement of inflammatory cells [52]. The presentation of radiation dermatitis ranges from erythema and dry desquamation to moist desquamation and ulceration with increasing severity [53]. Typically presenting within the first several weeks, it is mild to moderate in intensity in the majority of patients [52]. Two prospective double-blind RCTs demonstrated the potential beneficial effect of high-potency topically applied corticosteroids when used in a prophylactic manner. Both studies utilized the topical steroids starting at the beginning of radiotherapy until 2–3 weeks after the completion of treatment and resulting in diminished clinical manifestation of radiation dermatitis [54, 55]. The use of topical antibiotics should be restricted to cases of skin breakdown or suspected superinfection. The severity of rare grade 4 reactions mandates specialized wound care and requires attention from a wound specialist [52]. For a treatment algorithm, refer to Fig. 37.7.

When chemotherapy agents are administered either at the same time or within 1 week, they can potentiate the toxicity of the radiation therapy. This phenomenon is called radiation enhancement and can be induced by methotrexate, hydroxyurea, fluorouracil, doxorubicin, dactinomycin, bleomycin, and cisplatin [41]. In addition to conventional cytotoxic agents, there appears to be a synergistic effect of EGFRI and radiation with an increased risk of high-grade radiation dermatitis and a rash [56].

## Photosensitivity

A variety of chemotherapy agents have been associated with photosensitive reactions upon exposure to ultraviolet light. These broadly can be divided into a photoallergic and phototoxic reactions. Photoallergic reactions are less common, require prior sensitization, and are immunologically mediated. On the other hand, phototoxicity is much more common and is not immunologically mediated. Photoallergy shares similarities with eczematous dermatitis and is predominately limited to sun-exposed skin. The lesions can evolve from erythema and vesiculation to scaling and lichenification. Phototoxic lesions in sun-exposed areas are similar to severe sunburn, characterized by erythema and edema that with increasing severity can progress to vesicles, desquamation, and blistering. Patients may experience pain and burning sensations [57] (Fig. 37.8). Photosensitive reactions have been seen with a variety of agents (Table 37.4). In general, these reactions are phototoxic in nature [41]. Patients should be educated about the potential sensitivity to sun and encouraged to avoid

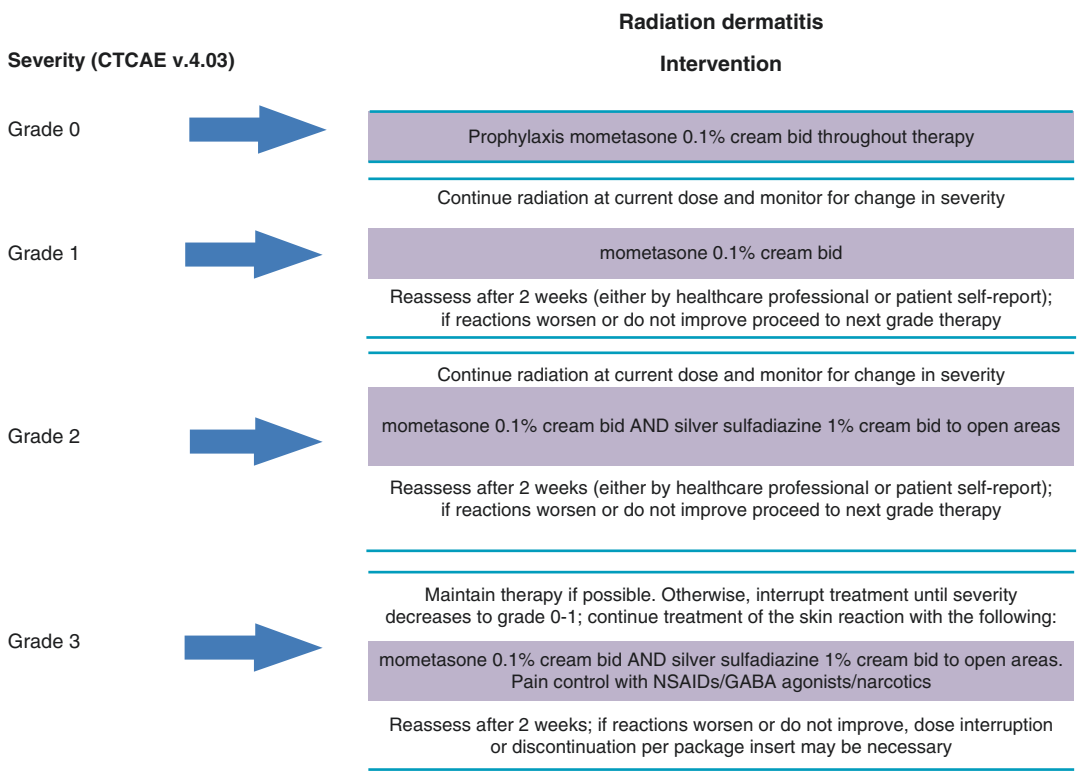


**Fig. 37.7** Treatment algorithm for radiation dermatitis

exposure. In addition, photoprotective methods should be utilized such as protective clothing and broad-spectrum sunscreens (containing zinc or titanium dioxide). Sunscreens with inorganic ingredients such as titanium oxide and zinc oxide should be recommended over organic ingredients, which are associated with these types of reactions as well. Only anecdotal evidence supports the use of topical corticosteroids to relieve the inflammation, but they are broadly employed. In addition, cold compresses and lotions can be employed to alleviate the symptoms [15, 57].

UV recall can be seen with chemotherapy agents as well. It is similar to radiation recall, whereby administered medication induces a rash in the distribution of previous sunburn. The rash induced by medication given within 1 week of exposure is termed UV enhancement. UV recall refers to reactions occurring weeks to months following UV exposure. Multiple agents have been observed to induce these reactions including methotrexate, paclitaxel, suramin, and etoposide [15, 58].

## Skin Changes

### Xerosis and Pruritus

Multiple agents can induce xerosis and pruritus. Both sorafenib and sunitinib can lead to xerosis seen in up to 31% of patients [3]. Similarly, EGFRI and cytotoxic agents are commonly associated with xerosis as well. It is seen in up to 35% of patients being treated with EGFRIs, gradually developing over weeks and presents with dry, scaly, and itchy skin [43] (Fig. 37.9). Additionally, newly developed monoclonal antibodies such as pembrolizumab and nivolumab are associated with pruritus and xerosis in around 15% of patients [14, 59]. Patients that are older and with history of atopic eczema tend to have a more pronounced xerosis [60]. This may progress into

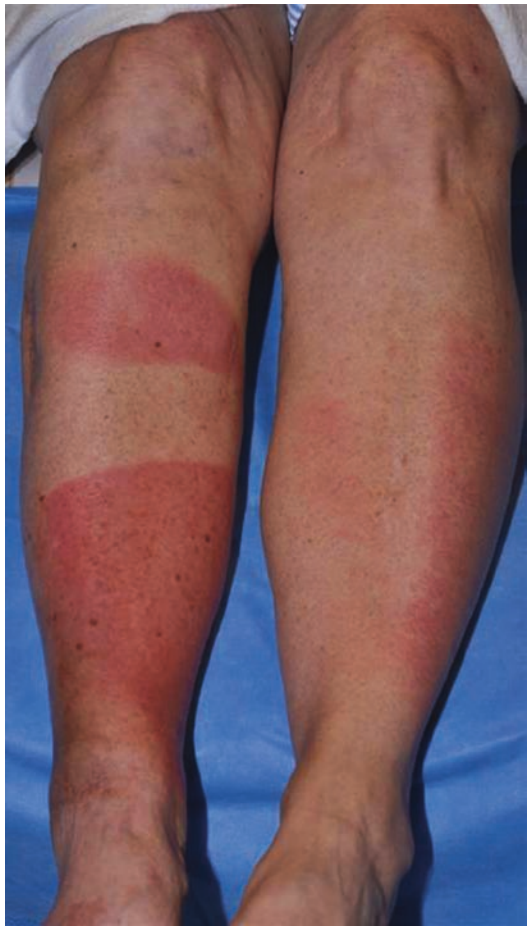

**Fig. 37.8** Photosensitivity rash

chronic xerotic dermatitis with a risk of being secondarily infected with *Staphylococcus aureus* or Herpes simplex virus. Xerosis involving hands or feet can potentially lead to painful fissures in the tips of fingers and/or toes [61]. Tepid water, minimizing showering, and avoiding using soap

**Table 37.4** Anticancer agents associated with photosensitive reactions

| | |
|---|---|
| 5-FU | Dasatinib |
| Dacarbazine | Fotemustine |
| Hydroxyurea | Taxanes |
| Imatinib | Tegafur |
| Doxorubicin | Anti-PD-1 therapy |
| Vemurafenib | Vandetanib |

Heidary et al. [13], Guillot et al. [28], and Sanlorenzo et al. [59]

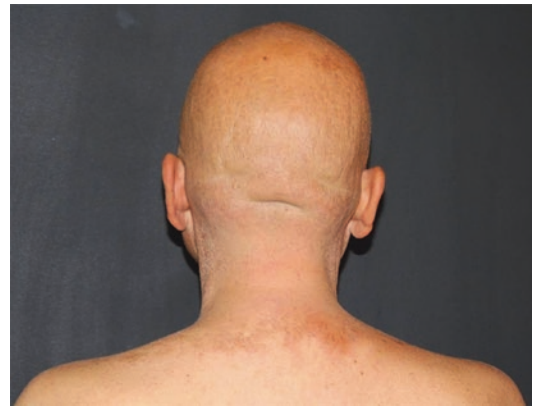

**Fig. 37.9** EGFR inhibitor xerosis

should be advised to patients to diminish xerosis of the skin. If eczema is present, treatment can be conducted with a short course (1–2 weeks) of topical corticosteroids [61]. Oral antihistamines and the gamma-aminobutyric acid analogs gabapentin and pregabalin can be utilized to decrease pruritus. In a prospective study, aprepitant (an oral neurokinin 1 receptor antagonist that blocks mast cell degranulation) has been used with promising results to decrease severe pruritus induced by biological treatments (e.g., erlotinib, cetuximab, imatinib) [62]. For a treatment algorithm, refer to Fig. 37.10.

## Pigmentary Changes

A variety of chemotherapeutic agents have been associated with a range of pigmentary changes. Both hyperpigmentation and hypopigmentation of the skin can be seen. Depending on the agent, different patterns of hyperpigmentation can be observed with various underlying mechanisms (Table 37.5). In addition, some anticancer therapies such as capecitabine and BRAF inhibitors may also stimulate development and/or regression of normal and dysplastic melanocytic nevi. Second primary melanomas and atypical melanocytic proliferations can also occur [63, 64]. Sun avoidance is critical and frequent use of sunscreens is recommended. Topical application of retinoids may be of benefit by facilitating rapid loss of keratinocytes along with their pigment.

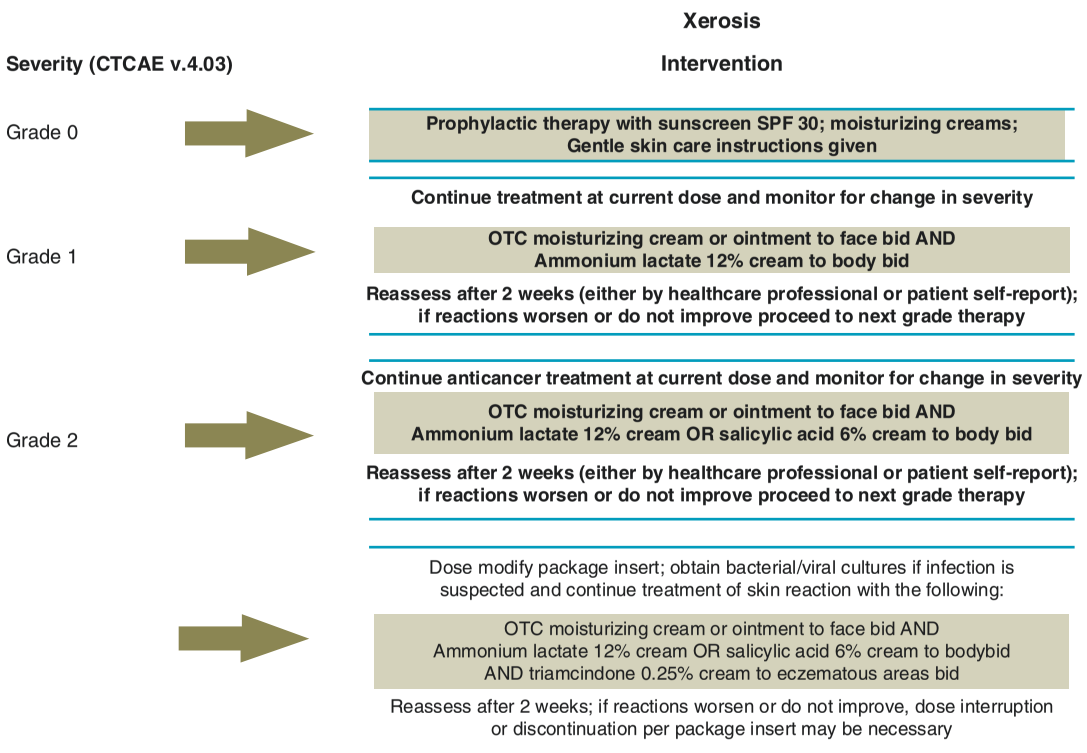


**Fig. 37.10** Treatment algorithm for xerosis

**Table 37.5** Anticancer therapies associated with pigmentary changes

| Pattern of pigmentary changes | Drugs |
|---|---|
| Hyperpigmentation | |
| Acral | Tegafur |
| | Capecitabine |
| Diffuse | Busulfan |
| | Cyclophosphamide |
| | Hydroxyurea |
| | Methotrexate |
| Irregular, patchy | Fluorouracil (5-FU) |
| Flagellate | Bleomycin |
| Supravenous serpentine | Docetaxel |
| | Paclitaxel |
| | Fotemustine |
| | Vinorelbine |
| | Vincristine |
| Transverse bands | Cyclophosphamide |
| Hypopigmentation | |
| Localized, patchy, diffuse | Imatinib<br>Pembrolizumab<br>Nivolumab |

Data from Wyatt et al. [15], Payne et al. [49], Heidary et al. [21], and Hwang et al. [14]

Formulations with hydroquinone or retinoids may diminish synthesis of melanin and diminish the degree of pigmentation [15]. Pigmentary changes can be diminished or prevented by trying to avert or aggressively treat rashes and eczema [44]. Refer to Fig. 37.11 for treatment of hyperpigmentation.

A range of pigmentary changes have been seen with imatinib including hypopigmentation and hyperpigmentation. Hypopigmentation tends to resolve upon reduction of the dose or discontinuation of therapy [21].

## Inflammation of Actinic Keratoses/ Accelerated Growth of Skin Carcinoma

Inflammation of actinic keratoses (AK) could be observed with multiple agents such as cytarabine, 5-fluorouracil, vincristine, doxorubicin, and capecitabine [15, 49]. Moreover, inflammation can actually be followed by clearing and resolution of AKs. Thus, this adverse event can be thought of as being beneficial since it leads to destruction of premalignant lesions. Chemotherapy should not be discontinued in a setting of this reaction, and topical application of corticosteroids can be used to ameliorate inflammation when it is severe [15].

Sorafenib, vemurafenib, and dabrafenib have been found to be associated with the development of AKs and invasive cutaneous squamous

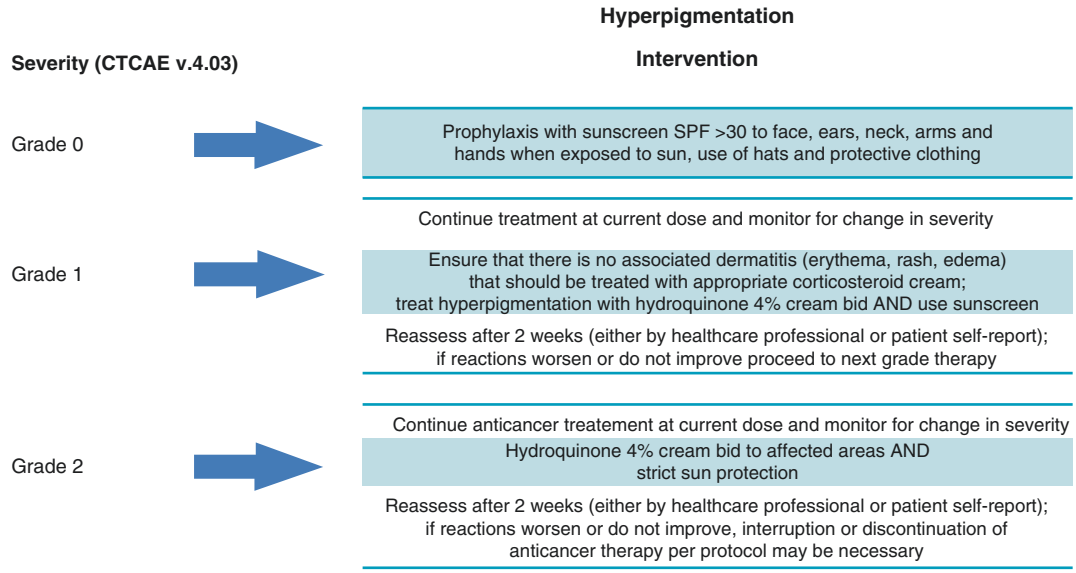


**Fig. 37.11** Treatment algorithm for hyperpigmentation

cell carcinomas (SCCs). It is possible that sorafenib can induce keratinocyte proliferation and lead to de novo formation of AKs and SCCs. These tend to regress after discontinuation of therapy but may recur with repeated treatments even with reduced doses [65]. In addition, long-term use of hydroxyurea has been linked to development of AKs and skin carcinoma including basal cell or squamous cell carcinomas that are photodistributed [41].

## Nail Toxicity

Various agents have been associated with nail toxicity, but taxanes are thought to be the most common culprits [66, 67]. In general, one can categorize nail toxicity as caused by damage to the nail bed (onycholysis, subungual hemorrhage), nail plate (pigmentary changes, grooves, brittle nails), or nail fold (paronychia).

## Paronychia

EGFRI have been associated with this type of nail toxicity. Paronychia (periungual inflammation), seen in up to approximately 15% of patients, can affect any finger or toe nail. It initially presents as erythematous inflammation of the lateral nail fold that can potentially progress into lateral nail fold pyogenic granuloma-like lesions which are very painful and can mimic an ingrown nail. This nail toxicity tends to manifest later in the treatment with EGFRI, usually occurring after 1–2 months of therapy [60]. Infection is not the primary event, but secondary impetiginization with *Staphylococcus aureus* or Gram bacteria can occur. Treatment with taxanes is also associated with acute exudative paronychia that may potentially progress to subungual abscess. Capecitabine has been known to induce periungual pyogenic granuloma-like lesions that spontaneously resolve with treatment interruption [66]. Treatment of the nail toxicity depends on the severity of the toxicity (Fig. 37.12).

Overall, therapy with cytotoxic agents and EGFRIs leads to slow growth of nails and brittleness [60]. Use of biotin 2.5 mg a day has been shown to strengthen nails and is recommended for patients affected with this disorder [68].

## Subungual Hemorrhage

Vascular endothelial growth factor receptor (VEGFR) inhibitors and MKIs have been associated with subungual splinter hemorrhages that more commonly affect fingernails as compared to toenails. They typically present as painless straight black or red lines, but their pattern and location (distal or proximal) can vary [60, 66]. Seen in approximately 30% of patients with sunitinib and 60% with sorafenib, they usually manifest within 2–4 weeks of treatment [69]. It is important to note that they are not related to thrombotic or embolic phenomena and are thought to arise due to VEGFR inhibition resulting in disrupted repair of tiny capillaries in the nail bed [69]. These do not warrant interruption or reduction of therapy and resolve spontaneously without any specific treatments [66].

Both docetaxel and paclitaxel have been associated with painful subungual hemorrhage that can secondarily be infected leading to subungual abscess and hemopurulent drainage [15, 70]. These changes lead to onycholysis. Broad-spectrum antibiotics and white vinegar in water 1:1 soaks can be employed in the case of subungual abscess formation. In addition, for large-sized abscesses, nail plate avulsion or fenestration can be attempted to drain the collection. After termination of the offending agent, normal regrowth of the nail should be expected [15].

## Onycholysis

Onycholysis, which is a separation of the nail plate from the underlying nail bed, occurs secondary to acute toxicity to the nail bed epithelium from a chemotherapy agent. Pain can often precede or occur simultaneously with nail plate separation. This adverse event has been observed with taxanes (paclitaxel and docetaxel), bleomycin, capecitabine, doxorubicin, fluorouracil,

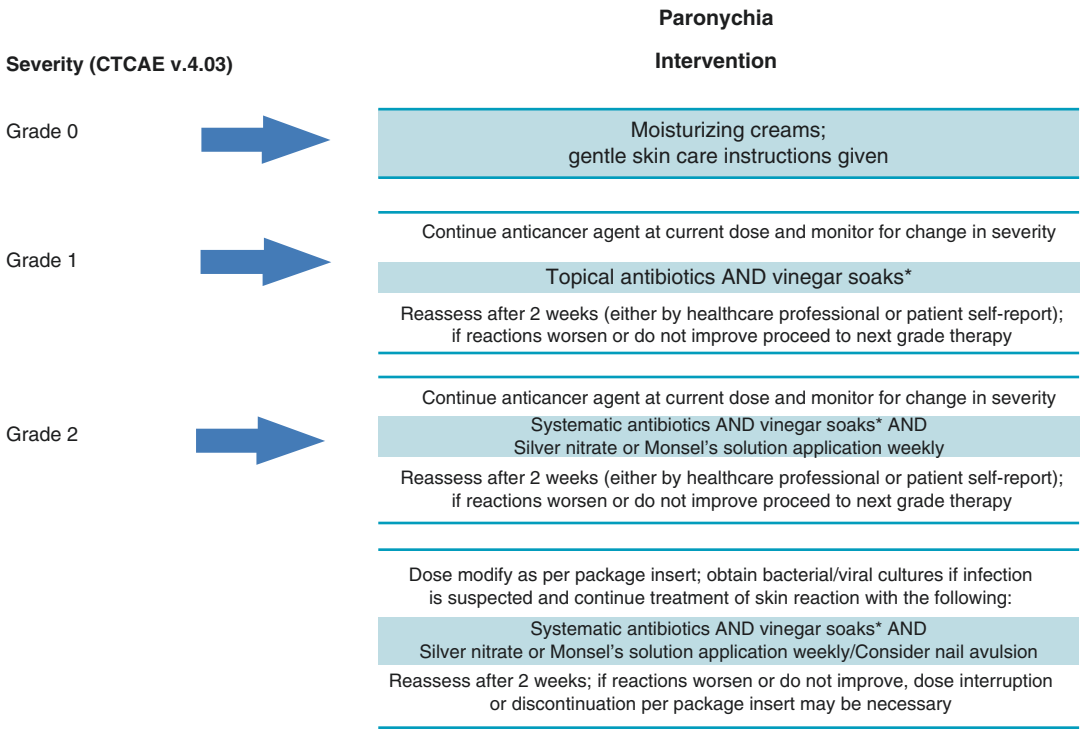


**Fig. 37.12** Treatment algorithm for paronychia. *Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 min every day

methotrexate, and etoposide [66]. Cutting the nails short, using topical antimicrobials, and minimizing exposure to irritants can be employed in treatment of onycholysis. Onycholysis along with other nail AEs induced by taxanes has been shown to be diminished by the use of frozen gloves and slippers, worn 15 min prior to, during, and 15 min post-infusion [71]. Frozen socks have also been shown to decrease taxane-associated nail toxicity including onycholysis [66]. This cryotherapy may potentially be of benefit in nail toxicity due to other agents as well, which share a similar half-life to docetaxel.

## Beau's Lines

Multiple chemotherapy agents result in a reduced or termination of nail plate synthesis, leading to horizontally oriented depressions called Beau's lines. No intervention is needed as depressions gradually move forward and resolve with growth of the nail [66].

## Leukonychia

An apparent and not true leukonychia is seen with various chemotherapy drugs and is secondary to damage to the nail bed. Apparent leukonychia manifests as horizontally oriented white lines with normal-colored nail bed (Muehrcke's lines) interspersed in between. No intervention is required, and spontaneous resolution is seen upon treatment discontinuation. True leukonychia arises from damage to the nail matrix and gives rise to transverse opaque lines (Mees' lines) in the nail plate which moves as the nail grows [66]. Leukonychia can be associated with cisplatin, anthracyclines, vincristine, and cyclophosphamide [41].

## Pigmentary Changes

Different patterns of hyperpigmentation are seen depending on the agent. Diffuse nail hyperpigmentation can be seen with cyclophosphamide, fluorouracil, and cisplatin. Partial hyperpigmentation with longitudinal bands is more common and is associated with cyclophosphamide, hydroxyurea, melphalan, busulphan, and doxorubicin. Anthracyclines, fluorouracil, hydroxyurea, and idarubicin have been linked to less common horizontal bands of hyperpigmentation. To improve cosmetic appearance colored nail varnish can be applied, but pigmentary changes can remain for several years despite discontinuation of therapy [66].

## Summary

Despite the fact that most of the dermatologic adverse events observed in patients receiving anticancer therapies are not life-threatening, their manifestation may result in dose interruptions or discontinuation, morbid interventions, hospitalization, and even death, all of which may affect clinical outcome with a negative psychosocial impact and an additional financial burden. Many treatment algorithms have not been validated by RCTs, but proposed guidelines exist. One critical aspect in management of several AEs described in this chapter is active patient involvement and education prior to initiation of treatment. Multiple preemptive strategies can be employed as well. These approaches along with careful monitoring of patients can facilitate early recognition of symptoms allowing for appropriate therapies to be employed. The ultimate goal of managing these patients is avoiding treatment modifications or interruptions to attain a maximum benefit from the anticancer agents and the most optimal quality of life.

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# 38 Management of Alopecia Due to Cancer Therapies

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## Hair Growth Cycle and the Impact of Anticancer Agents

Normal hair growth proceeds through a series of phases, with anagen being the proliferative phase when stem cells in the hair bulb are most active and fast-acting cytotoxics have their greatest impact [1] Table 38.1. A short apoptotic catagen phase is followed by telogen, the resting phase [2]. Hair follicles in different areas of the body have different cycle dynamics, with the scalp bearing the highest density of anagen follicles. This leads to vulnerability of proliferating keratinocytes in the bulb to early damage by anticancer therapies such as taxanes, anthracyclines and radiotherapy (anagen effluvium), with loss of fractured terminal hairs. In addition, damage to hair follicle vasculature and melanocytes may increase the injury and subsequently contribute to alterations in regrowing hair. Other cytotoxic combinations drive anagen hairs into apoptosis and thence heightened telogen effluvium. Abnormal shed telogen hairs are also thinned, with proximal tapering and diminutive bulbs, and are shed later in the course of chemotherapy [3]. Regrowth in general may take up to 6 months, and the hair may be thinner, curlier and/or depigmented [2, 4].

Permanent damage to follicle stem cells may be at the basis of persistent alopecia from

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**Table 38.1** Anticancer agents that cause alopecia

| Mild alopecia (grade 1) | Moderate alopecia (grade 2) | Severe alopecia (grade 3) |
|---|---|---|
| Aromatase inhibitors | Actinomycin | Cyclophosphamide |
| Bleomycin | Busulfan | Daunorubicin |
| Chlorambucil | Eribulin mesylate | Docetaxel |
| Cisplatin | Mitomycin | Doxorubicin |
| Cytosine arabinoside | Irinotecan | Epirubicin |
| Fluorouracil (IV and oral) | Methotrexate | Etoposide/ifosfamide |
| Gemcitabine | Vinorelbine | Paclitaxel |
| Hydroxyurea | | Vinblastine |
| L-asparaginase | | Vincristine |
| Melphalan | | |
| Mercaptopurine | | |
| Oxaliplatin | | |
| Palbociclib | | |
| Tamoxifen | | |
| Thioguanine | | |
| Vismodegib | | |

Severity (as single agents) graded using WHO gradings [15]. Combination therapies typically cause higher-grade alopecia

chemotherapy or radiotherapy, where follicles may be miniaturised as well as overall hair coverage thinned [5]. Radiation damage occurs in the first 5 millimetres (mm) of the hair-bearing scalp. Typically, whole-brain radiotherapy (WBRT) delivered by large opposed lateral fields was used in late-stage palliative settings and would cause alopecia that persisted until death [6–9]. High-dose chemotherapy for bone marrow transplant, particularly if it provokes graft-versus-host disease, has historically been the most frequent setting for permanent alopecia. More recently, some routine regimens for breast cancer treatment with anthracyclines and taxanes have been reported to lead to this disfiguring and distressing outcome of potentially unnecessary treatment [10, 11]. A survey of patients who had received docetaxel quoted a persisting scalp alopecia frequency of 10–15% and also identified some reports of persistent hair loss on other parts of the body [12]. Other contributing factors such as pre-existing alopecia areata, female pattern alopecia and thyroid dysfunction should be ruled out in this setting (Table 38.2). Breast cancer agents which block estrogen action such as aromatase inhibitors and tamoxifen, or menopause induced by chemotherapy, may also contribute to persistent hair loss and hair thinning in up to 30% of patients, through triggering of androgenetic alopecia (Fig. 38.1a) or female-pattern alopecia (Fig. 38.1b) [13].

Loss of eyebrows and eyelashes (madarosis) and body hair typically occurs later than scalp alopecia, due to greater proportions of hair being in telogen phase (approximately 50% versus 1% of the scalp) [2]. Madarosis also causes irritating eye symptoms, and patients report that it affects body image, contributing to the "cancer look", and being harder to disguise than scalp alopecia [14].

Other anticancer therapies, targeting the epidermal growth factor pathways (e.g. gefitinib/erlotinib), angiogenesis (e.g. pazopanib), Hedgehog signalling pathway (e.g. vismodegib) and cyclin-dependent kinase inhibitors (e.g. palbociclib) may also cause low-grade alopecia [15]. BRAF inhibitors (e.g. vemurafenib, dab-

**Table 38.2** Comorbidities to be screened for when alopecia is unexpectedly severe and/or persistent >6 months post-chemotherapy

| | |
|---|---|
| Endocrinopathies | Thyroid dysfunction<br>Ovarian hypofunction<br>Pituitary hypofunction |
| Nutritional deficiencies | Iron<br>Vitamin D<br>Zinc |
| Other causes of alopecia | Female-pattern alopecia<br>Androgenetic alopecia<br>Alopecia areata<br>Inflammatory (scarring) alopecia |

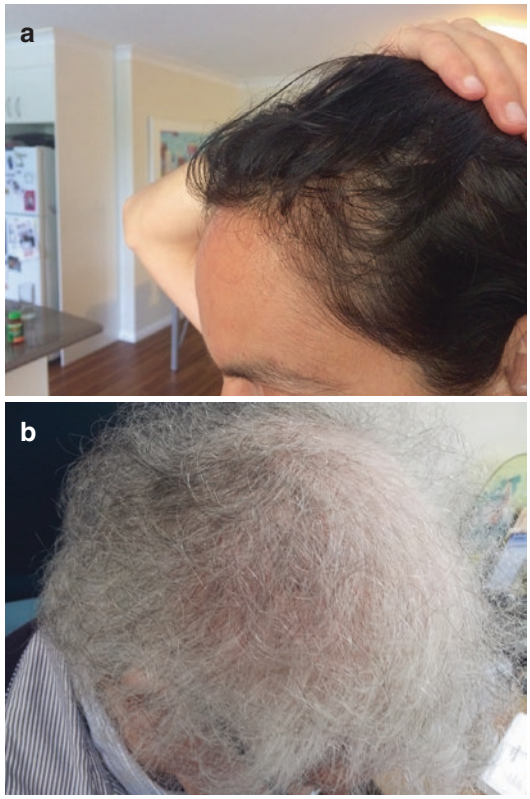


**Fig. 38.1** Ongoing alopecia in women receiving endocrine therapy for breast cancer. (**a**) Androgenetic alopecia in a patient taking an aromatase inhibitor, showing receding hairline. (**b**) Female-pattern alopecia in a patient receiving tamoxifen, showing grade 2 hair loss on the crown (Boyle et al., MASCC alopecia chapter Figure Legends)

rafenib) may cause depigmentation and kinking in addition to hair thinning [16].

## Measurement of Alopecia and Hair Changes During Cancer Treatment

Typical clinician grading scales for chemotherapy-induced alopecia (CIA) have either 3 grades [17] or 4 [18, 19]. These have been used in most chemotherapy trials and give rise to great variation in the quoted rates of alopecia [1]. In the setting of endocrine therapy, under-reporting of alopecia has been suggested by Sagger [13]. The need for improved precision has been highlighted in the previous MASCC textbook chapter by Olsen [4], particularly when alopecia is patchy, as may occur after scalp cooling. An update of the Severity of Alopecia Tool (SALT II) by Olsen may prove to be a valuable research tool in this regard [20].

The need for patient-reported outcome measures for both CIA and madarosis has been recommended by other researchers, given the underestimation of the impact of hair changes within standard quality-of-life instruments, e.g. EORTC QLC-BR23 [21, 22]. In prevention studies, satisfaction with hair, visual analogue scales and use of wigs/head coverings have been other useful measures [23]. Devices such as the cross-sectional trichometer [24], photographs with or without digital scanning [25], morphology of shed and plucked hairs [3] and comparison with standard diagrams may all have a role in future clinical trials and biological investigations, and cross validation studies are needed.

## Psychological Impact of Alopecia

Although chemotherapy-induced alopecia (CIA) is not life-threatening, is temporary for the majority of patients and is unlikely to lead to dose reduction, it causes significant distress to most patients [26]. The influence it may have on patient treatment decision-making is concerning, with approximately 8% of patients refusing potentially curative chemotherapy due to the fear of alopecia [27]. The importance of CIA to patients is underscored by its ranking as one of the top five most distressing chemotherapy side effects [28–30], whilst it is the side effect most often underestimated by clinicians [29]. Furthermore, a recent study conducted in Australia [31] highlighted ambivalence amongst health professionals to intervene, even when recognising the negative impact of CIA on patients. Patients frequently report not being prepared emotionally for the impact of alopecia and madarosis [1, 14].

Despite the prevalence of CIA, there have been relatively few studies that have explored its impact on patients, with much of what we know based on small qualitative studies exploring chemotherapy side effects more generally. These

studies confirm alopecia resulted in lower quality of life, higher levels of distress, negative body image and feelings of loss of control [23, 26, 32], which may persist after therapy is completed [33]. A study by Jayde et al. [34] that qualitatively explored the experience of CIA in Australian women with ovarian cancer found CIA to be the *most* distressing aspect of treatment. Similarly, in a study with early breast cancer patients, alopecia was considered more distressing than losing a breast [35]. In both of these studies, CIA represented a public confirmation of a cancer diagnosis and for women with ovarian cancer particularly, highlighting patient's fears of mortality [34]. Negative body image in women is compounded by loss of eyebrows and lashes [36], as alopecia challenges women's conceptualisation of femininity and attractiveness.

Although most studies of CIA have focused on women, particularly those with breast cancer, there have been some studies that report CIA is also a distressing side effect for males [37, 38], and similar levels are reported across tumour groups and countries. Hilton showed that whilst women are more distressed at losing hair above the eye line, men are more concerned at alopecia from other parts of the body, such as face and limbs. Only women reported being encouraged by others to disguise alopecia. Furthermore, the impact on body image is not age-related, with both younger (<50 years) and older patients reporting decreased body image related to CIA [30]. Studies in populations where headscarves are traditionally worn to cover hair demonstrate similar levels of distress in women who experience alopecia, irrespective of head cover use [39].

Studies that focus on the meaning of CIA to patients highlight the link between alopecia and illness representation. CIA is perceived as a visual indication of illness. For some, the alopecia is a constant reminder of their cancer [1]. However for others, CIA represents a public acknowledgement of cancer and patients report losing control over the choice about disclosure of their diagnosis [5, 34] in personal relationships and professional settings, limiting social interactions. Women with children report that alopecia causes distress to their children and was also one of the most difficult side effects for partners to come to terms with [30].

## Strategies to Manage Alopecia

Providing information on alopecia and teaching self-care strategies to minimise alopecia have been found to facilitate coping and adjustment [1], and increasingly health professionals may refer to group support programmes such as "Look Good, Feel Better" [40]. An alternative approach using a computer imaging program has also been found to be acceptable and supportive [28]. Typically both women and men take active steps to manage their alopecia as soon as it becomes noticeable [37, 41]. However some women find the act of cutting their hair or shaving their head as a traumatic blow and experience difficulties looking at themselves in the mirror [42].

Many women camouflage CIA by wearing a wig or head cover, particularly in public. Wearing a wig is a compensation for the changed appearance and is aimed at trying to look normal again, for both oneself and others [36]. Other patients choose to shave their head when CIA begins due to both practical and emotional considerations. Both men and women report shaving reduces the physical sensations such as itching and reduces the need to clear fallen hair from pillows and the shower. Shaving rather than waiting for hair to fall out is reportedly a strategy used by some to gain control over CIA [41, 43]. Pre-emptively purchasing wigs and head coverings was also reported to be another means women sought to come to terms with their altered appearance and gain a sense of control over CIA [1, 41–43].

Some patients see CIA in a more favourable light, choosing to consider alopecia as reflective of "strong therapy" that will translate into better outcomes [36, 43]. A meta-analysis of patients with ovarian cancer treated with platinum- and taxane-based chemotherapy showed that early onset of alopecia *did* correlate with improved survival [44] suggesting it may be a biomarker of metabolism or sensitivity. Despite these patients being less concerned about alopecia, reports suggest that patients who do not hide their alopecia

can experience stigma as they are perceived as breaking social norms by not covering up [36]. Male patients reported generally less pressure to hide their baldness [37], although some perceived negative assumptions about them were made based on their sudden change in hair status.

## Treatment of Scalp Alopecia

The use of 2% topical minoxidil has been shown to be of benefit in reducing time to the start of hair regrowth [45] in a small randomised trial in women with early breast cancer.

Strategies to manage non-scalp alopecia are limited, although pharmaceutical agents to reduce eyelash loss are being trialled [46]. Protecting the eyes with sunglasses and lubricant drops and the head from sunburn is important [1].

## Prevention of CIA

### Scalp Cooling

Scalp cooling (SC) is a supportive care intervention that is increasingly being utilised in many cancer centres as a strategy to reduce CIA. The principles of SC involve cooling of the scalp to below 22 °C before, during and after chemotherapy infusion, as it is hypothesised that vasoconstriction reduces blood flow to hair follicles during peak plasma concentrations of chemotherapy agents [47], which in turn reduces their cellular uptake [48]. SC reduces biochemical activity, making hair follicle keratinocytes less vulnerable to the damage of chemotherapeutic agents [49]. Optimal cooling in patients receiving anthracycline containing regimens may be related to the achievement of scalp skin temperatures below 18 °C [50]. Duration of cooling after chemotherapy infusions is somewhat arbitrary, since the concentration and duration of exposure needed to cause alopecia is not known for most regimens, and there may be significant inter-individual variation in clearance. For example, initial recommendations for 90 min of post-infusion cooling were made for single-agent docetaxel, but shorter times have also been found to be effective (45 and 20 min) [51, 52]. This may assist implementation, since chair occupancy reducing patient throughput due to extended cooling times is one of the major barriers to implementation in the clinic [31].

Application strategies have evolved from frozen caps requiring frequent changes (e.g. Penguin™, Elastogel™ and Chemo™ Cold Caps) to continuous cooling of the scalp with silicone caps infused with liquid coolant (Paxman Orbis™, Dignitana DigniCap™) (Fig. 38.2). Coolant devices are generally more convenient for patients and nurses [31, 43]. Scalp cooling has been widely used in patients with solid tumours in the Netherlands and the UK for the past decade, and more recently it has been introduced in Australia and the USA.

There is a growing body of literature confirming scalp cooling is an effective treatment to reduce chemotherapy-induced alopecia with selected regimens. A recent meta-analysis summarising the available data confirmed scalp cooling significantly reduced CIA (RR 5 0.38, 95% CI 5 0.32–0.45) [53]. Additionally, a large cohort study conducted through the Dutch Scalp Cooling Registry confirmed 50% of the patients with scalp cooling had good hair preservation, with a range between 8% (docetaxel, Adriamycin and cyclophosphamide chemotherapy (TAC)) and 95% (single-agent docetaxel) [54]. The study also reported that higher dose and shorter infusion time, older age, female gender and non-West-European type of hair significantly increased the proportion of patients resorting to a head cover. Despite the variability, the technology is reported to be well tolerated, and there is high patient satisfaction in European reports [48, 55]. For example, Betticher and colleagues in a non-randomised study of patients with metastatic breast, lung or prostate cancer receiving docetaxel found that cooling with frozen gel caps or the Paxman™ coolant system reduced hair loss by 78%. Thirty patients (13%) discontinued due to tolerability issues such as headaches, sensation of cold or pain [55]. Cold thermal injuries are likely to be infrequent and are generally preventable with appropriate application techniques [56].


**Fig. 38.2** Scalp cooling devices in use (**a**). Coolant devices use a refrigerated unit beside the chair that circulates cold fluid through an inner silicon cap, held in place by an outer neoprene cap to ensure a tight fit. (*i*) Dignitana Dignicap™ (*ii*) Paxman Orbis™. (**b**) Penguin Cold Caps™ in use. A freezer at −35 °C is used to pre-cool up to ten caps for each patient to use in a chemotherapy session. They are changed every 20 min. (**c**) Typical Dean's grade 2 result (<50% loss) after four cycles of docetaxel and cyclophosphamide for early breast cancer with scalp cooling. Regrowth is demonstrated. Images used with patient permission (Boyle et al., MASCC alopecia chapter Figure Legends)

In the USA, cooling devices have not been generally available, and three recent studies have been completed to assess efficacy and safety. Penguin Cold Caps were evaluated in a prospective study of women receiving docetaxel/cyclophosphamide adjuvant therapy for breast cancer [57]. Dean's alopecia grade was used to quantify alopecia, and 90% of women reported preservation of over 50% of their hair (Dean's grade < 3). An open-label non-randomised study of the Dignitana DigniCap™ device in women with early breast cancer receiving various anthracy-

cline/taxane regimens reported 66% of women with Dean's alopecia grade < 3 [58]. Safety was satisfactory and FDA approval was achieved for this indication. In a similar population, the SCALP study compared cooling with the Paxman system with no cooling in a study using a 2:1 randomisation. After 182 patients were randomised, 50% of scalp cooled patients had satisfactory hair preservation (CTCAE version 4 < 2) compared with no patients in the control group, and the study enrolment was ceased [59].

In the Netherlands, the number of hospitals offering scalp cooling has increased from 6% in 2005 to 89% in 2015 [60], although still not all eligible patients are offered cooling. Research in Australia on barriers to implementation has highlighted the need for close communication between oncologists and nursing staff, and managing of patient expectations, since almost all patients will lose some hair [31, 43]. Cap fitting is essential to efficacy and requires nursing staff training and commitment [61]. The additional time in the clinic for pre- and post-cooling also requires modification of practice and staffing in the infusion area [31]. Concern about patient discomfort has been largely resolved by the coolant devices, although the first 10 min of cooling has been highlighted as an important time for patient observation and support, and warm blankets and analgesia may be needed. Additional advice on hair care during treatment and information for hairdressers have also been highlighted as unmet needs by patients [1, 43]. Video educational materials have been developed to address this gap [62].

Concern that protection of the scalp from chemotherapy might lead to an increased risk of scalp metastases has not been borne out in large breast cancer cohorts [63, 64]. Long-term follow-up of current trials is planned to further inform this important issue, and extension of scalp cooling to patients with haematological malignancies remains an area for research.

## Pharmacological Approaches

Clinical trials of other prevention strategies for CIA have included the vitamin D analogue calcipotriol, following suggestive results in animal models. Unfortunately, protection from alopecia induced by CMF chemotherapy in women with breast cancer was not observed [3]. Similarly, topical lovastatin, a cholesterol lowering agent, was ineffective against anthracycline and taxane-induced alopecia [65]. Modulation of cell signalling pathways with alpha MSH has shown promise in model systems, and further trials are planned [66].

Minoxidil, which is known to improve hair growth in men with androgenetic alopecia, was investigated as a 2% topical solution in women receiving doxorubicin-based therapy. No protective effect was observed [67]. A post-chemotherapy study did however demonstrate a reduction in time to regrowth by 50 days [45], and minoxidil has also been used with effect in small numbers of patients with permanent alopecia after chemotherapy [5]. These investigations suggest that for pharmacological agents, timing of administration may be important.

The prostaglandin-based glaucoma therapy bimatoprost was noticed to cause growth and darkening of eyelashes as a side effect. It has been adapted into a gel formulation for use as a lash stimulant. A small clinical trial in breast cancer patients with hypotrichosis either during or after breast cancer chemotherapy suggested improved lash recovery in treated eyes [46]. Further clinical trials are planned to investigate optimal timing of application.

## Alopecia from Other Anticancer Therapies

The incidence of alopecia associated with use of antiestrogen therapies from breast cancer has been recently highlighted in a systematic analysis of clinical trials [13]. The overall incidence was 4.4%. Highest grades were seen in patients treated with tamoxifen, with 6.4% experiencing over 50% loss. In another registry-based study, 31.8% of patients on aromatase inhibitors reported hair thinning, and 22.4% reported hair loss [68]. In the clinic, many women receiving endocrine therapies may have received previous chemotherapy, which may be a contributing factor, along with menopause induced by chemo-

therapy or ovarian suppression, or combinations with other agents (e.g., palbociclib). Alopecia was not reported with antiandrogens used to treat prostate cancer. The suspected mechanism of alopecia included increased telogen effluvium and a reduction in shaft thickness, leading to breakage [2]. Loss on the frontal region seen with aromatase inhibitors mimics that seen in androgenetic alopecia (Fig. 38.1a). Loss on the crown seen with tamoxifen is consistent with female pattern alopecia, associated with estrogen deficiency (Fig. 38.1b). Patients presenting with alopecia should be evaluated for other potentially correctible factors (Table 38.2). Scalp biopsy may be of assistance in making a diagnosis. Topical minoxidil may be useful in therapy, as may oral spironolactone [13].

Alopecia from scalp radiation has typically been attended by a much slower regrowth rate than CIA [8]. Scalp cooling is not effective for protection against alopecia caused by standard planning techniques [69]. Techniques such as volumetric modulated-arc therapy that may enable scalp sparing are being investigated [70, 71].

## Current Research

Attention of the oncology community to the management of alopecia has been focused by recent technological developments, as well as the recognition of the importance of this treatment side effect to patients. Although scalp cooling technology has been available in Europe for more than a decade, it has until recently been unavailable in Australia and the USA. Introduction of scalp cooling into cancer centres requires a significant change to current clinical practice. Uptake in Australia and the USA has been primarily driven by individual oncologists or cancer nurses, and access has been largely limited to patients with breast cancer in a few metropolitan centres. Ongoing research to address the barriers and facilitators to wider implementation is currently underway, but clinician familiarity with the efficacy data and attitudes appear to be key factors [31]. The recent publication of the US trials will be beneficial in this regard [57–59]. Post-infusion cooling time, and its impact on clinic utilisation, also appears to be a major factor in busy units. Further trials addressing shorter cooling times may assist in this regard, along with pharmacological studies that address individual variability in drug clearance, so that cooling times might be more tailored. Costs of scalp cooling in the USA may be an additional barrier, with the emergence of not-for-profit organisations to assist patients to access treatment [72]. Equipment provision by health services or philanthropic organisations has been the norm to date in Europe, the UK and Australia.

Internationally, there is research being conducted to build the evidence base for scalp cooling, both in terms of greater understanding of treatment protocols and pathophysiology [2] and on investment in time and costs of scalp cooling from a health service and cost-effectiveness perspective [73]. Ongoing monitoring of safety and the possibility of use for haematological malignancies such as Hodgkin's disease are important areas for research. Additionally, recent explorations of the scalp cooling and CIA/madarosis/endocrine therapy literature have highlighted the need for common objective measures and patient-reported outcomes for trials and benchmarking [74]. A consortium of Australian, Dutch, US and UK researchers is currently validating such measures [61]. A register of patients with persistent CIA is also being developed to facilitate research and treatment (M Lacouture, personal communication). Decision tools in Dutch have been piloted to assist patients considering scalp cooling [75].

Stimulating research in this important area of supportive care is vital to ensure improved patient experiences of cancer treatment.

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# Part XII

# Survivorship

# Rehabilitation and Survivorship

# 39

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## Rehabilitation in Cancer

### History of Rehabilitation

Cancer rehabilitation, as defined by Cromes, involves helping a person with cancer to help himself or herself to reach the maximum physical, social, psychological, and vocational functioning within the limits imposed by the disease and its treatment [1].

Rehabilitation derives from the Latin "rehabilitare" meaning to make fit again. In 1969, Dietz introduced the first conceptual framework for designing a successful rehabilitation program triaging the patients based on their rehabilitation goals and needs [2]. These specific rehabilitation needs of patients with cancer were further defined by other practitioners such as Rusk, DeLisa, and deLateur. Historically, the concept of cancer rehabilitation stems from an integral component of the [US] *National Cancer Act of 1971*. That legislation declared cancer rehabilitation to be an objective, and it directed funds toward the development of training programs and research projects. In 1972, the US National Cancer Institute sponsored the National Cancer Rehabilitation Planning Conference, which identified four objectives for the rehabilitation of cancer patients, viz., (a) optimization of physical functioning, (b) psychosocial support, (c) vocational counseling, and (d) optimization of social functioning.

### Population

There were 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide. The overall age-standardized cancer incidence rate is almost 25% higher in men than in women, with rates of 205 and 165 per 100,000. It is estimated that 70% of all the patients with cancer survive for more than 5 years after the date of diagnosis and the majority of the cancer survivors are of working age (<55 years)

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I. Olver (ed.), *The MASCC Textbook of Cancer Supportive Care and Survivorship*,
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[3]. Improved outcomes have, therefore, created a constantly growing population of patients living with a cancer diagnosis.

In 2016, there were an estimated 15.5 million cancer survivors in the United States [4]. Breast cancer survivors continue to represent the largest segment of the survivor population (23%), followed by prostate cancer survivors (21%) and colorectal cancer survivors (9%) [5]. By January 1, 2026, it is estimated that the population of cancer survivors will increase to 20.3 million: almost 10 million males and 10.3 million females [6].

## Impact of Cancer

The extent of the impact of cancer on an individual is influenced by:

- Location and stage of the disease
- Treatment modalities used
- Duration of treatment
- Disease response
- Time elapsed since last treatment
- Psychosocial environment
- Patient comorbidities

The functional autonomy of patients with cancer is compromised throughout the trajectory of illness in different ways and influenced by different factors. The severity of this compromise ranges from negligible to profound.

While some patients experience symptoms during the initial phases of diagnosis and treatment, others experience treatment-related, long-term, debilitating, side effects. Post-cancer diagnosis, patients react differently, progressing through different phases, characterized by symptoms which affect specific functional domains of the patients, requiring specific rehabilitation interventions.

Phase 1: *Staging and pretreatment phase*, characterized by anxiety, fatigue, and pain. During this phase, patients may be preoccupied with the diagnosis and consequences thereof. A drastic change in the patients' daily routine, sleep pattern, and social interaction is usually evident.

Phase 2: *Primary treatment phase*, during which in addition to the above-mentioned symptoms patients experience other disease-specific symptoms such as impaired speech with head and neck surgery or change in body image post-mastectomy. Acute effects of chemotherapy and/or radiation therapy such as nausea, vomiting, and infections are also prominent. Aspects of the daily routine, such as self-care, cosmesis, and social interaction, such as eating together at mealtimes, are frequently interrupted.

Long-term survival rates have increased in the last few decades due to:

- Improvements in and broader use of newer cancer screening technologies, such as mammography, prostate-specific antigen (PSA) test, colonoscopy, and Pap test.
- Effective multimodal and multi-agent combination therapies, such as tyrosine-kinase inhibitors and monoclonal antibodies: For cancers, such as testicular, childhood cancers, and Hodgkin's disease, improvement is mainly attributable to breakthroughs in treatment.
- Greater application of adjuvant treatments for very early breast, lung, and colon cancer.
- Better supportive, rehabilitative, and survivorship care.
- Attention to posttreatment surveillance for early detection of recurrence and second primaries.

Phase 3: *Posttreatment phase*, wherein patients often experience treatment-related symptoms such as pain after surgery or lymphedema post-mastectomy. Decreased movement, loss of strength, anxiety, and depression are also reported. Problems with interpersonal relationships and economic hardship related to the cost of care and job losses are often encountered. Activities of daily living and cosmesis are affected.

Phase 4: *Recurrence phase* is characterized by shock, disbelief, anxiety, fear, grief, and a feeling of betrayal and anger that are common. Patients feel weak both physically and psychologically, losing appetite and feeling depressed. Symptoms related to local growth of tumor which cause pain, for example, may predominate. The activities of daily routine are disrupted and patients are usually preoccupied with negative thoughts and emotions about their existing condition and their future.

Phase 5: *End-of-life phase*. During this phase there may be a feeling of alienation or isolation and fear of impending death and concern over the events preceding death. The most common complaints during this phase are anasarca (generalized edema), pain, fatigue, crumbling autonomy, and lack of appetite. Patients are usually bedridden and there is an obvious dependency on others for their activities of daily living.

## Caregivers

Cancer affects the QoL of individuals with the disease and also that of their family members and close friends. Informal care provided by family caregivers includes:

- Treatment monitoring for side effects and help with reporting them to the physician
- Treatment-related symptom management
- Emotional, financial, and spiritual support
- Assistance with personal and prosthetic care

Family caregivers experience problems from their caregiving experiences, including conflict about their social roles, restrictions of activities, strain in marital and family relationships, psychological distress, and diminished physical health [7]. The degree to which family caregivers have negative and positive experiences in caregiving may affect their ability to care for the patient. This ability also relates to their own QoL, which includes psychological, mental, social, physical, spiritual, and behavioral components, not only during the time that they are providing care but also throughout the trajectory of the illness. Follow-up studies of caregivers show increased morbidity after a patient's death [8]. In a meta-analysis, palliative care was associated with statistically and clinically significant improvements in patient QoL at the 1- to 3-month follow-up. Palliative care was associated consistently with improvements in advance care planning, patient and caregiver satisfaction, and lower healthcare utilization [9].

## Classification of Rehabilitation According to Dietz

Owing to the nature of the cancer trajectory, rehabilitative goals have been divided into preventive, restorative, supportive, and palliative [2].

I. *Preventive rehabilitation* aims at reducing the burden of morbidity/mortality of the disease and/or treatment. This includes interventions such as preoperative education to maintain strength and range of motion in the upper extremity following breast surgery and educating caregivers to reduce predictable complications such as skin ulcers resulting from immobility and chemotherapeutic neuropathies. Rehabilitation interventions include education concerning the functional impact of the treatment and specifically preserving social function and activities of daily living.
II. *Restorative* care aims to return the individual with minimum functional impairments to their premorbid state. For example, after mastectomy, restorative approaches can restore shoulder range of motion and upper extremity strength. Structured progressive aerobic conditioning represents a very effective restorative technique for patients undergoing bone marrow transplantation. It can allow them to recover their premorbid fitness levels. Psychological interventions and social approaches help to allow families to reach their previous equilibrium. Issues requiring attention during this phase include adequate control of symptoms with appropriate medications. Management of pain,

sleep hygiene, and evaluation of the effects of treatments are required.

III. *Supportive* efforts seek to reduce functional difficulties and compensate for permanent deficits. An example of this approach would include the multimodal techniques used to rehabilitate patients after amputation. Teamwork includes reeducating the person regarding care of the prosthesis, learning to walk again, interacting with peers, and returning to work. Rehabilitation intervention aims at developing a program to restore mobility and management of symptoms that occur as a result of treatment. Equipping patients with education for self-monitoring of possible side effects of treatment, and maintaining a healthy lifestyle, is addressed.

IV. *Palliative* treatment aims to eliminate or reduce complications, especially pain and any other symptoms. Emotional support is also important. Prevention of bedsores can be achieved by education of caregivers. Existential issues can also be addressed by clergy. Rehabilitation intervention for this phase is to educate the patient and their caregivers on how to conserve energy. Training about body mechanics; educating the patients about the use of assistive devices to minimize energy expenditure while maintaining independence; and pharmacological treatment of symptoms such as pain, delirium, and constipation are addressed.

## Psychosocial Rehabilitation

"Distress"

- Refers to emotionally difficult experiences that may be in response to psychological, social, spiritual, or other sources of suffering.
- A certain degree of distress is expected when a person or loved ones are dealing with cancer.
- Becomes a clinical concern when it interferes with one's ability to engage or function in daily life.

As noted previously, psychosocial problems and psychological distress are common consequences of cancer and its treatment. In cancer care, this may manifest as difficulties engaging with clinicians, seeking appropriate medical or supportive care, adhering to treatments, coping with losses, or adjusting to life during or after cancer. Psychosocial clinicians are specially trained in helping patients with cancer and their loved ones manage distress. Interventions help patients attend to factors of distress that interfere with their functioning or QoL. These may involve attending to their emotions, challenging problematic beliefs, finding personal strengths and bolstering adaptive behaviors, facilitating self-expression, or coping with difficult physical symptoms [10]. In addition to helping patients attend to distress, psychosocial clinicians can also help patients improve physical difficulties, such as pain [11], sleep [12], fatigue [13], or other debilitating concerns. With proper comprehensive assessment, a psychosocial clinician can help his or her patient understand the different components of their own distress and how these aspects may influence or exacerbate each other. With this thorough understanding, the patient and clinician can then work together with the goal of easing the patient's suffering. Accordingly, there is growing recognition that psychosocial care is an essential component of a comprehensive approach to the treatment and rehabilitation of people with cancer.

Screening is the first step in identifying unaddressed distress [14] although it is not sufficient on its own: appropriate follow-up care is necessary. Canadian psychosocial scientist-practitioners spearheaded efforts to successfully have distress recognized as the sixth vital sign in cancer care [15, 16]. In 2008, screening for distress became an accreditation standard for all Canadian cancer programs under Accreditation Canada [17]. In the United States, the American College of Surgeons Commission on Cancer (CoC) adopted a similar screening policy in 2015 for all CoC-accredited cancer programs [18]. Guidelines for screening have been published by a number of professional bodies to provide frameworks for the effective delivery of psycho-

social services to cancer patients [18]. The consensus report issued by the US Institute of Medicine (IOM) specified processes that need to be in place to (a) identify distressed patients; (b) link patients and families to needed psychosocial services; (c) support patients and families in managing the illness; (d) coordinate psychosocial and biomedical care; and (e) follow up on care delivery to monitor the effectiveness of services provided and make modifications if needed. These recommendations are similar to those contained in the Clinical Practice Guidelines for Management of Distress developed by the US National Comprehensive Cancer Network (NCCN) [19]. The NCCN guidelines were developed based on the recognized need for better management of distress and with the intent of promoting best practice for the psychosocial care of cancer patients. Although too detailed to be fully summarized here, the NCCN guidelines are presented in the form of clinical pathways that describe recommended procedures for evaluating patients and recommended uses of psychological, psychiatric, social work, and pastoral care services to treat a wide range of psychosocial problems. Similar to the IOM report, the NCCN guidelines recommend that all patients be routinely screened with validated measures to identify the level and sources of their distress. This could be accomplished using the single-item Distress Thermometer [20] and the accompanying problem checklist described in the guidelines. Canadian guidelines recommend the Edmonton Symptom Assessment System (ESAS) and the problem checklist as the minimal toolkit. The ESAS provides nine single-item scales that screen for the severity of nine common symptoms, including depression and anxiety [21]. The specific services and resources subsequently recommended are designed to be appropriate to the nature and severity of the problems identified through the initial screening and further evaluation [16].

A recently published study demonstrated the benefits of an approach to psychosocial care similar to that described in the NCCN guidelines. In this study, cancer patients found to have major depressive disorder through screening were randomly assigned to usual care or usual care plus a collaborative care intervention [22]. Findings showed significantly lower scores on a measure of depression 3 months post-randomization for patients who received the collaborative care intervention. The beneficial effects of collaborative care observed at 3 months were still evident at 6- and 12-month follow-up assessments. Distress manifests at different points of the cancer trajectory, in different forms. Anxiety is frequently associated close to the diagnostic phase, whereas depressive symptoms are more insidious and increase in incidence later in the trajectory [23].

## Survivorship and Rehabilitation

A new model to describe palliative care was recently introduced, one that prepares the patients for the worst (death), but still allows hope for the best (cure). It helps illustrate the possibility of dying at a time when patients'/families' thoughts may be occupied by hope of cure. The model consists of two overlapping triangles resembling a bow tie (Fig. 39.1). The first triangle represents disease management and the second triangle is palliative care. The base of the palliative care triangle (end of the model) includes both death and survival as possible outcomes. The arrow, pointing from left to right, signifies this dynamic process with a gradual switch in focus. Survivorship, a unique aspect of this model, is included as a possible outcome. It may be used to illustrate where the various components of modern supportive and palliative care might fit into the patient's journey along with anticancer treatments [24].

## Breast Cancer and Colorectal Cancer Survivorship Guidelines

The American Cancer Society (ACS) and the American Society of Clinical Oncology (ASCO) have developed new guidelines on breast and colorectal cancer survivorship care to help identify and manage possible physical and psychoso-

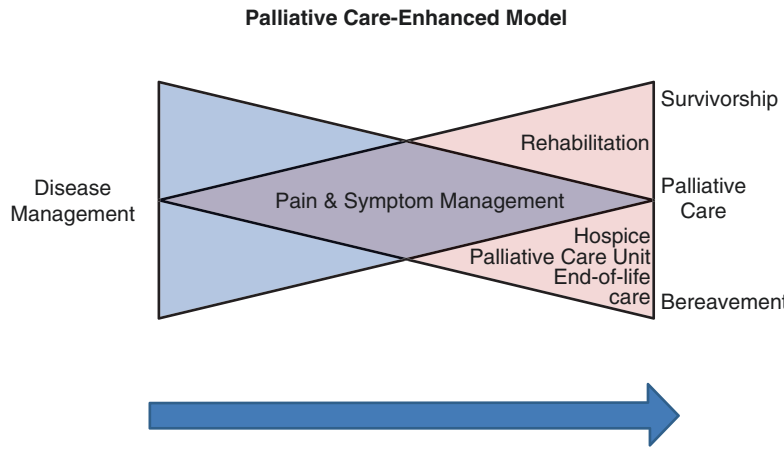


**Fig. 39.1** Bow-tie-palliative care enhanced model (*courtesy Dr. Pippa Hawley*)

cial long-term and late side effects of cancer and its treatment.

**The breast cancer survivorship guidelines** address five areas that are considered most important for women who have been treated for breast cancer. The recommendations include information on (a) surveillance for breast cancer recurrence, including what lab tests and scans should and shouldn't be done; (b) screening for second primary cancers such as cervical, colorectal, endometrial, and lung; (c) extensive guidance on the management of long-term and late effects of treatment, including body image issues, lymphedema, cardiovascular issues related to treatment, chemo brain, anxiety and depression, fatigue, bone health, musculoskeletal health, pain and neuropathy, infertility, sexual health and premature menopause, and hot flushes; (d) health promotion that includes counseling for obesity, physical activity, nutrition, and smoking cessation; and (e) care coordination including survivorship care plan, communication with oncology team, and inclusion of caregivers and spouses in usual breast cancer survivorship care and support.

**The colorectal cancer (CRC) survivorship guidelines** address four areas intended to assist primary care clinicians in delivering risk-based health care for CRC survivors who have completed active therapy: (a) surveillance for recurrence and screening for second primary cancers; (b) methods to identify and manage the potential physical and psychosocial long-term and late effects of CRC and its treatment, including gastrointestinal issues, cardiovascular effects, cognitive functions, dental issues, distress/depression/anxiety, fatigue, neuropathy, ostomy, pain, sexual function/fertility, and urinary bladder issues; (c) health promotion, including giving information about the late effects of treatment and impact of obesity, physical activity, specific dietary patterns, or tobacco use on CRC progression and mortality; and (d) care coordination and practice implication guidelines on how to enhance communication between the oncology team and primary care clinicians. The goal of these guidelines is to optimize the care delivered for cancer survivors and to help improve the overall health and QoL of CRC survivors.

## Approach to Identification and Management of Specific Patient Groups Requiring Rehabilitation

### Specific Rehabilitation Situations in Patients with Breast Cancer

Treatment for breast cancer can be associated with a number of localized physical sequelae including arm edema (AE), impaired shoulder mobility, chronic pain, neurologic deficits, and reduced upper body function. Psychological, social, and sexual dysfunctions are also prevalent.

Women with breast cancer can experience early menopause as a result of their treatment including higher frequency of menopausal symptoms than women in the general population [25].

Severe persistent fatigue is experienced during and shortly after breast cancer treatment and is often related to depression and pain.

Female breast cancer patients often avoid sexual intercourse especially due to negative emotional effects, changes of female body image, and fear of partner rejection.

## Specific Rehabilitation Situations in Patients with Colorectal Cancer

### Bowel Changes/Dysfunction

Following rectal resection common symptoms include increased frequency of bowel motions, urgency, fecal leakage, and incontinence. These are important issues for survivors because even though their cancer may be cured, their function and QoL may be severely diminished as a result of bowel-related symptoms. In patients who undergo abdominoperineal resection, the presence of a permanent colostomy has a strong influence on the various domains of QoL [26].

### Sexual Dysfunction

Sexual problems are associated with surgical and radiation therapies; a conventional rectal cancer resection in men is associated with postoperative impotence, retrograde ejaculation, or both in 25–100% of cases [27]. In females, the most common postoperative sexual complaint is dyspareunia, which may include loss of vaginal lubrication and inability to achieve orgasm.

### Urologic Dysfunction

Incomplete emptying, urgency, overflow or stress incontinence, loss of bladder sensation, dysuria, and chronic urinary tract infections occur in 7–68% of patients following low rectal resection [28].

## Specific Rehabilitation Situations in Patients with Gynecologic Cancer

These patients report more gastrointestinal symptoms like stomachache, diarrhea, and nausea. Frequent diarrhea is associated with higher fatigue and poorer social functioning. Women with advanced gynecologic cancer receive neurotoxic chemotherapy regimens. Neurotoxicity symptoms were associated with poor physical and psychological well-being, depression, sexual discomfort, difficulty with sexual desire, excitement, orgasm, and resolution and low confidence for managing cancer [29].

### Pain

Approximately half of the 200 ovarian cancer survivors in one study reported pain or discomfort in the bowel, pelvis, bladder, or groin [30].

### Menopausal Symptoms

Endometrial/cervical cancer patients have noted significant problems with menopausal symptoms (e.g., hot flashes, vaginal dryness/irritation). Younger survivors also have an increased risk of osteoporosis.

### Psychological Distress

Survivors, who are at increased risk of recurrent or persistent disease, reportedly experience higher levels of anxiety and depression.

## Specific Challenges Facing Patients with Head and Neck Cancer

Head and neck cancers and their treatments contribute to changes in eating, breathing, speaking, and physical appearance of patients. Although reconstructive surgeries restore contour and functioning, patients often experience residual cosmetic and/or functional alterations. Facial disfigurement is a major concern for patients and family caregivers, particularly in relation to the patient's diminished self-esteem, the effect on family relationships, and the ability to work, thus increasing their feelings of distress, self-awareness, and social anxiety. Ongoing protective care is important to minimize skin breakdown and infections.

### Changes in Eating, Saliva, Taste, Chewing, Swallowing, and Sense of Smell and Drooling

Difficulties with eating, chewing, and swallowing as well as changes in taste and smell and drooling are commonly reported, contributing

to weight loss. Dysphagia is considered to be the most common nutrition-related problem resulting from head and neck cancer. Long-term side effects and symptoms of radiation therapy include xerostomia (dryness of mouth due to dysfunction of the salivary gland), mucositis, and anorexia [31].

### Changes in Speech and Voice

Loss of a voice or intelligible speech is distressing and isolating, and creates major difficulties for individuals in their interpersonal communications.

### Shoulder Dysfunction

Shoulder dysfunction and pain after radical neck dissection are reported as activity limiting and interfere with performing daily activities and ability to return to work.

## Specific Challenges Facing Patients with Lung Cancer

### Dyspnea

The loss of functional lung tissue as a result of lung cancer surgery may result in transitory and permanent reductions in pulmonary function and, for some, physical disability. In addition to dyspnea, respiratory symptoms such as cough, phlegm, and wheezing also affect long-term survivors and diminish health-related QoL.

### Pain

Frozen shoulder, a potential postsurgical risk, affects lung cancer survivors. Rib fractures and bony metastasis cause pain as well [32].

### Altered Functional Status/Fatigue

In the above study of lung cancer survivors, almost all the survivors reported significant decreases in their energy (84%). Fatigue was the most commonly reported symptom more than 1 year after surgery for patients undergoing thoracotomy, as was the case with long-term survivors of small-cell lung cancer [33].

### Emotional Distress and Depression

Depression and emotional distress are seen more often among people with lung cancer than people with other cancers (15–44%) [34]. In a qualitative study, survivors described existential changes prompting them to "seeing life as a gift," "appreciating the little things in life," and "trying to live life to its fullest."

## Rehabilitation: Using the McGill Cancer Nutrition-Rehabilitation Program—An Innovative Team

The McGill Cancer Nutrition-Rehabilitation (CNR) Program was set up to provide treatment and lifestyle interventions targeting the population of cancer survivors [35].

> The global objective of the McGill CNR program is to use an interdisciplinary approach to empower individuals who are experiencing loss of function, fatigue, malnutrition, psychological distress, and other symptoms as a result of cancer or its treatment to improve their own quality of life.

An imperative in accomplishing these goals is a coordinated interdisciplinary team approach that addresses the potential rehabilitation needs of the individual from the time of the cancer diagnosis onward. The CNR assumes that the patient and the patient's environment are the center toward which all interventions are directed. The program recognizes that each patient is an individual and therefore requires different types and levels of intervention. Depending on the needs of the individual patient and family, members of the rehabilitation team may include the services of any or all of the following: physicians, oncology nurses, dieticians, physical and occupational therapists, social workers, psychologists, recreational therapists, vocational therapists, case managers, patient coordinators, chaplains, and relevant volunteers.

Patients that are referred are those who, as compared with their level before diagnosis, are experiencing changes in appetite (with or without associated weight loss); physical functioning, such as walking; and fatigue and coping with the consequences of their disease. All new-patient visits begin in the morning. On arrival, patients complete the following questionnaires: the Edmonton Symptom Assessment Scale (ESAS) [21]; the Patient-Generated Subjective Global Assessment (PGSGA) [36]; the Brief Fatigue Inventory (BFI) [37]; and the Distress Thermometer (DT) [20]. The various professionals see each patient during this first visit. Each member of the team evaluates the patient individually for 30 min with their own set of evaluations. The dietician evaluates the patient's current nutrition status and provides recommendations regarding specific dietary needs. Dietary supplements and alternative foods are discussed and prescribed. The dietician also teaches the family members about the importance of appropriate diet in successful rehabilitation. The physical therapist evaluates the patient's muscle strength, mobility, and joint range of motion; conducts the 6-min walk test, gait speed test, timed two times sit to stand, and Berg balance test; and if warranted performs assessment of arm girth and assessment of the scar. The treatment interventions provided include therapeutic exercises to maintain or increase range of motion, endurance, and mobility training (e.g., transfers gait, stair climbing). The occupational therapist conducts an activity interview and evaluates a patient's ability to carry out activities of daily living such as washing, dressing, preparing meals, working, driving, or performing leisure activities. Education on energy conservation, including the use of compensatory techniques, how to plan and set priorities, and the use of adaptive equipment, is part of the therapeutic armamentarium. The psychologist assesses and treats social, emotional, and mental functioning through patient and family education and counseling for stress, anxiety, and depression management. Using cognitive behavioral therapy, mindfulness-based cognitive therapy, existential psychotherapy, couples therapy, and support groups, the psychologist helps the patient to adjust to actual, perceived, and potential losses. The social worker provides counseling to patients and families regarding emotional support, community resources, finances, lifestyle changes, and their participation in treatment. During all this time, the patient remains in a single location, and team members move between patients.

Once accepted into the program, patients have biweekly exercise sessions with the physiotherapist. A fortnightly (or more frequent, if needed) visit to the dietician, occupational therapist, nurse, physician, and other relevant team members is scheduled. If judged necessary, or if specifically requested by the patient, a detailed psychological assessment is undertaken, and specific therapy is given. At the end of the 8 weeks, a full repeat of the baseline assessment is conducted. For patients that require still more formal supervision in any component of the CNR program, a personal referral to other rehabilitation units is made. All patients are referred back to their original physician with a full follow-up summary and recommendation.

## Palliative Rehabilitation: Using the Elisabeth Bruyere Palliative Rehabilitation Program—An Innovative Team Approach to Palliative Rehabilitation

"Palliation" is derived from the Latin word *palliare* meaning *to cloak*; that is, palliative care aims to soothe symptoms without the intent to cure disease or alter survival.

One of Dietz' rehabilitation categories, palliative rehabilitation, was largely neglected until approximately the past decade [4]. Palliation and rehabilitation both focus on QoL and function as opposed to cure or survival. They are person centered, involving the patient, the family, and other aspects of environment. They incorporate the expertise of multiple professionals and accordingly both have biopsychosocial traditions [38, 39]. Together, palliation and rehabilitation stand to improve function and QoL for patients with complex or advanced cancer.

The Elisabeth Bruyere Palliative Rehabilitation Program (PRP) in Ottawa, Canada, was modeled after the McGill CNR program with some notable differences. The PRP specifically took a palliative rehabilitation approach, targeting patients with complex cancer. Patients of the PRP were adults with diagnosed incurable heterogeneous cancers, typically defined as stage 3 or 4. Others with less disease progression but complex symptomatology would have been admitted as well but are not included in the report herein. Patients had completed their cancer treatments, were medically stable, were motivated to participate in the program, and were experiencing symptomatology that impaired their ability to engage in daily life (e.g., physical dysfunction, malnutrition, mental health concerns). They needed to have a palliative performance status of 50% or greater [40]. By the time that the program discontinued, 366 patients had successfully completed the 8-week program. The population was 48% female, with a median age of 64 (ranging from 21 to 90; 50% of the sample was between 55 and 73 years). While the PRP was in operation, clinical measurements and a questionnaire packet were administered at the beginning of the program (T1), at the 8-week completion point (T2), and the self-report questionnaire package was readministered by mail 3 months following completion (T3) and 6 months following completion (T4). There were 8 months between T1 and T4. Completion rates reveal that 64.3% of patients who began the program completed T2. Of those who did complete T2, 25.4% completed T3 and 13.4% completed T4.

Pilot data [41] in 2013 revealed that with interdisciplinary palliative rehabilitation, patients reported improvements in physical function (increased endurance, mobility, balance, and decreased fatigue), nutrition, severity of burden of multiple symptoms, and symptom interference in a number of domains of daily life (mood, enjoyment, general activity, and work). Patients did not report improvements in pain, shortness of breath, or mental fatigue. Longitudinal follow-up revealed that despite indications of progressing disease many of the gains reported earlier were maintained. These included symptom interference in walking, enjoyment in life, improvements in malnutrition, and reported "anxiety." The approach of the PRP team is one of empowerment, bolstering the patients' perception of their ability to deal with the multiple stressors (i.e., general self-efficacy) [42], which is innate in the experience of living with advanced cancer.

## Chemotherapy-Induced Peripheral Neuropathy

Peripheral neuropathies are a major cause of pain in cancer survivors, arising at any stage of the disease trajectory. Causes of peripheral neuropathy in cancer vary, but it can result from direct effects of the tumor itself as observed in paraneoplastic polyneuropathies or from its treatment with chemotherapeutic agents, termed chemotherapy-induced peripheral neuropathy (CIPN) [43]. CIPN is one of the major sources of morbidity in cancer survivors, afflicting an estimated 30–40% of patients undergoing chemotherapy [44]. Agents known to cause CIPN include platinum analogs, antitubulins (taxanes, vinca alkaloids, eribulin), proteasome inhibitors (bortezomib), immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), and some of the newer biologics (alemtuzumab, ipilimumab, brentuximab) [45].

Development of CIPN is usually related to the commencement of chemotherapy with peak incidence dependent on agent and dose, and is cumulative in nature, with higher doses of drug leading to greater neurotoxicity.

The pathogenesis of CIPN is different for each class of chemotherapeutic agent. However, patients exhibit similar symptoms of sensory loss in a glove and stocking distribution, typically associated with a loss of deep tendon reflexes, paresthesias, dysesthesias, and numbness. Clinical examination may also yield loss of perception to touch, vibration, and proprioception [46]. Cessation of antineoplastic treatment, however, does not guarantee resolution, with symptoms persisting in a large proportion of patients [47], resulting in marked reductions in posttreatment QoL [48]. In a meta-analysis of 31

studies of CIPN involving a total of 4179 patients, the aggregate prevalence of CIPN was 48%. Sixty-eight percent of patients reported CIPN at the end of first month post-chemotherapy, but the prevalence decreased to 30% after 6 months [49]. A recent cross-sectional multicenter study to select outcome measures for CIPN evaluation included the NCI-CTC, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and QLQ-CIPN20. The study demonstrated good validity and reliability scores for the set of selected impairment and quality-of-life outcome measures [50]. Further studies are being conducted to investigate the responsiveness aspects of these measures and to select the right tool.

At present, there is also not enough evidence to support effective prevention of CIPN using any agent. The latest guidelines from the American Society of Clinical Oncology (ASCO) acknowledge this limitation and recommend against offering any CIPN-preventive drug to patients undergoing neurotoxic cancer treatment [51]. Regarding treatment of CIPN, the ASCO guidelines state that clinicians may offer duloxetine to symptomatic patients [51] and should consider offering tricyclic antidepressants, gabapentin, or pregabalin to manage the positive symptoms associated with CIPN. The complications of CIPN, which include gait abnormalities, falls, muscle weakness, and skin breakdown, are best managed comprehensively (often in consultation with a multidisciplinary rehabilitation team) and may include both physical and occupational therapists [52]. Exercise is one of the hallmark treatments of OT and PT for CIPN; weakness, fatigue, and neuromuscular deficits are often treated with exercises. While there is no conclusive evidence that exercise improves CIPN symptoms, it has been shown to reduce falls and improve performance status and overall QoL [53]. Patient education on skin care, foot/hand safety with impaired sensation, use of assistive devices to aid in proprioception, and ADLs is also an important aspect of therapy treatment for CIPN. Several other modalities to treat CIPN like acupuncture, Calmare pain therapy, whole-body vibration, and laser treatment with low-level energy laser (LLEL) are currently being studied; more research is needed to validate these modalities.

## Physical Activity in Cancer: Guidelines

General consensus about physical activity in cancer is that it is safe and feasible, and improves health-related fitness (e.g., aerobic fitness, muscular strength) and QoL. Evidence suggests that exercise improves several cancer-specific symptoms such as fatigue, sleep dysfunction, and depression in several cancer survivor groups both during and after treatments [54]. A recent systematic review and pooled analysis of 26 studies looking at the potential role of exercise in improving cancer outcomes reported that cancer survivors who exercised the most had a 37% lower risk of dying from cancer than survivors who exercised the least [55]. In the first randomized exercise trial to examine long-term cancer outcomes, Courneya et al. [56] reported an exploratory follow-up of the Supervised Trial of Aerobic versus Resistance Training (START). After a median follow-up of almost 8 years, disease-free survival was 82.7% in the exercise groups compared with 75.6% for the control group. The trial suggests that exercising during breast cancer chemotherapy may actually improve long-term cancer outcomes.

Similarly, some other ongoing trials provide the first definitive evidence on the role of exercise in improving cancer-related outcomes. The Colon Health and Life-Long Exercise Change (CHALLENGE) Trial is examining the effects of a 3-year exercise program on disease-free survival in high-risk stage II and III colon cancer patients who have completed chemotherapy [57]. To date, the trial has demonstrated the feasibility of accrual [58] and exercise behavior change [59]. Likewise, a multinational Intense Exercise for Survival (INTERVAL) phase III trial is examining the effects of a 2-year structured exercise program on overall survival in 866 men with metastatic castrate-resistant prostate cancer [60].

## Exercise for Patients with Cancer: Clinical Practice Guidelines

Seagal et al. reviewed the outcomes of 3 major exercise guidelines, 18 systematic reviews, and 29 randomized controlled trials and formulated a clinical practice guideline for exercise in patients with cancer [61]. This guideline provides an outline for the appropriate duration, frequency, and intensity of exercise. The recommendations are as follows: (a) People living with cancer can safely engage in moderate amounts of exercise while on active treatment or post-completion of treatment. (b) Moderate amounts of exercise are recommended to improve the QoL, as well as the muscular and aerobic fitness of people living with cancer. (c) Clinicians should advise their patients to engage in exercise consistent with the recommendations outlined by the Canadian Society of Exercise Physiology and the American College of Sports Medicine. (d) A pre-exercise assessment for all people living with cancer before starting an exercise intervention is recommended to evaluate for any effects of disease, treatments, and/or comorbidities. (e) Where possible, people living with cancer should exercise in a group or supervised setting as it may provide a superior benefit/outcome in QoL and muscular and aerobic fitness. (f) And lastly it is recommended, where possible, that people living with cancer perform exercise at a moderate intensity (three to six times the baseline resting state) on an ongoing basis as a part of their lifestyle so that improvements in QoL and muscular and aerobic fitness can be maintained for the long term.

## Cancer Cachexia

Diagnosis of cancer cachexia can be made if there is:

- Weight loss >5% over the past 6 months (in the absence of simple starvation)
- BMI <20 and any degree of weight loss >2%
- Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m$^2$; females 5.45 < kg/m$^2$)
- Any degree of weight loss >2% [62]

Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism [62].

Cancer cachexia is a continuum (with three stages of clinical relevance: precachexia, cachexia, and refractory cachexia). Not all patients traverse the entire spectrum. In precachexia, early clinical and metabolic signs (e.g., anorexia and impaired glucose tolerance) can precede substantial involuntary weight loss (i.e., ≤5%). The risk of progression varies and depends on factors such as cancer type and stage, presence of systemic inflammation, low food intake, and lack of response to anticancer therapy. Patients who have more than 5% loss of stable body weight over the past 6 months, or a body mass index (BMI) less than 20 kg/m$^2$ and ongoing weight loss of more than 2%, or sarcopenia and ongoing weight loss of more than 2%, are classified as having cachexia. In refractory cachexia, the cachexia can be clinically refractory as a result of very advanced cancer (preterminal) or the presence of rapidly progressive cancer unresponsive to anticancer therapy. The burden and risks of artificial nutritional support are likely to outweigh any potential benefit. Recently, a cancer weight loss (WL) grading system was developed that incorporates the two dimensions of %WL and BMI and links them to survival. Data representing the spectrum of these features demonstrated that both %WL and BMI predict survival independently of conventional prognostic factors including cancer site, stage, and PS. This large study also validates the concept [63] that the severity of WL should be evaluated based on the rate of WL and the level of depletion of body reserves.

There is no consensus on how to assess cachexia and outcomes are challenging. Equally, no consensus on the optimal treatment for cancer

cachexia exists; however, there is an urgency for improving management. There have been several trials examining various modalities and/or therapies for cancer cachexia, but overall the results have been inconclusive [64]. Megestrol acetate and medroxyprogesterone have an effect on appetite and weight. Dexamethasone, methylprednisolone, and prednisolone report positive but short-lived effects on clinical outcomes such as appetite and QoL, with minimal or no effect on weight gain. Side effects, such as muscle wasting and immunosuppression, make long-term use less appropriate [65, 66]. There is no definitive data suggesting effectiveness of cannabinoids such as Dronabinol in promoting weight gain and appetite [67, 68]; however taste perception may be altered [69]. Anti-inflammatory agents such as thalidomide and omega 3 fatty acids (EPA), peptide immunomodulator, and cytoprotective drugs such as OHR118 [70] decrease TNF-α levels; however, there are conflicting results regarding weight gain and appetite stimulation. Anabolic agents like oxandrolone, nandrolone decanoate, and fluoxymesterone have limited published data to support their effectiveness [66]. Similarly, role of anamorelin, a selective agonist of the ghrelin with appetite-enhancing and anabolic effects, also remains controversial in the treatment of cancer anorexia cachexia syndrome [71]. Newer novel therapies under investigation include the SARMs (selective androgen receptor modulators), mechano growth factors such as IGF-1, anti-myostatin antibodies, ACE inhibitors, aldosterone antagonists, and insulin treatment.

The impact of other interventions which are now being considered as vital includes an appropriately devised physiotherapy program to build muscle bulk and improve muscle strength and endurance and an ergonomically focused assessment by an occupational therapist to aid a patient in his or her home environment to adapt to the limited mobility and loss of independence that may accompany the patient with cachexia. As multiple factors are responsible for the development of cachexia, it has been argued that optimal cachexia intervention should target all components, multimodal therapy for a multimodal problem [72–74]. It is believed that treatment of cachexia needs to be delivered in a precachectic or cachectic phase to be successful [74]. To this effect, a multicenter, open, randomized phase III study comparing a multimodal intervention (oral nutritional supplements, dietary support, ibuprofen, and physical exercise) and standard cancer care versus standard cancer care alone—MENAC trial [75]—aims to intervene at an early stage in cancer patients with a high probability of developing cachexia in order to treat or prevent the development of the syndrome. Preliminary data is encouraging and the trial is currently active.

When caring for patients, it is imperative to recognize the influence of their psychological state, nutrition, physical activity, symptoms, and functional status on their disease and response to therapy. A truly comprehensive care program incorporates elements that address each of these aspects. Evidence from nonrandomized studies indicates that full-service programs can ameliorate the symptomatic course of cancer. Data on survival are lacking; however, exercise and nutritional counseling are integral to "survivorship" models (i.e., rehabilitation designed for patients receiving treatment for cure) during and after treatment. Adding exercise and nutrition to a care program creates a logical model for introducing early rehabilitative, palliative, and survivorship care. Numerous pronouncements and consensus statements call on physicians to treat the "whole person," and to introduce palliative care principles early [76]. Evidence of the success of conventional palliative care programs exists [77].

## Future Directions in Cancer Rehabilitation and Survivorship

As more physicians and other health caregivers become more aware of the additional benefits awarded to patients by rehabilitation, more research questions will be posed such as the following:

1. Research on the causative factors of weight, appetite, and function loss
2. Importance of regular physical activity after cancer: Does it increase length and quality of survival?

3. Research on muscular fatigue and loss of strength in patients undergoing treatment for cancer
4. Psychosocial and behavioral consequences of long-term physiological sequel for survivors' health and well-being
5. Duration of the follow-up care and the role of the survivor in his or her own recovery
6. Meaning-making coping processes of patients with cancer
7. Long-term impact of cancer on the functioning and well-being of the caregivers

Similar concerns were raised in a cancer survivorship research consortium in Canada [78]; the identified priorities included (a) preventing and ameliorating (late) effects of cancer and its treatment; (b) effective interventions, particularly psychosocial interventions; (c) determining optimal models of follow-up care; (d) needs of unique (high risk or needs) populations; and (e) risk assessment for adverse survivorship outcomes. Future research needs to focus on developing a rehabilitation and survivorship care evidence base and exploring strategies to facilitate provision of survivorship and rehabilitative care to diverse patient population around the globe.

## Conclusion

Advances in screening, better health care, and treatments have led to improved survival rates in patients with cancer. Consequently, patients are expected to live longer with the physical psychosocial and other impairments that result from their disease and/or its treatment. Cancer rehabilitation empowers individuals to regain strength, preserve function, and improve QoL. Rehabilitation improves patient's perceptions of themselves and equips them with the tools necessary for successful reintegration. To effectively improve the care and management of the patients, it is crucial to educate and create more awareness among healthcare professionals and rehabilitation specialists. The importance of recommendations and guidelines, psychosocial rehabilitation, and multimodal approach by an interdisciplinary team must be emphasized and implemented early in the course of the disease. A well-functioning interdisciplinary team is vital to achieve these objectives.

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# 40 Oral Health and Survivorship: Late Effects of Cancer and Cancer Therapy

Joel B. Epstein, Derek K. Smith, and Barbara A. Murphy

## Oral Health-Related Issues in Cancer Survivors

Various cancer therapies can result in substantial changes in the physiology of the oral environment. These changes are often permanent and can cause the development or progression of a variety of oral diseases for the duration of the patient's life. The particular changes a patient will experience are based on the type of cancer therapy administered, the patient's baseline oral condition, comordities, and genetic susceptibility. Commonly reported oral side effects include inflammation and ulceration of the oral mucosa (mucositis), decreased salivary function (hyposalivation), oral pain, surgical defects, altered sensation including taste, difficulty swallowing (dysphagia), decreased oral opening (trismus), radiation-induced dental caries, ill-fitting dentures, oral manifestations of graft-versus-host disease secondary to stem cell transplant, and an increased risk of osteonecrosis of the jaw (ONJ).

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Although it is evident that these effects would have a profound impact on patient's everyday activities, they also have a number of secondary effects including weight loss, dehydration, malnutrition, decreased body image, increased social isolation, increased financial toxicity, and decreased quality of life. It is therefore vitally important that the oral changes induced by each cancer treatment modality are widely well-understood.

## Oral Quality of Life and Symptom Burden

Quality of life (QOL) is a global construct that reflects a patient's general sense of well-being. A number of tools have been developed to measure QOL in the oncologic population. Commonly used QOL tools in the oncology population are the Functional Assessment of Cancer Therapies (FACT) and the European Organization for Research into the Treatment of Cancer (EORTC QLQ-C30). Both of these tools assess physical, functional, social, and emotional well-being. Subscales have been developed to assess tumor- and treatment-specific symptoms and functional issues.

QOL must be distinguished from the assessment of specific symptoms or functional loss. Symptoms may be defined as the patient's perception of alteration in sensation and functional



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loss related to organ system abnormalities. While patients may perceive alterations in function, it should be noted that functional loss may be subclinical. Thus, objective measures of functionality are needed to assess the full spectrum of function loss. Although QOL questionnaires contain items that query symptoms and functional outcomes, assessment of symptom burden is not the primary intent of QOL tools. Tools have been developed to assess specific symptom and functional outcomes, and they should be used when the description of symptom burden or functionality is the desired study outcome.

A number of investigators have reported the results of oral health outcomes in the context of QOL assessments in head and neck cancer survivors. In one study of HNC patients who had completed radiotherapy more than 6 months earlier [1], persistant symptoms included dry mouth (92%), change in taste (75%), and difficulty eating (40%). In a second study of patients surviving 5 years or longer, the majority of patients experienced pain (58%), with 17% reporting moderate or severe pain. Thirty-one percent stated that pain interfered with daily activities. Oral health outcomes were assessed in HNC patients followed up to 5 years after treatment with 87% of survivors participating at the 5-year follow-up point. Dental problems, trismus, xerostomia, and sticky saliva increased over time after 1 year and persisted at 5 years. Oral complaints were related to gender, age, stage, and site of disease [2].

Similar results have been reported by others. The late effects of oral cancer and its treatment were assessed in a prospective, multicenter study of QOL using patient-reported outcomes (PRO) pretreatment and 1–5 years following treatment [3]. Dry mouth, sticky saliva, speech changes, dental problems, and sleep disturbance were all associated with a decrease in QOL ($p < 0.01$). In another study, patients completed QOL surveys up to 36 months after HNC treatment [4]. Most short-term morbidity resolved in 1 year of cancer treatment; however, at the last follow-up time point, physical function, taste/smell, dry mouth, and sticky saliva were significantly worse than at baseline. Females, higher stage of disease at entry, and combined treatment were associated with increased symptoms and worse function. A gradual improvement in depression and global QOL was seen in survivors. A prospective study of nasopharyngeal cancer patients assessed before treatment and up to 24 months following treatment found poorer global health, fatigue, loss of appetite and dysphagia (all $P < 0.01$), xerostomia and sticky saliva ($P < 0.001$), taste change, dental problems (both $P < 0.05$), pain, and emotional function ($P < 0.005$) [5]. In a separate study of nasopharyngeal cancer survivors (median follow-up: 3.6 years), xerostomia, hearing loss, dysphagia, and trismus were frequently reported [6].

## Late Oral Effects of Cancer Therapy

### Hyposalivation and Xerostomia

Hyposalivation may be defined as a decrement in stimulated or unstimulated salivary flow. Saliva assessment is incorporated into the Common Terminology Criteria for Adverse Events (CTCAE) for xerostomia. Patients with hyposalivation may complain of the sensation of oral dryness which is commonly referred to as xerostomia. It should be noted that patient perception and objective measurement of salivary flow may not correlate. Thus, when reviewing literature it is important to consider the measurement techniques employed.

Saliva has numerous critical functions. It provides oral and pharyngeal wetting and lubrication in order to maximize swallowing and speech, moistens food, allows preparation of a food bolus for deglutition, and initiates digestion. Saliva allows food molecules to be presented to taste receptors. Importantly, saliva helps to preserve dental integrity by maintaining normal oral flora, oral pH, and providing calcium and phosphate to reduce demineralization and to promote remineralization of enamel. Furthermore, it aids in the control of oral infections and maintains mucosal integrity.

Hyposalivation and xerostomia are commonly noted in patients treated with chemotherapy and radiation therapy. Furthermore, medications

commonly used in the supportive care of chemotherapy patients (e.g., antiemetics, analgesics, antianxiety/antidepressants) may affect salivary gland function. Xerostomia associated with standard-dose chemotherapy is usually mild and transient. Studies evaluating the frequency and severity of chronic xerostomia in this setting are limited. In one study of breast cancer patients undergoing chemotherapy, both resting and stimulated flow rates were decreased during chemotherapy and remained reduced at 6 months, with return to baseline at 1 year [7]. Changes in the composition of saliva including decreased phosphate and secretory IgA were also noted.

Hyposalivation and xerostomia are more common and protracted in patients undergoing high-dose chemotherapy with stem cell rescue. In one study, 16% of patients had persisting xerostomia up to 3 years posttransplantation [8]. In the setting of stem cell transplant, chronic hyposalivation may be secondary to progressive salivary gland damage resulting from chronic graft-versus-host disease (GVHD) [9, 10]. GVHD is characterized by acute or chronic donor T-cell reactivity against the host tissues. The damage may be due to direct target tissue damage or may be secondary to inflammatory mediators. The gastrointestinal tract, including the oral mucosa, is one of the primary target organs. In one report of patients with chronic GVHD, the oral cavity was involved in almost 80% of patients who underwent a bone marrow transplant and almost 90% of patients who underwent peripheral blood stem cell transplantation [11]. Similar results have been reported by others [12, 13]. Symptoms are more severe in myeloablative transplantation as compared to reduced intensity conditioning.

Patients receiving radiation therapy for treatment of locally advanced HNC experience severe hyposalivation and xerostomia. The salivary glands are highly sensitive to the radiation. Dramatic decrements in salivary flow are noted within 1–2 weeks of initiating standard-dose radiation therapy. Hyposalivation may be permanent if the salivary gland receives doses of greater than 3500 cGy. The sequelae of hyposalivation in the HNC population are profound. Hyposalivation may result in devastating radiation caries (see dental health section below). In addition, patients with severe xerostomia may experience dietary maladaptations due to the need to intake moist or pureed consistency foods and taste change. Patients frequently drink large amounts of fluid in order to moisten and swallow solid foods. Although it is clear that hyposalivation results in dietary changes, the long-term effect on nutrient intake and diet quality is unknown. It may be hypothesized that patients with significant dietary adaptations may experience long-term macro- and micronutrient deficiencies that are associated with adverse health effects.

Several approaches have been examined to prevent xerostomia and hyposalivation in HNC patients receiving radiation therapy. The first approach is the use of pharmacologic agents to prevent tissue damage. Amifostine (WR-2721) is a free radical scavenger that was FDA approved to prevent hyposalivation in patients undergoing radiation therapy to the salivary glands [14, 15]. A meta-analysis demonstrated that amifostine resulted in a decrease in acute (OR, 0.24; CI 0.15–0.36; $p < 0.00001$) and late hyposalivation (OR 0.33; CI, 0.21–0.51; $p < 0.00001$) [16], and there is limited evidence of clinically significant improvement in dental outcomes in patients receiving amifostine [16]. A more recent study has focused on intramuscular delivery of amifostine, which is associated with fewer and less severe side effects and lower cost, than intravenous delivery [17]. Nonetheless, due to side effects, cost, and the administrative burden, amifostine has not been widely used in clinical practice.

Pharmacologic agents have also been used to maximize residual function of salivary glands in patients with posttreatment hyposalivation. Saliva stimulation with secretogogues, such as pilocarpine [18, 19], cevimeline [20, 21], and bethanechol, may impact symptoms of xerostomia and has been shown to increase stimulated and unstimulated salivary flow; however, the effect on important sequelae such as dental caries or dietary adaptations has not been documented. Studies have also been conducted to determine whether secretogogues are effective preventive agents when administered concurrently with

radiation. A double-blind, randomized study of prophylactic bethanechol administration at 25 mg bid demonstrated a significant reduction in the complaint of Grade 3 xerostomia (71.42% placebo vs. 38% bethanechol), as well as improvements in stimulated and unstimulated salivary flow. The bethanecol group had mean unstimulated and stimulated salivary flow rates of 0.19 mL/min and 0.27 mL/min, respectively, compared to rates of 0.05 mL/min and 0.21 mL/min in the placebo group [22].

Salivary gland transfer is a surgical technique where transplant of the salivary gland outside of the radiation port is conducted, thus sparing it from radiation-induced damage. Currently available data demonstrates that this is an effective method for preventing the development of xerostomia and hyposalivation [23, 24]. However, the use of this technique is limited due to the increased use of intensity-modulated radiation therapy (IMRT).

IMRT is a radiation technique that allows the radiation beam to be targeted specifically at the tumor volume while sparing adjacent normal tissues to the extent possible. Proton beam for HNC may further reduce irradiation of adjacent tissues. One of the primary benefits for the use of IMRT in the HNC population has been the demonstrated ability to limit radiation to the salivary glands. Measurements of salivary flow after IMRT where the major glands are spared high-dose exposure show decrease in hyposalivation and improved QOL compared to patients treated with standard irradiation techniques [25–27].

Regardless of the cause of hyposalivation and/or xerostomia, supportive measures are indicated to maximize comfort and to minimize the adverse effects on dental health, dietary intake, and quality of life. As noted above, sialogogues may increase salivary flow and diminish xerostomia and should be considered as the preferred treatment if residual function of salivary glands remains as benefit can only be accomplished in patients with residual salivary gland function. Frequent oral rinsing with water, sodium bicarbonate solution, or products for mouth wetting ("salivary substitutes") may provide symptomatic palliation when saliva production cannot be stimulated. There has been no assessment of saliva viscosity and related function, and while mucolytics such as guafenasin and acetyl cysteine can be considered for patients with thickened secretions, their effectiveness is not well-documented.

## Dental Health

Dental enamel is composed largely of hydroxyapatite crystals containing calcium and phosphate. Although commonly thought of as static structures, dental enamel is dynamic and in constant flux. Depending on the oral environment and availability of enamel substrates, demineralization or remineralization will predominate. Demineralization predominates in an acid environment. The oral pH commonly reaches an acidic range when eating. Bicarbonate, which is present in saliva, helps buffer the change in pH accompanying a normal meal. Hyposalivation leads to a diminished buffering capacity that may lead to an acidic pH and favors demineralization. Furthermore, calcium and phosphate, which are critical in maintaining mineralization of enamel, are largely supplied by submandibular saliva, and lack of dental substrates may inhibit remineralization. Hyposalivation may also lead to a shift in the oral flora with high levels of colonization by cariogenic and acidogenic bacteria such as streptococcus and lactobacillus species.

Cancer therapies, particularly radiation therapy to the head and neck region, which are associated with hyposalivation, may lead to demineralization and dental decay. Of note, radiation-associated dental demineralization and caries are particularly problematic. They may develop within months after completing treatment and may progress rapidly. Due to the underlying pathology, reversal of the process once initiated may be difficult; thus, prevention is critical. Prevention requires recognition of the risk to salivary gland function during treatment planning and attention to preventive measures such as excellent oral hygiene and maintenance of a non-cariogenic diet. Cariogenic bacterial load can be reduced using a chlorhexidine rinse. Topical fluoride application promotes the deposition of

fluorapatite, a more acid-resitant version of the typical hydroxyapatite typically found in enamel, and has some antibacterial effects. Remineralization is favored in the presence of calcium, phosphate, and fluoride. Prophylatic fluoride administration should be used to optimize the structural integrity of the teeth. Additional studies into the additional benefit amorphous calcium phosphate may confer in this population are warranted.

## Oral Pain

In the acute setting, oral pain may be secondary to cancer, cancer therapy, or complications of cancer therapy. Cancer-related oral pain is most commonly seen in patients with HNC in which the tumors ulcerate or infiltrate into the soft tissue or bone. Less commonly, oral pain may be due to bone metastases from other sites or infiltration of oral tissues by hematologic cancers. The most common cause of treatment-related oral pain is mucositis secondary to chemotherapy and/or radiation therapy. However, oral infections such as candidiasis or ulcerations secondary to herpes viruses may also cause considerable discomfort in the acute setting. Less commonly recognized, but clinically important, is chronic oral discomfort after completion of therapy. Chronic oral discomfort after completion of therapy may be problematic in HNC patients, stem cell transplant patients with GVHD, and patients treated with standard-dose chemotherapy and targeted therapy.

Postradiation mucosal sensitivity is a commonly reported syndrome in patients who have received radiation therapy to the oral cavity. Although data regarding this phenomenon are limited, it appears to be more common and severe in patients with high-grade, diffuse, or protracted mucositis. It is hypothesized to be a neuropathic pain syndrome resulting from peripheral nerve sensitization secondary to release of inflammatory mediators. Clinically, patients describe the discomfort as a "burning" pain which is worsened by acid or spiced foods and dry air. The characteristics of pain suggest neuropathic mechanisms as well as potentially local factors such as hyposalivation and mucosal infection. Characteristically, postradiation mucosal sensitivity responds poorly to opioid analgesics. Agents used for neuropathic pain, such as clonazepam and gabapentin, may be more effective.

Patients who undergo hematopoietic stem cell transplantation are also at risk for chronic oral pain. In this cohort of patients, pain is most commonly secondary to GVHD. In the oral cavity, this may present as mucosal "autoimmune" disease (lichenoid, lupus-like or systemic sclerosis, Sjogren-like) which may cause considerable symptomatic difficulties [28]. The clinical manifestations of chronic GVHD in the oral cavity include mucosal inflammation, atrophy, hyperkeratosis, ulcerations, and perioral fibrosis. Patients complain of oral pain, mucosal sensitivity, xerosotmia, and taste alterations.

A number of less common oral pain syndromes warrant discussion. Some chemotherapeutic agents are neurotoxic (e.g., vinca alkaloids, platinum agents, taxanes) and may lead to peripheral neuropathy, orofacial dysesthesia, and pain that can be confused with pulpal disease, which must be recognized by dental providers [29]. Some patients may develop dental hypersensitivity following cancer therapy that may be due to dental demineralization and possibly neuropathy. Patients may experience symptomatic relief with topical application of fluorides and/or a desensitizing agents including toothpaste. Pain may be impacted by anxiety, depression, and sleep disturbances that a cancer diagnosis and cancer therapy can create. Clenching and bruxism may be increased and result in dental discomfort and orofacial pain including temporomandibular disorders. These patients may benefit from physical therapy including massage, physiotherapy, and/or muscle relaxants, depression or anxiolytic management, sleep hygiene, and sleep medications. Custom-made occlusal bite guards for use during sleep may be beneficial.

## Taste Alterations

Taste is related to a combination of sensory mechanisms including taste, texture, temperature, and

smell that is perceived when placing food or other agents in the mouth. Taste comprises five basic qualities: sweet, bitter, salty, sour, and umami. Umami is a taste sensation more recently described that is associated with pleasure or desirable flavor [30, 31] which may have the strongest correlation with impact upon quality of life. Taste is mediated by epithelial receptors distributed throughout the oropharynx, larynx, and upper esophagus. Other taste functions such as "fatty taste" and spicey taste are being investigated [32]. Taste is impacted by hyposalivation, as saliva allows food particles to reach the receptor sites. Oral factors impacting taste include oral hygiene, dental and periodontal disease, mucosal infection, diet, and oral products used.

Both standard-dose and high-dose chemotherapy with stem cell rescue have been reported to cause reduced or alterations in taste. Chemotherapy has been shown to be secreted in saliva, thus resulting in taste change until the drug is cleared. In addition, chemotherapy may cause direct damage to taste receptors. Taste changes associated with standard-dose chemotherapy may be less severe and more transient [33]. Similar to xerostomia, taste alterations are more severe in myeloablative transplantation as compared to reduced intensity conditioning. Hyposalivation and reduced sweet/salt taste are noted up to 3 years posttransplant [28]. Interestingly, no correlation was seen between GVHD and taste change, suggesting an independent relationship.

Radiation therapy causes direct damage to receptors and results in synaptic uncoupling. Taste is affected in up to 100% of HNC patients during and following radiation therapy with or without chemotherapy. Taste change typically begins in the second week of radiation therapy [34, 35]. Recovery of taste is variable, in some studies improving in 2–6 months following radiation; however, taste alteration may continue indefinitely. IMRT may spare salivary glands and thus reduce the impact of radiation therapy upon taste. However, low-dose irradiation of wider areas of the oral cavity which may be experienced with IMRT may impact taste. Radioprotectors, such as amifostine, may have utility in affecting taste by direct cellular protection or indirectly by maintenance of saliva.

In addition, taste disorders may follow oncologic surgery. Surgical trauma to the lingual branch of the glossopharyngeal nerve may result in ipsilateral alterations in taste. The true incidence of postsurgical taste changes is unknown because it may be underreported due to the fact that damage is unilateral and may resolve over time without treatment.

A number of nontreatment-related factors may impact taste function. Taste is impacted by altered quality or reduced volume of saliva by altered delivery of tastants to receptors. In addition, hyposalivation may lead to increased secondary infection, alterations in taste, and lead to compromised oral hygiene. Tissue necrosis, oral bleeding, and postsurgical wounds may lead to taste change, halitosis, and altered smell.

The sequelae of altered taste are significant. Patients with altered taste no longer enjoy food. This has a dramatic impact on social interactions and quality of life. When severe, taste alterations may result in nausea and gagging with oral intake. Oral intake may be diminished, resulting in weight loss and nutritional compromise. To date, there are no treatments which have demonstrated efficacy in improving taste. Although preliminary data supported the use of zinc supplements to treat and prevent taste changes, a large randomized phase III trial failed to confirm any benefit at the doses studied [36]. Other agents with preliminary study are megestrol and cannabinoids [37]. Dietary counseling/modification, adding seasoning to food, avoiding unpleasant foods, and food rotation are recommended. Local infection and hyposalivation should be managed if possible.

## Trismus

Radiation therapy and surgery may lead to fibrosis and scar tissue formation in the orofacial region, neck, and shoulders. Fibrosis leads to decreased tissue compliance and contracture. In the oral cavity, this may involve the oral aperture, tongue mobility, and the masticatory musculature

and the surrounding temporomandibular joint. It has been hypothesized that prevention of radiation exposure to the tissues of the TMJ through techniques such as IMRT may decrease the development of trismus; however, confirmatory data is lacking [38, 39].

The incidence of trismus is as high as 45% in patients who undergo surgery or radiation therapy which involves the tissues surrounding the TMJ [40, 41]. Trismus is defined as decrease in oral opening due to any cause, with most studies reporting the inter-incisal distance as the primary measurement technique (normal >40 mm in adults). Although there is no consensus on how to define mild, moderate, and severe trismus, in general an inter-incisal distance of between 25 and 35 mm reflects mild-to-moderate trismus, while severe trismus is present in patients with an inter-incisal distance of less than 25 mm. When trismus is severe, patients may be restricted to a liquid or puree diet. Severe trismus also limits the mobility of the tongue impacting speech, mastication, and deglutition. Finally, trismus impacts on oral access for dental care (hygiene, dental treatment, and dental prostheses fit and function) and intubation if needed.

To date, there are no rigorously tested treatments with established efficacy for patients with moderate-to-severe trimsus. Early identification of trismus with active physical therapy intervention is the most appropriate course of action. Although studies demonstrate that physical therapy produces only a modest improvement in established trismus, it may prevent progression of disease [42]. In patients with trismus who failed to improve with physical therapy, coronoidectomy may lead to increased jaw opening [43]; however, surgical intervention in fields of radiation therapy requires extreme caution. Early studies with pentoxifylline, which affects fibrogenic cytokine production, indicate the potential for improving established trismus; however, the studies are small and require confirmation [44]. Botulinum toxin has been assessed for management of trismus, although benefits are not clearly documented [45].

## Infection

Acute and chronic oral infections are associated with systemic chemotherapy and local radiation therapy to the head and neck. Several factors predispose to the development of clinical important infections including (a) mucosal barrier injury, (b) alterations in oral flora, (c) decreased saliva, (d) preexisting chronic dental and periodontal infection, and (e) poor dentition. Chemotherapy can be associated with myelosuppression which compromises immune defense mechanisms leading to local and systemic infections. Common microbial organisms associated with oral infections include anaerobic bacteria, fungal infections such as candidiasis, and activation of latent herpes viruses. Salivary gland hypofunction with resultant reduction in the antimicrobial functions of saliva and myelosuppression may lead to exacerbation of preexisting sites of chronic infections. The manifestation of oral infections varies from superficial candidal infections that result in mild discomfort to dental abscesses requiring extraction and protracted antibiotic therapy. Pretreatment dental assessment, appropriate dental hygiene, and routine oral examination are mandatory to prevent, diagnose, and treat oral infectious complications of therapy.

## Growth and Development of Children

High-dose chemotherapy can impact orofacial and dental development in children. Radiation therapy in the head and neck in children may impact growth and facial and dental development. The possible effects upon the dentition of cancer therapy include agenesis and alterations in tooth formation and tooth eruption, morphologic changes in enamel, altered crowns of teeth, and shortened and/or conical shape root structures. Dental malformations may result in reduced occlusal vertical dimension and mobility of teeth with agenesis of roots. These changes may not be readily clinically apparent. Diagnostic imaging including cephalometric study is important for documenting the extent of skeletal changes. Individuals in whom the hypothalamus is affected

may have delayed or altered maturation and sexual development.

## Compromised Wound Healing

High-dose chemotherapy, selected targeted agents, radiation therapy, myelosuppression, and poor nutritional status may compromise tissue healing. In addition to cancer therapy, comorbid conditions may affect wound healing (e.g., diabetes mellitus, myelosuppression, anemia, nutritional compromise). In patients who are at risk for poor wound healing, dental procedures including extractions must be done with due consideration. Guidelines have been developed for dental extractions in oncology patients; however, they are primarily based upon expert opinion. The evidence base for clinical practice is limited; current recommendations include the following:

- Expert and minimally traumatic extractions, at least 10 days prior to radiation therapy, or anticipated absolute neutrophil count becoming <500 $mm^{-3}$; antibiotic prophylaxis if neutrophil count is <1000 $mm^{-3}$ is often recommended
- Minimizing tissue trauma and primary closure of surgical site, if possible
- Platelet support if baseline platelet levels are <40,000 $mm^{-3}$

## Halitosis

Halitosis is a poorly studied but a not uncommon complaint in the cancer population. In the general population, halitosis is postulated to be secondary to the production of volatile sulfa compounds by oral bacteria. In one study halitosis was reported in 40% (10% mild, 8% moderate, 22% severe) of patients with recurrent, metastatic head and neck cancer [46]. Clinical experience suggests that halitosis may be associated with tissue necrosis, hyposalivation, mouth breathing, poor oral hygiene, altered diet, infection, and oral bleeding. Treatment is directed at the cause when possible [47]. Of particular importance is the identification and treatment of oral infections and persistent or recurrent cancer and tissue necrosis. Increased intensity of oral hygiene including tongue brushing/scraping and frequent use of oral rinses may improve symptoms. The use of agents such as chlorine dioxide, chlorophyll, green tea, or peppermint oil may mask the odor. Severe halitosis may cause significant emotional burden for patients and families and may result in social isolation, and thus it should be treated aggressively.

## Osteonecrosis

Increased risk for osteonecrosis of the jaws is seen in patients following head and neck radiation therapy (osteoradionecrosis—ORN) and in patients treated with bisphosphonates and denosumab (medication-associated osteonecrosis of the jaw—MONJ). A number of physiologic changes occur in irradiated bone that may contribute to the development of ORN. The traditional view of ORN pathogenesis is that radiation causes a hypoxic, hypocellular environment accompanied by oxidative stress leading to a chronic, non-healing wound. More recently, a new theory of ORN pathogenesis has been put forward which suggests dysregulation of fibroblasts resulting in fibrosis is the key etiological factor. It has also been suggested that bacteria may play a role in pathogenesis [48].

Mucosal necrosis and bone exposure can be asymptomatic or minimally symptomatic and therefore not recognized until late-stage disease is present. Comorbid risk factors include diabetes, use of immunosuppressive therapy, immmunosuppression, local trauma, and tobacco use. Prevention is the primary goal, and pretreatment dental management and preventive dental care to reduce local tissue irritation and dental disease following treatment are critical for both patients undergoing radiation therapy and those for whom bisphosphonate therapy is being initiated [49–52]. In ORN management may include antimicrobials, hyperbaric oxygen, sequestrectomy, and surgery with vascularized free flaps in advanced cases [51, 52]. Observational studies based on the

recent advances in understanding ORN's pathobiology have suggested that pentoxifylline and tocopherol have potential for the management and prevention of ORN, but these studies require verification by larger, randomized trials [53–55]. Other adjunctive approaches are being studied [52]. In MRONJ, management includes antimicrobials, gentle sequestrectomy, and avoidance of surgery if possible with a number of approaches under investigation [49, 50].

### Second Cancers

Patients with prior cancers are at increased risk for new secondary malignancies. In patients following stem cell transplant, increased risk of oral cancers is seen 5–9 years after treatment; three-quarters of these patients have GVHD before oral malignancy, and these cancers are associated with past mucositis, xerostomia, and erosive lichenoid changes [28]. The majority of oral cancers are SCC of the tongue, followed by salivary gland [28]. The increased risk is related to prior exposure to carcinogens (e.g., tobacco, alcohol) and viral cofactors and possibly related to prior cancer therapy. Survivors of transplant are at risk of developing recurrence of the primary cancer and posttransplant lymphoproliferative disorders (PTLD), which can manifest in the head and neck and oral cavity as gingival enlargement and masses requiring early detection and diagnosis [56].

## Targeted and Immunotherapy

Targeted therapies directed at specific molecular pathways are increasing in use. As experience with these agents increases, oral toxicities are being elucidated. The incidence and severity of oral toxicities is agent and class specific. A review of studies of mTOR inhibitor therapies found that mucositis was the most commonly reported adverse event occurring in 74.4% of patients (all grades). That being said, less than 10% of patients experience Grade 3 or 4 toxicity. Mucositis resolved and did not recur with dose reductions [57]. In a retrospective review of 747 patients on VEGFR-directed multitargeted tyrosine kinase inhibitors, oral adverse events were noted in 23.7% of patients. The most common toxicity were oral dysesthesia without evident mucosal pathology (12%) followed by altered taste (9.8%), ulcerative lesions (6.8%), xerostomia (3.5%), and paresthesia (0.7%) [58]. Toxicities occurred shortly after intitiation of the therapy (within 1–2 months). The highest incidence of oral adverse events was seen with sunitinib (40.4%) followed by regorafenib (33.3%), sorafenib (26.7%), and pazopanib (21.2%). EGFR inhibitors are also associated with oral mucositis; however, the incidence and severity are lower than with either mTOR inhibitors or VEGF-directed multi-targeted TKIs [59]. However, when used in combination with radiation, EGFR inhibitors result in an increased grade and severity of mucositis [60, 61].

Immunotherapy in its various forms heralds an exciting new approach to cancer therapy. The late effects of immunotherapy on oral health have not been well-characterized. Its toxicity however is likely to share many clinical features with oral GVHD [62]. Potential complications therefore may include hyposalivation, oral lichenoid reactions, increased risk for dental caries, limited opening, and the development of periodontal disease. Studies investigating the incidence and severity of these potential sequelea of immunotherapy are needed to more fully understand the impact of immunotherapy on oral health and quality of life.

## Prevention

The most impactful treatment for most of the late oral complications of cancer therapy is preventative care. The National Institute of Dental and Craniofacial Research [63] and the Royal College of Surgeons of England [64] have each published clinical guidelines for the oral care of cancer patients. The first step toward prevention is assuring that the patient begins from a state of good oral health. An oral evaluation should be done as soon as is feasible in the treatment planning process. Early involvement will

give oral health-care providers the necessary time to schedule and complete any treatment integrated with cancer therapy; planning is required to achieve an acceptable level of oral health prior to the initiation of cancer therapy. Whenever possible, dental procedures should be completed 14 days prior to the initiation of radiation therapy and 7–10 days prior to the initiation of myelosuppressive therapy whenever possible. The nature and timeliness of care is facilitated by intergrated oral care and oncology care teams. This early dental consultation provides an opportunity for oral care providers to prepare the patient for secondary effects of their cancer therapy, providing patients with additional psychological and emotional support with respect to these changes and potentially relieving associated anxiety. Patient education on the increased oral hygiene and additional preventive adjuncts should also be initiated at this first visit including but not limited to additional fluoride application, diet modification, chlorhexidine administration, and a stretching regimen for the prevention of trismus.

During and after cancer therapy, the patient should be placed on a regular recall regimen for the first 6 months after which each patient can have their needs reassessed. Frequent visits allow for supportive care for adverse oral effects of cancer therapy and early intervention on dental sequelae.

## Conclusion

With increasing numbers of cancer survivors, it is important to identify and understand the late oral effects of treatment. Unfortunately, our knowledge of the risk factors, manifestations, sequelae, and treatment of late oral effects is limited. Further research in this arena will enhance our understanding of oral late effects of therapy, thus enabling us to identify preventive strategies and interventions with the potential to ameliorate the symptom burden and improve functional outcomes and quality of life.

Although there are many oral late effect issues that require additional research, several recommendations can be made to clinicians based on our current knowledge. First and foremost, prevention and management of oral health is best achieved by integrating oral and medical care of cancer survivors. Close communication between the oral health providers and the medical staff is critical. Hyposalivation and xerostomia is the most common and severe late effect of cancer therapy. Aggressive oral hygiene with regular dental follow-up can impact dramatically on dental outcomes. Dietary and nutrition consults can be used to help assess the adequacy of diet, to identify dietary deficiencies, and to develop strategies for dealing with barriers to adequate nutrient intake. Appropriate referral to speech and language pathologists, lymphedema therapists, and physical therapists can impact physical functioning and minimize symptom burden. Cancer survivors require access to a comprehensive and integrated multidisciplinary cancer care team. By attending to preventive protocols and treatment of late oral effects in a timely and aggressive manner, we can optimize long-term quality of life and limit the impact of treatment sequelae.

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# Psychosocial and Spiritual Issues in Supportive Cancer Care

41

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## Part I: Spiritual and Religious Issues in Supportive Care in Cancer

"Spirituality" refers to the subjective experiences that relate to an individual's sense of connection with something transcendent—a deity, truth, values, beauty—that are manifested by the complexity of emotions of awe, gratitude, compassion, and forgiveness.

The human capacity for positive emotions, such as empathy, humility, and compassion, provides humanity with a sense of the spiritual.

The scope of spiritual and religious areas of inquiry gradually became integrated within the oncology and health psychology professions, as patients and medical healthcare began to recognize the spiritual dimensions within the therapeutic relationship [1]. Diverse spirituality concepts, assessment tools, and interventions have been proposed, yet their validation and application across multicultural societies are complex and inherently difficult [2].

Concepts based on V. Frankl's theory of "logotherapy" have been adapted and redefined into new models of psychotherapy such as "meaning therapy," "dignity theory," and "mindfulness" for cancer patients in palliative care settings, as a possible metaphor for spirituality [3–7]. Outcome evaluation of these and other structured forms of psycho-oncology intervention settings poses methodological bias, as spirituality is ineffable, complex, and interconnected within diverse fields of inquiry.

In light of the diversity and limitations of the concepts related above, we provide the following clinical vignette from within the culture and religious dimension of an Arab Muslim patient and family.

One Story—One Journey: Much to Learn for All Oncology Professionals.

### Alesha–Salah: A Narrative

(Patient and family have given permission to publish the story. Identifying biographical data was changed.)

Alesha was a 40-year-old woman, the oldest of eight siblings, born in a small village in Syria. Her family arranged a marriage at age 13 to an older cousin. Salah, her husband, was a 47-year-old man who was already considered mature

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when he married at age 19. He is a religious Arab Muslim with a strong belief of total obedience to the Qur'an. Alesha and Salah fled as refugees from Syria to Jordan, arriving in Israel in 2001. They already had family members residing in Israel for many years, and they moved into the same household with Salah's parents and brothers. The couple had five children, three daughters, and two sons, who were all living at home.

## Alesha: Medical History

Alesha experienced symptoms of pain, weakness, enlarged breast, and dyspnea, which were already present at age 37, more than 3 years before her death. She felt tired most of the time and tried to conceal her symptoms, ashamed of her condition. Women in the family attributed her symptoms to menopause, "a normal process of life when a woman starts to become old." Alesha was hospitalized for a few days in 2010, with severe pain and anorexia. She begged to return home.

The medical team diagnosed "invasive breast cancer" Stage IV, with metastasis to bone, liver, and brain. Alesha's oncologist, a religious Christian Arab, recommended hospice care and prescribed strong narcotics to help control her pain. He hoped this would allow her to benefit from a few hours of undisturbed rest and sleep. Alesha's family felt ashamed and believed they were cursed when they understood which disease she was suffering from. Moreover, it was completely forbidden to mention the name within her home, family, or community. If it became known that she had cancer, her sons and daughters would never be able to marry. Other than Salah and his parents, no one else knew the true nature of Alesha's illness. Salah perceived his parents as his emotional support system, honoring their religious wisdom and devotion to Allah. The extended family and neighbors within the village described Alesha as suffering from a "stomach virus that will clear up in a few days." According to Alesha, her own family in Syria had a medical history of cancer. Two of her sisters and aunts died of the disease, but they were not allowed to speak its name. Alesha absolutely and forcefully rejected the suggestion that she have a conversation with a nurse about genetic testing for her daughters. She responded: "This is a shameful disease that eats away one's impure insides. If anyone finds out about it, my family will be disgraced and stigmatized forever. God is our salvation. God has blessed me alone, to purify my soul before I can encounter him."

Alesha prayed day and night, believing that her illness was "a test from Allah," a purification of her body. "Allah gives and Allah takes" (Qur'an).

Alesha's embedded cultural beliefs enabled her to "be with Allah," without dimensional constrictions of time or space. She only implored that she be allowed to stay at home in her bed and not be hospitalized. She felt that her home was rooted within the soul and spirit of Allah. Alesha whispered to herself, "My eyes inside my old body are only dreaming of Allah's forgiveness and compassion. I am ready to die." Alesha died at home, at the age of 40, her bed facing Mecca, in the twilight of the evening. Salah, his family, and all the angel's prayers accompanied her at her death, blessing her new life in paradise. And, just as her name means "protected" and "embedded," Alesha is now forever "protected and embedded" at home with Allah [8].

## Alesha: Thoughts of Her Spiritual Journey

Alesha's spiritual life was rooted in her religious beliefs. Within her world of illness, she sought the hope and acceptance of an integration of life and death beyond any doubt or regret. Her vision of and devotion to her "new life with Allah" transformed the transition of dying into something positive and rewarding. Alesha's children and family believed that according to the Qur'an, there is no "right" age to die and accepted the physical reality of death. "There are events in the spiritual life of the devoted believer that are beyond human interference."

## The Muslim Spiritual Path

The Arabic word *Islam* means "total submission" to the will of Allah, the Creator of the Universe, by conforming inwardly and outwardly to his law. The Guide of Humanity is deep inside the spiritual Muslim's soul, and each deed is presented to Allah daily, as mentioned in the "prophetic Muslim tradition." This is the spiritual state where one worships God, realizing that God is watching and no secret lies hidden from the Creator of the Universe [9]. Muslims believe in the hereafter, where final judgment will take place and people will be adjudicated to heaven or hell based on their lawful or unlawful deeds, respectively [10]. Death is a subject often avoided, much less remembered, although the Qur'an alludes to death in several writings. A verse from Chap. 3, called the "Family of Imran" (Aal 'Imran) reads, "Every soul shall taste death and you will be paid in full only on the Day of Resurrection. Whoever is kept away from the Fire and admitted to the Garden will have triumphed. The present world is only an illusory pleasure" (Qur'an 3:185).

## Family in Islam: Norms of Behavior

In the Western world, individual autonomy, truth, and open communication are the core of the dominant bioethical cancer framework [11]. The perception of autonomy and openness as empowering and providing a sense of control tends to be blind to the fact that the decision-making process of the individual is involved in a complex relationship to his/her social surroundings.

In Islam, families live with uncertainty about the fate of one of its members, rather than confront an accurate prognosis or threat of dying. The total involvement of the family in Islamic culture is natural in the context of the long-held values of respect for unconditional solidarity in accordance with the normative religious-cultural tradition. The family is identified as a social entity whose being, integrity, and cohesion are only understood within its own dynamic and not within its individual members [12]. For Islam, the debate concerning knowledge and consent with respect to illness and healthcare revolves only around family norms based on the Qur'an. The family as the basic unit of authority is responsible for decisions about treatment and disclosure. In such cultures, the model is non-malfeasance (to do no harm) and to protect patients from any emotional and physical harm that may be caused by directly addressing illness and/or end-of-life care. Whether or not a medical team will be permitted to prolong life by introducing invasive treatments without causing further harm is a joint decision, made mostly by the males in the family together with the physician and not with the patient.

In some instances the matter is even referred to the religious leaders, who provide prescriptive rulings for the families' consideration [13]. In a reflection of religious idealism rather than practicality, patients have stated that they would prefer to die at home, in a holy place such as a mosque or in Mecca or Medina.

Care for the patient is a family responsibility, with illness and death being managed at home and not in the hospital [14].

Table 41.1 describes the family in Islam.

## Alesha's Beliefs

Was Alesha's spiritual life an outcome of her family and social religious archetypes? Or were her religious beliefs inspired and guided by her spiritual perception of life and imposed norms of behavior?

What role might professionals play in Alesha's story and in similar narratives? Perhaps that role should be … just to be there—to be present—to respect and understand the spiritual dimension of Alesha's and others' religious beliefs, of each individual's private "god." Not to judge, but to be open, to learn about the needs and priorities of each patient's inner self [15].

In Alesha's narrative, the professional's role may be to provide all the medical and paramedical options to alleviate her physical suffering, without imposing any moral values. Furthermore, private beliefs do not justify confrontation with

**Table 41.1** The family in Islam

| |
|---|
| 1. Honor, self-respect/self-esteem, and religious beliefs |
| 2. Imposed rules or decisions sanctioned by religious norms and spiritual family traditions |
| 3. Unquestioning loyalty to the family and the religious community and absolute solidarity, with, and obedience to, the male authority of husband-father |
| 4. Family is the basis for self and religious identity |
| 5. The individual identity is "the family" |

Alesha's dimensional beliefs or those of her family. With respect to questions about the life prognosis of a loved one, Muslim families are usually skeptical about definitive responses from healthcare professionals. They are likely to be more comfortable with responses like "This is in Allah's hands, and we can never predict this accurately." Muslims believe the life of every person is known only to Allah who predetermines the exact time of death [8].

## Spiritual as a Multidimensional Concept

Spirituality seems an abstract term. There is no one universal meaning, since the word "spirituality" represents distinct concepts for each individual, depending upon his or her world overview. Spirituality is associated with many descriptions, making the formulation of a universal definition theoretically complex.

The outcome is the outline of multiple concepts of spirituality, each presuming to incorporate the length, breadth, and depth of the diversity in an eclectic approach [16]. While the meaning of spirituality is still controversial, it is generally defined by scholars in a variation of distinctive paradigms.

One of the standardized forms of religion is handed down by religious authorities; another is a more highly individualistic way of belief system. Hence, Myers's definition of religion: "a continuing search for meaning and purpose in life—an appreciation for the depth of life—the expansive universe—and natural forces which operate a personal belief system" [17]. According to Koenig [18], spirituality possesses little empirical utility and should be replaced by emotional and moral terms. Furthermore, it is still possible to be "spiritual" without being religious. In a similar way, Harris [19] advocates that the term "spiritual" may refer to meditation, as a person becomes totally immersed in his or her "being" and submerges the body and soul in a deep spiritual consciousness.

Foucault's spirituality comprises the discursively mediated acts, practices, and exercises through which certain individuals seek to transform themselves into the kind of subject or self that is capable of acceding to truth: "we could call 'spirituality' the search, practice, and experience to which the subject carries out the necessary transformations on himself in order to have access to the truth."

"We will call spirituality then, the set of these researches, practices, and experiences which may be purification, ascetic exercises, renunciations, conversions of looking, and modifications of existence" [20].

Contemporary definitions of spirituality may be interpreted by each society and each individual, emphasizing that meaning and language are not always synonymous. It seems that one could have a term—"spirituality"—but no common set of defining characteristics of the term that are universally transferable and/or recognized [21, 22] (Tables 41.2 and 41.3).

## Family Cultural and Spiritual Care

For whom should interventions be designed and addressed—for the patient, the couple, the children, the medical team, or all of them? The professional's responsibility to every individual and system is not necessarily diverse or unidirectional, and helping one may result in a disservice to the other. The challenge for the healthcare professional should be to integrate and tailor interventions suitable to the specific needs of the family and patient and to relate directly to the cultural and spiritual perception of the illness.

Evidence-based data indicates that patient adaptation to the process of illness, or the proximity of loss, is facilitated by family trust,

**Table 41.2** Features of spirituality [23]

| |
|---|
| 1. Meaning: the ontological significance of life, making sense of life situations, deriving purpose and meaning for existence |
| 2. Value: beliefs and standards that are cherished; having to do with truth, beauty, and worth of a thought, object, or behavior; often discussed as "ultimate values" |
| 3. Transcendence: experience and appreciation of a dimension beyond the self; expanding self-boundaries |
| 4. Connecting: relationship with self, others, God/higher power, and the environment |
| 5. Becoming: an unfolding of life that demands reflection and experience; includes a sense of who one is and how one knows |

communication, and involvement of professional empathy and compassionate care [24] (see Table 41.4).

Which interventions might facilitate communication, emotional support, and compassionate language, within their own spiritual values? The healthcare professional should begin by normalizing the disruptive effect of cancer on family life and its tendency to foster chaotic, paralyzing, and bewildering behavior. Heightened stress should be reframed as a function of and reaction to illness, rather than family inadequacy, a normal reaction to an abnormal situation. The professional's attitude of respectful understanding and empathy may help to engage the family in meaningful dialogue about how the illness has affected each member's roles, as well as relationships, and religious life.

A broad range of learning processes, drawn from theoretical family models, should be employed to help families share their experiences, explore changes in relationships, and raise awareness of cancer as a family culture, rather than an individual illness [25].

**Table 41.3** Patient's search for spirituality [23]

| |
|---|
| 1. Who am I? Who is the I? |
| 2. How do I show my need for compassion? |
| 3. How do I share uncertainties and hopes? |
| 4. What are my thoughts about searching for spirituality? |
| 5. How do I find the right prayers for myself? |

## Spirituality in Cancer Care: Research on Cultural Perspective

A broad Medline search including the terms "spirituality" and "cancer" revealed that during the past 6 years (2010–2016), the number of publications with those keywords (720 publications) was larger than the number of publications with the same keywords in the former decade (2000–2009: 573 publications). There is cumulative research evidence concerning the central role that spirituality and religiosity play for cancer patients and their caregivers [26–28].

More and more, solicitude for spiritual symptoms is considered an integral part of holistic cancer care, with a growing recognition of the need for more evidence-based outcomes [29, 30].

Relevant developments contributed at least partially to position statements like that of the Multinational Association of Supportive Care in Cancer (MASCC), concerning the role of psychosocial and spiritual care through the journey of cancer and dying [2].

The Joint Commission, a nonprofit accreditation agency for hospitals and healthcare settings in the United States, requires the routine assessment of spiritual needs for most patients. The spiritual evaluation consists of questions like: "Do the patients use prayer in their life? How do the patients express their spirituality? How do the patients describe their philosophy of life? What type of spiritual/religious support do the patients desire?" [31, 32].

A Consensus Conference held in the United States in 2009 centered on recommendations for advancing the delivery of quality spiritual care in every palliative care center and program [33]. Nevertheless, in spite of the subject relevance, there continues to be a gap between the understanding of the importance of spirituality and its actual integration into clinical work by healthcare professionals.

An international survey of the MASCC members indicated that while professionals acknowledge the importance of spiritual care for cancer patients, they seldom have formal training and are reluctant to provide such care [34].

**Table 41.4** Basic variables

| |
|---|
| 1. Family |
| 2. Gender, age, culture, and religious beliefs |
| 3. Perception of the illness according to patient and family values |
| 4. Communication between family and healthcare team |
| 5. Degree of objective and subjective burden, experienced by family members (male vs. female) |
| 6. Extent to which the disease is perceived as a threat, stigma, taboo, or punishment |
| 7. Disease- and cancer-related outcomes from family traditions |
| 8. Availability of family members who can provide spiritual, religious, emotional, and instrumental support |

Another large survey among pediatric centers in Italy and Spain also reveals the need for spiritual counseling while acknowledging there is a lack of formal training both for chaplains and professionals [35].

The complexity of spirituality in cultural concepts described by Surbone, Konishi, and Baider focuses on relevant areas of spirituality within the cancer patient's trajectory of illness [2]. Cultural definitions of spirituality and religion leave space for the understanding of spiritual well-being as an essential component of medical and psycho-oncology care in every culture, manifested in a variety of coping skills, adaptive mediations, and social behaviors [23, 36, 37].

One study shows that spirituality-based interventions for religious Muslim cancer patients reduce dopamine gene receptor expressions, in comparison with those of pretest scores in the control group [38]. Such interventions are supported by the Qur'an and include issues like prayer, repentance, altruism, dedication through quality of beliefs, and preparation for death within Islamic culture [39].

Similarly, religious Indian Muslims in palliative care were found to more frequently associate meaning of life with spirituality, in comparison to Western patients. Concepts like "karma" and "rebirth" were found to help patients, providing them with existential meaning for their suffering and thus improving their sense of well-being [40, 41].

The authors emphasize the importance of timely and culturally sensitive provisions of religious and spiritual support for patients, at all stages of the cancer continuum [42].

We need validated instruments for different cultures and languages, to be able to identify spiritual distress and provide meaning, compassion, guidance, and subjective support for patients facing terminal illness and death [43].

## Spiritual Assessment Tools

How does the psycho-oncology team provide spiritual care? Are dedicated spiritual teams necessary, and to what extent are they available?

The answers to these questions require the input of oncology professionals, chaplains, and other potential members of spiritual teams, as well as the commitment of institutions' policy-makers, based on different local resources and cultures [27].

The following considerations may be of help to workers in supportive cancer care. In addition to being a professional in a particular field, every team member has a spiritual dimension and thus is also capable of connecting with patients on a spiritual level.

Conversely, oncology professionals should not be expected to act as spiritual advisors, since this role requires specific education and training so as to avoid any potential risk of conflict or imposition of their roles beyond due limits [1].

Common methodologies of spiritual assessment have been developed in recent years and validated in Western settings, to assist health professionals in gathering a "spiritual history" of cancer patients [44].

These instruments measure multidimensional indicators of religion and spirituality and have demonstrated good psychometric properties, including self-ratings used to predict a range of social attitudes and health behaviors [45].

The SPIRIT scale, developed by Maugans [46], is based on an assessment of spiritual beliefs, personal spirituality, integration within a spiritual community, and ritualized practices and restrictions with implications for use in medical care terminal event planning.

The Systems of Belief Inventory (SBI-15R) is a brief self-report inventory designed and validated by Holland and Baider, and their colleagues

[47], for use in quality-of-life and psychosocial adjustment to cancer. The inventory measures religious and spiritual beliefs, and the social support derived from the community in sharing those basic spiritual assessments, as recommended in the United States by the Joint Commission.

While this is necessarily limited, it may open the doors for patients to feel at ease in raising spiritual concerns [48].

### Spirituality in Multicultural Clinical Settings

Respecting cultural diversity implies more than treating individuals as equal; it encourages healthcare professionals to strive for a fuller understanding of cultural and ethnic differences. Care providers must understand that basic values of Western medicine are not necessarily shared by patient families of all cultural backgrounds. Providers should seek knowledge about the communities they serve ("cultural competence"), while being reflective about their own values and cultural beliefs, and how these shape the care they provide ("cultural humility") [49].

Focusing on each person's positive emotions and values is the best and safest route to spirituality found within ourselves and our patients [50]. Spirituality and religion are different concepts and dimensions of any one person's search for meaning and connection beyond the self, yet many people express their spirituality through religiosity and it's rituals, which are different in the various religions. These therefore need to be known, appreciated in their diversity, and fully respected by all health and oncology professionals. Relevance of various themes should be identified by observing and describing the significance of spirituality in chronically and terminally ill patients [51].

## Part II: Psychosocial Issues in Supportive Care in Cancer

In this section on psychosocial issues in supportive care for cancer patients, we review the most common concerns and needs of our patients and summarize the literature on specific assessment tools and clinical interventions for psychosocial needs of cancer patients. In 2010, as Multinational Association of Supportive Care in Cancer (MASCC) Psychosocial Study Group, we published a position paper entitled "Psychosocial care for patients and their families is integral to supportive care in cancer: MASCC position statement" [27]. The article asserts the importance of recognizing and addressing psychosocial issues during all phases of the cancer course, from diagnosis to death or survivorship. We stressed the need for culturally sensitive psychosocial support to patients, families, and caregivers providing assistance to cancer patients at home, cancer facilities, and hospices during all phases of the communication and decision-making process, through innovative psychosocial interventions. We also emphasized the importance of developing and implementing effective programs to support patients and their caregivers who face substantial emotional and financial costs. We concluded that it is necessary to overcome institutional and structural barriers to psychosocial support during the illness trajectory of cancer patients through a shift in the culture of cancer care, as well as through our full commitment as individual oncology professionals dedicated to supportive care and as members of MASCC—an association with potential large impact also on institutions and policy-making [27].

The 2007 Institute of Medicine (IOM) report entitled "Cancer for the whole patient: meeting psychosocial health needs" [52] stated that the psychosocial dimension, including appropriate assessment and interventions, must become an integral part of routine cancer care for all patients. While cancer care and supportive care during the treatment phase has improved considerably during the last decades, the study and inclusion of psychosocial issues of cancer patients and their families and caregivers started more recently. The literature rapidly grew at first and is now consistently stable with a large number of yearly publications in this field. Similar to what we did with regard to the literature on spirituality, we conducted a broad APA

PsycNet search including the keywords psychosocial and cancer, which shows that the number of publications including these terms in last 6 years (2010–1016: 3922 publications) was as large as the number of publications with the same keywords in the former decade (2000–2009: 2975 publications). Also a broad PubMed search including the keywords psychosocial and cancer showed that the number of publications including these terms in last 6 years (2010–1016: 5317 publications) was as large as the number of publications with the same keywords in the former decade (2000–2009: 3412 publications).

## Common Psychosocial Concerns and Needs of Cancer Patients

Psychosocial concerns and needs of cancer patients should be addressed as integral part of oncology care at all stages, as they are inextricably intertwined with medical aspects at all stages of cancer care [27, 52]. The psychosocial dimension is integral to supportive care from the time of diagnosis to that of relapse or death, as well as through the various "seasons of survival" [27, 53, 54]. Studies show that cancer affects all aspects of the patient's life, and it is now considered as a disease of the entire family [55]. Consequently, also families' and caregivers' specific concerns and needs should be studied and considered in delivering psychosocial care, and specific psychosocial interventions should be developed and implemented for caregivers. Furthermore, guidelines and models of psychosocial care should be culturally sensitive, feasible, and applicable to different local contexts with different human and financial resources [27].

The basic psychosocial concerns and needs of cancer patients appear to be similar and can be classified according to concrete and practical categories that change over time, as the patient's cancer trajectory evolves from diagnosis toward progression and death or toward remission and survivorship in various forms and stages [56] (Table 41.5).

## Psychosocial Concerns and Needs of Cancer Survivors

Due to earlier cancer diagnosis and more effective risk reduction, improvements in cancer treatments, and the aging of the world population, especially in Western countries, with increasing cancer rates in developing countries, the number of cancer survivors is rapidly growing worldwide. In response to the emerging reality of cancer survivorship, in 2006, Institute of Medicine (IOM) issued a report detailing plan for cancer survivors, including how to write a survivor prescription. In 2007, the American Society of Clinical Oncology (ASCO) included survivorship in mission priorities and issued guidelines for fertility preservation in young cancer patients. In 2007 National Cancer Institute (NCI) instituted dedicated survivorship program for oncologists and patients. In 2009 Multinational Association for Society for Supportive Care (MASCC) extends supportive care to cancer survivors. In 2010 the American Society of Clinical Oncology (ASCO) established the ASCO Survivorship Committee, which has since issued many clinical guidelines and educational recommendations, where the need for psychosocial care as part of survivorship care is stressed [54, 57].

When patients are diagnosed and treatment is initiated, the primary goal is therapeutic, and psychological, emotional, and social factors tend to become secondary to immediate treatment decision-making. Yet, most of the issues that characterized survivorship arise at diagnosis, and they should be addressed as early as possible during the illness's course.

Before analyzing in detail the psychosocial concerns and needs of cancer survivors, it should be stressed that the definition and perception of

**Table 41.5** Common cancer patients' psychosocial concerns and needs

| |
|---|
| 1. Follow-up care beyond treatment to survivorship |
| 2. Emotional and spiritual needs and concerns |
| 3. Special needs in end-of-life care |
| 4. Special care for elderly cancer patients |
| 5. Family and caregiver support |

the word "survivor" is evolving and it is not the same in all countries. In the US literature, survivorship begins at diagnosis and includes the reentry phase, the transition from the treatment to the posttreatment stages [53, 58]. In many other countries, however, survivorship is considered to start 3–5 years after the completion of treatment [59]. While endorsing the NCCS definition of cancer survivor, the American Society of Clinical Oncology in its 2013 statement developing optimal survivorship care models and guidelines adopted a "functional definition" of long-term survivorship as "individuals who have successfully completed curative treatment or … transitioned to maintenance or prophylactic therapy …" [59].

A categorization of survivors based on their actual disease and risk status has been proposed, including also the possibility to use the term "cured" under strict criteria, to allow tailored survivorship care to be delivered more effectively and sensitively to different individuals belonging to different categories and facilitate individual patients' adherence to clinicians' proposed surveillance and follow-up, including measures to foster good general health. Finally, categorization of survivors may contribute to reducing the stigma of the disease that still persists in many cultures and countries and thus increase the psychosocial well-being of survivors worldwide [56].

The psychosocial concerns and needs of cancer survivors, connected with their medical, rehabilitation, and mental health concerns, belong to different categories, as shown in Table 41.6.

These vary with age at diagnosis, cancer type and stage; long-term toxicity of treatment; actual or potential long-term repercussions of the cancer diagnosis on their relational and social life, including different forms of stigmatization or discrimination; access to survivorship care; and human and financial resources of different sociocultural contexts.

Despite growing research and clinical efforts, psychosocial concerns and needs are still rarely discussed during the initial acute phase of diagnosis and treatment, where the focus tends to be on the immediate medical aspects. Moreover, they are especially ignored at the time of transition from acute care to follow-up, where still many patients are "lost," despite the intense and rapid development of survivorship care as a new branch of oncology.

The National Cancer Institute's (NCI) Office of Cancer Survivorship recommends that oncology professionals acquire specific education on both immediate treatment decisions and long-term sequelae of cancer treatment and study, develop, and implement appropriate interventions [60]. These include medical counseling about lifestyles to maintain and improve health; prevention and surveillance for recurrences, new primaries and second tumors; measures to maintain/improve fertility; and physical and occupational therapy. The most common psychosocial factors affecting the quality of life of survivors are listed in Table 41.7. Psychosocial counseling and assistance include also education of patients, families, and the public [61].

The experience of survivorship is different for each cancer patient and is related to many individual and societal variables, including age, gender, socioeconomic status, family support, community resources, and different cultural views of the meaning of cancer and disability. Many survivors adapt to their posttreatment situations and continue to successfully engage in productive or otherwise meaningful activities. Others struggle with persistent psychological vulnerability or physical disability. Others still experience difficulties in resuming their jobs and may be stigmatized or, at times, openly discriminated against. By promoting survivors' emotional and social adjustments, supportive care experts can contribute to identifying resources and overcoming barriers among diverse populations and to develop models for evidence-based research with diverse populations, including minority and

**Table 41.6** Psychosocial concerns and needs of cancer survivors

| |
|---|
| Informational |
| Practical (financial, assistance) |
| Emotional |
| Interpersonal |
| Existential |

**Table 41.7** Psychosocial factors affecting quality of life of cancer survivors

| |
|---|
| 1. Fear of relapse |
| 2. Body image and self-awareness consciousness, awareness of "being different" |
| 3. Concerns about sexuality and fertility |
| 4. Stigmatization and taboos |
| 5. Employment, financial, and insurance issues |
| 6. Shifts in family roles and dynamics after a cancer diagnosis |
| 7. Concerns about meeting family's expectations |
| 8. Social support and validation of needs |

underserved ones in Western societies [62]. Models and standards of psychosocial care include preventive strategies and detailed recommendation plans for follow-up care based on the specific needs of individual cancer survivors and the local resources of each community [27, 54, 62].

## Psychosocial Concerns and Needs of Cancer Patients at Advanced Stages and at the End of Life

Palliative and end-of-life care address the patient experience of terminal illness in a multidisciplinary, multidimensional, patient- and family-centered way. According to the WHO, palliative care is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [63]. Supportive and palliative care experts work together as part of teams that address all medical, psychosocial, and spiritual dimensions of the dying person with utmost respect for her individual preferences and vulnerabilities and always considering her family and loved one. They help alleviate physical, psychological and spiritual suffering, offering competent compassionate care during the dying and grieving process.

Cancer patients' experiences in dying need to be understood and integrated within the context of their cultural values and community, which entail different meanings, life narratives, and spiritual and religious elements [11]. Across different cultures, cancer patients' families assume the role and the burden of providing care toward the end of the patient's life: as a consequence, a functional interaction among families, patients, and oncology professionals needs to be established [27]. The emotional, social, and financial tolls of informal caregiving is generally very high, and assessing the quality of life of caregivers and providing them with psychosocial assistance are part of delivering optimal palliative and end-of-life care.

## Psychosocial Concerns and Needs of Families

The experience of chronic illness is inseparable from the family life history and is embedded within cultural, religious, and historical contexts that shape families' appraisal and value orientations toward cancer. Family has been described as the basic social and ethical unit of cancer care, since all confrontations with patients' illnesses and with their death and dying belong to the moral realm of family boundaries [55].

The threat that cancer poses to the family can be understood in light of how different members, individually and as a whole, construct and share meanings about specific stressful situations, their identity as a family, and their view of the world. Neither patients nor their families can ever return to a pre-illness situation, and successful coping with the separations and losses that accompany cancer patients in their illness trajectory is dependent on solid and mature family relationships, as shown thorough assessment of their cohesiveness, mutuality, flexibility, and shared needs [64]. Supportive care professionals can help to identify adaptive, functional, and nonadaptive family coping mechanisms, as well as family conflicts, and refer family to psychologists or mental health providers, when these are needed and available, for specific interventions.

All members of the family should ideally participate in psychological intervention to enhance quality of life, to regain control and autonomy,

and to share common meanings, according to different family dynamics [65]. Many different types and modalities of psychological interventions have been published in the literature [66]. Table 41.8 summarizes the key variables that should always be taken into considerations (Table 41.8).

Also in context with limited human and financial resources, identifying potential issues or conflicts within the family and recognizing the psychosocial concerns and needs of family members are possible through the establishment of an open and honest relationship among all parties involved in the care and assistance of cancer patients at all stages of their illness course. Interventions may be simple supportive measures offered by the medical team in concert with the community, and support to the whole family should be offered in all contexts.

## Psychosocial Concerns and Needs of Informal Caregivers

As the number of cancer patients and survivors of all ages rapidly increases in the developed and developing world, the role of caregivers also grows. Most caregiving to cancer patients is provided by families and friends, taking a major toll on them from an emotional and economic standpoint. Providing care to cancer patients may be especially demanding, because of the sudden onset of cancer, its potentially life-threatening nature, and the need for supportive care, which is initially sporadic yet tends to become more intense and constant as the illness evolves [67, 68]. Most cancer caregivers are women, yet the number of men is increasing, especially for older patients.

**Table 41.8** Family intervention should be attentive to several variables

| |
|---|
| 1. Family structure and dynamics |
| 2. Gender, age, education, socioeconomic status, culture, religious beliefs |
| 3. Medical status, perception of the illness, and treatment consequences |
| 4. Communication between patient, family, and healthcare team |
| 5. Degree of objective and subjective burden experienced by family members |
| 6. Extent to which the disease is perceived as a threat or as a life challenge |
| 7. Past meaningful events, coping styles |
| 8. Locus of attributions made for the disease- and cancer-related outcomes and the meaning made of personal experience |
| 9. Availability of a network of friends and family members who can provide tangible emotional and instrumental support |

Regardless of gender, age, and ethnicity, caregivers are at risk for major stress, anxiety, and depression and are vulnerable to possible emotional, physical, and financial repercussions [69]. A meta-analysis of different psychological interventions for family caregivers of cancer patients concluded that "clinicians need to deliver evidence-based interventions" to help caregivers and patients to cope effectively, maintain their quality of life, and increase resilience and meaning [66]. Supportive care specialists can assist in developing effective strategies for family and friends to ask for help, enjoy aspects of their own lives without feeling guilty, recognize signs of stress and depression, and seek professional help when needed. Part of psychosocial care entails making caregivers aware of their country's laws and regulations in matters of employment and leaves of absences and of available support structures in their communities [27]. An equally important aspect of psychosocial care is to provide support to those caregivers who assist cancer patients at home during the dying and death process [70]. The cultural and religious beliefs and norms of different patients and families should always be acknowledged and respected in providing psychosocial support [71].

## The Cultural Dimension of Psychosocial Care for Cancer Patients and Their Families

Culture refers to the patterns of knowledge, beliefs, and behaviors of a given community, shaped and sustained by many contributing factors that include, but also go beyond, ethnic and geographic boundaries, age, gender, religion, and

educational level [49]. Culture influences values and lifestyle choices, including those related to health matters. Cross-cultural differences may have an impact on cancer care along its continuum, from prevention, screening, and early detection to treatment access and response, rehabilitation, and palliative care and finally to end-of-life care or survivorship. Cultures are responsive, adaptive, and evolving especially in multiethnic societies where acculturation and assimilation take place at varying paces and degrees with regard to health attitudes and practices [72]. Without knowledge and skills in cultural competence, certain cultural beliefs or behaviors may appear unnecessary or maladaptive. Furthermore, most published studies in the medical literature focus on the vulnerabilities of non-industrialized cultures, rather than on different cultural strategies to promote and protect and health in non-dominant cultural groups. By contrast, in our growing multicultural societies, we should develop individual and institutional sensitivity in order to respond appropriately to different health values and coping strategies of diverse cultural communities and integrate them in the care of each patient [72]. For example, in many cultures based on family- and community-centered values, cancer patients are still not told the truth about their diagnosis, and often the family is informed instead of the patient and makes decisions for him or her [73]. With sensitivity to the different health values and attitudes of each patient and cultural group, it is possible learn cross-cultural communication and cultural competence to negotiate between discordant cultural views among oncology professionals, patients, and families in order to achieve a common therapeutic goal [72, 74].

Assessing psychosocial concerns and needs of patients and families and communicating and planning psychosocial interventions may be especially difficult in the presence of cultural differences, as there may be different norms and habits regarding discussing information that is considered private or extremely delicate, such as financial or sexual issues. Formal teaching and training of patient-centered approaches to cross-cultural care, based on assessing core cross-cultural issues, exploring the meaning of illness to patients, determining patient's lived social context, and negotiating adherence to recommendations and treatments, is now mandatory in many countries and must be accompanied by the establishment of culturally competent healthcare systems with the capacity to adapt their services to meet the culturally unique needs of their patients, also through the involvement of their different communities [72, 74]. Learning and mastering cross-cultural communication is a basic requirement for all health professionals practicing in multiethnic and multicultural societies and requires knowledge and sensitivity [75].

## Guidelines and Models of Psychosocial Evaluation and Intervention in Cancer Care

Studies on how to identify and address the psychosocial needs of cancer patients in different contexts are growing and guidelines are being developed and tested [76]. Due to cross-cultural differences that shape patients' and families' health beliefs and values, as well as ethical norms and health policies in different countries, the implementation of single therapeutic models to fit all socio-cultural contexts is impossible. By contrast, there is a need to evaluate which model could be more easily absorbed and integrated in diverse local realities across the world, taking into account the scarcity of human and financial resources of most non-industrialized countries. In order to adapt the model to a given setting, oncology and supportive care professionals need to identify not only the needs of each patient but also the services provided by their communities, according to their local resources and manpower. The "Tiered" model, for example, is an integrated multidimensional approach to implementing psychosocial care through a community-based approach that tailors the level of intervention to the degree of patients' and families' psychosocial distress, integrating different services and sectors within each community [77]. In many small communities and in poverty settings, where there are not sufficient human and financial resources to organize com-

prehensive teams and psychosocial units, locations such as schools, places of prayer and worship, and social settings for elders or for youth can be channels of information about psychological support and effective instruments for its delivery [77].

The economic impact of psychosocial interventions needs to be taken into consideration, and appropriate outcome evaluation measures are needed. While standards for evaluating cost-effectiveness of psychosocial end points in interventional supportive trials have not yet been fully developed and validated, the most cost-effective interventions depend on different variables, including individual factors, readiness to transition from one phase to another of the cancer trajectory, and the illness stage at which they are performed. For example, counseling patients in person can be complemented with the distribution of educational and self-help material, from booklets to videos and professional referral to reliable internet sources. Educational videos, for example, are cost-effective ways to improve the transition of breast cancer patients from the acute treatment phase to survivorship worldwide [78]. Yet they may not be feasible in all sociocultural contexts. Furthermore, all psychosocial interventions should be subject to validation through outcome measures that evaluate intermediate- and long-term cost-effectiveness on the basis of the end point, whether personal or clinical improvement. Intermediate outcomes are especially useful to measure the results of interventions on fatigue and low energy, which can seriously affect patients' emotional and psychosocial well-being, as well as individual and family productivity [79].

Regardless of the model of psychosocial evaluation and intervention chosen, physicians and nurses should always work together and with other members of the medical team to deliver optimal psychosocial care to cancer patients and survivors and their families and caregivers. Case discussions should never be limited to the evaluation of patients' treatment progress but rather always should include a wider evaluation of the quality of patients' and families' life, acquiring and sharing knowledge and specific expertise among all team members.

## Conclusion and Future Perspectives

To find meaning in memories as part of constructing value in life is an important function of each person's life review process. Recognition of spirituality, the confrontation of limitations, and the awareness and acceptance of both the positive and negative aspects of life provide the opportunity to seek forgiveness and humility within ourselves and in all human encounters.

As oncology and psycho-oncology professionals, we need great tenacity to develop our own path to spirituality and sustain our patients in embracing the present moment, appreciating the preciousness of time. To do so, we must identify and acknowledge the many barriers that oncology professionals perceive and encounter in approaching spiritual issues with their patients and respectfully try to overcome them to achieve a higher quality of psychosocial and spiritual care, as integral part of medical and supportive cancer care [80].

We need to be truly present in the here and now, no matter how painful this can be or how short a time may be left, caring for each other as patients and as professionals. We also need a paradigm shift in supportive cancer care where the psychosocial concerns and needs of cancer patients and survivors are always approached timely at every stage of the illness, including those of patients' families and caregivers. Existing institutional and structural barriers within different communities and healthcare systems must be identified and overcome. The role of culture, spirituality, religion, families, and caregivers still needs to be better understood, defined, and be subjected to rigorous empirical research. Institutions and individual professionals must receive proper training in assessing psychosocial and spiritual concerns of cancer patients and survivors and addressing them. Guidelines and models of psychosocial care should be culturally sensitive, feasible, and applicable to different local contexts with different human and financial resources. Studies on legal and financial issues that affect patients' and families' psychosocial well-being should be conducted in all patients' groups, including minority

and underprivileged ones. Finally, existing gaps in cancer treatment and psychosocial care across different countries and practice settings must be identified and adequately addressed.

As a large international multidisciplinary organization, dedicated to improve the quality of life of cancer patients and survivors, MASCC is committed to making cancer patients' psychosocial and spiritual concerns and needs a priority not only for all oncology professionals but also at institutional and policy-making levels across countries and healthcare systems.

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# Survivorship: Physical Issues

# 42

Paul A. Glare and Ian Olver

## Introduction

Patients who have been treated for cancer may experience various symptoms that result from tissue damage caused by the various modalities of anticancer therapy. Poorly controlled symptoms in survivors are often more prevalent and severe during treatment but can persist for years afterwards, impairing quality of life and preventing them from returning to a normal life. This chapter focuses on the late effects of cancer treatment, including second malignancies and organ-specific damage, followed by a consideration of the common treatment-related symptoms of pain. Other common symptoms in survivors are described in other chapters. The chapter concludes with the challenges of returning to work after cancer treatment.

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## Physical Symptoms

Having survived cancer and its treatment, the physical sequelae are often the result of the interaction of the late side effects of treatment, the persisting effects of the tumor, and comorbid conditions impacting on organ systems. The number of cancer survivors is increasing in high-income countries such as the USA [1]. These survivors are often in older age groups, and risk factors such as poor diet, lack of exercise, and smoking tobacco which increased their risk of cancer also put them at higher risk of developing other chronic conditions like diabetes and heart disease. It is estimated that over 70% of cancer survivors have multiple chronic conditions [2].

## Late Effects of Cancer Treatment

There are side effects of cancer treatments that can persist and impact on the quality of life of cancer survivors. The occurrence of these depends on the treatment modality and the extent of the treatment. Treating children is particularly problematic as damage to organs such as the heart and lungs can have life-threatening consequences in adulthood, and the expected lifespan can encompass the development of second cancers.



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## Second Cancers

Of the late side effects of treatment, the most confronting is the development of a second malignancy. Much of the data of the risk of radiation comes from diseases treated with curative intent, like Hodgkin disease, or the treatment of childhood cancers [3].

Children who have been treated with radiotherapy, alkylating agents, anthracyclines, and epipodophyllotoxins and some who are genetically predisposed are more likely to develop second cancers [4]. Radiation can result in cancer in the field that is irradiated, most commonly breast cancer in girls after chest wall irradiation, thyroid cancer, and central nervous system cancers [5]. There is a long latency between exposure and the development of the cancer (median 7 years) in tissues in the radiation field. The risk increases with radiation dose and is greater in younger patients and when concomitant chemotherapy is given. The major secondary malignancy induced by chemotherapy is acute myeloid leukemia [6]. Up to 10% of childhood cancer survivors may develop a second cancer over three decades from their original diagnosis [5]. Moreover, even after 40 years of age during their fifth and sixth decade of life, they remain at increased risk [7].

## Organ Damage by Radiotherapy

In adults common sequelae to radiation therapy occur with irradiation of the prostate gland which can result in impotence and incontinence as long-term effects. Also chronic diarrhea occurs due to radiation damage to the rectal wall [8]. Chronic bladder problems will likewise occur with pelvic radiation, as exemplified by the treatment of rectal cancer.

Radiotherapy to the chest for lung cancer or even breast cancer may result in decreased lung function secondary to pulmonary fibrosis, if any lung is included in the radiotherapy field. Preceded by the measurement of reduced diffusing capacity due to the restrictive defect, the clinical manifestations are breathlessness and a dry cough, which can be accompanied by fevers and malaise. Significant damage may result in bronchial stenosis or hemoptysis [9, 10].

Cardiovascular disease with radiation fields which overlap part of the heart, such as when irradiating the left breast, is a late effect of therapy. However, the incidence of this toxicity is reducing with newer techniques such as three-dimensional planning, deep inspiration breath holding, and accelerated partial breast irradiation [11].

Lymphedema of the upper limb can occur after surgery and radiation therapy to the axilla. Although occurring in 20% of patients who have axillary dissection, it has also been recorded in up to 6% of patients having a sentinel node biopsy [12]. Similarly lower limb edema can occur following pelvic or inguinal lymphadenectomy and radiotherapy [13]. Early intervention with exercise and other physical measures help to alleviate the symptoms from this adverse effect of treatment [14].

Radiation fibrosis can damage the nervous system in the periphery, particularly in areas such as the brachial plexus, and the patient may complain of muscle cramps, pain, and weakness [15]. Late cognitive dysfunction can be a problem with cranial irradiation, particularly in the aged. Radiation necrosis in the central nervous system can manifest with symptoms ranging from headaches to seizures, paralysis, and coma. Other organs in the field can include the pituitary gland causing multiple endocrine and biochemical abnormalities, the optic chiasm, which when irradiated with too high a dose can result in blindness, and the lens of the eye, which can develop cataracts [16].

## Late Effects of Systemic Therapy

The major secondary malignancy induced by chemotherapy is acute myeloid leukemia. Treatment-related acute myeloid leukemia and myelodysplastic syndromes are believed to be a direct consequence of mutations triggered by chemotherapy and immunotherapy or combinations with radiation therapy [17]. In the common form associated with alkylating agents, the onset

is 5–7 years following the chemotherapy. The characteristic chromosomal abnormalities are deletions of parts of chromosomes 5 and 7 [18]. Patients present with fatigue, weakness, anemia, and thrombocytopenia, and they may have fever. The epipodophyllotoxins and the intercalating anthracyclines have a shorter induction period (2–3 years) and are associated with translocations such as those involving chromosome bands 11q23 and 21q22 [19]. The first of the patients reported as developing leukemia as a late effect of chemotherapy were the long-term survivors of Hodgkin disease, but more recently the focus has been on the women having adjuvant chemoradiotherapy for breast cancer. The risk of developing leukemia is elevated in those receiving high doses of doxorubicin and cyclophosphamide and among those who received G-CSF, even after controlling for the chemotherapy doses, and is greater if radiotherapy was also used [20].

Other second cancers include non-Hodgkin lymphomas after treatment of Hodgkin lymphoma [21]; bladder cancer after cyclophosphamide; lung cancers after treating non-Hodgkin lymphoma; leukemia and solid tumors after treating testicular cancer; leukemias, gastrointestinal, and urogenital cancers after treating ovarian cancer and indeed second primary breast cancer; ovarian cancer or leukemia after treating breast cancer; and specifically endometrial cancer after the treatment of breast cancer with tamoxifen [22]. The newer targeted therapy drugs vemurafenib and dabrafenib that target the BRAF protein and are used to treat melanoma result in a higher risk of squamous cell carcinomas of the skin. These maybe delayed by administration of celecoxib [23].

Some drugs result in cumulative damage to organs. Anthracyclines progressively impact on the cardiac ejection fraction, and cardiomyopathy is a late effect of treatment. Moreover, if other cardiotoxic drugs like trastuzumab are subsequently given, as may be the case in HER 2 positive breast cancer, the cardiac function can further deteriorate [24].

The late effect of drugs with pulmonary toxicity is pulmonary fibrosis. The symptoms include breathlessness and a dry cough which can be accompanied by fevers and malaise. The restrictive defect results in a reduced diffusing capacity. Bleomycin at cumulative doses over 360 mg or other drugs including the alkylating agents, cyclophosphamide, busulfan, carmustine, antimetabolite methotrexate, cytosine arabinoside, and procarbazine can result in late pulmonary toxicity [25]. Pneumonitis is one of the immune toxicities of the checkpoint inhibitors like ipilimumab and pembolizumab. It often responds to treatment with steroids and is worse if there is preexisting lung damage [26].

Peripheral neuropathy is a common chronic late effect of a many chemotherapy agents including the platinums (cisplatin, carboplatin, and oxaliplatin), the taxanes (paclitaxel and docetaxel), the vinca alkaloids (vincristine vinblastine, vinorelbine), and targeted therapies such as bortezomib and thalidomide. Platinum analogues damage the neuron cells causing severe sensory deficits, sensory ataxia, and pain. The other agents cause a motor and sensory length-dependent axonal neuropathy, resulting in paresthesias and weakness in a distal glove and stocking pattern [27].

Encephalopathy can be a late effect of chemotherapy. Methotrexate can cause motor symptoms and cranial nerve palsies, particularly when given intrathecally or with radiation. Cytosine arabinoside is associated with ataxia and disorientation, while 5 fluorouracil is associated with cerebellar ataxia as well as upper motor neuron symptoms and somnolence [28].

The most common cytotoxic to cause renal toxicity is cisplatin which causes proximal tubular damage. Methotrexate can damage kidneys by precipitating in the tubules in an acidic environment, while supportive care drugs such as the bisphosphonates used to treat hypercalcemia and reduce bone symptoms can also result in decreased renal function [29, 30]. Newer agents can damage kidney function by a variety of mechanisms. Gemcitabine can cause a thrombotic microangiopathy and a hemolytic uremic syndrome, while bevacizumab is associated with hypertension and proteinuria which can also occur to a lesser extent with sunitinib and sorafenib [31].

A large number of anticancer drugs can compromise liver function. Dose reductions for compromised liver function are required for drugs cleared by the liver including methotrexate, sorafenib, dactinomycin, ifosfamide, gemcitabine, etoposide, irinotecan, procarbazine, 6-mercaptopurine, cytarabine, crizotinib, and cyclophosphamide. Some liver toxicities can be idiosyncratic, but some drugs need to be dosed cautiously with liver disease, and these include anthracyclines, taxanes, vinca alkaloids, temsirolimus, imatinib, axitinib, lapatinib, erlotinib, nilotinib, pazopanib, ponatinib, and ruxolitinib [32]. Hepatic damage can range from cholestatic hepatitis progressing to cirrhosis through to veno-occlusive disease and rapid liver failure. Tyrosine kinase inhibitors cause grade 3 hepatic events in 1–12% of cases. The newer checkpoint inhibitors such as pembrolizumab can induce an autoimmune hepatitis which may respond to steroids [33].

The immune checkpoint inhibitors such as pembrolizumab also cause autoimmune endocrinopathies: hypophysitis (9%), thyroiditis (15%), and adrenalitis (1%). These all need hormone replacement which will alleviate symptoms such as fatigue, weakness, and depression, which otherwise could be attributed to general symptoms of cancer [34]. Around 50% will not recover from the thyroid or gonadal dysfunction.

Patients who have successfully been treated for leukemias and lymphomas can nonetheless still have problems with recurrent infections and anemia [3].

Those patients with breast and prostate cancer who are receiving hormone therapy can experience a variety of late effects. Prolonged use of aromatase inhibitors can result in osteoporosis, myalgias, and arthralgia [35]. They may also develop cognitive impairment and fatigue [36]. The anti-androgen treatments for prostate cancer are associated with impotence, hot flushes, night sweats, and gynecomastia, and the patients are also more prone to osteoporosis, anemia, and metabolic syndrome [37–40].

### General Comments on Late Effects

Many other late sequelae of treatment relate to the ongoing consequences of surgery and reconstruction, whether that be in organs such as breast, bladder, or bowel, and many of these issues will be detailed in specific organ-related chapters. Likewise, there are ongoing symptoms of fatigue or insomnia that continue to impact on the quality of life of survivors, and these will be specifically detailed in other chapters of this text. There is one other physical symptom which is vital to ongoing well-being, and that is pain and its control which will be discussed in detail here.

Also, although the whole field of psychosocial and spiritual well-being has been given a separate chapter, as has the emerging problem of the "financial toxicity" of cancer treatment, the specific topic of return to work will be highlighted.

## Chronic Pain in Cancer Survivors

Cancer treatment, whether it is surgery, radiation therapy, chemotherapy, hormonal therapy, or a bone marrow transplant, is often painful [41]. As it may be administered for a prolonged period, it is not surprising that chronic pain is a common problem in cancer survivors. It is estimated to affect up to 40% of survivors, equivalent to 3000–4000 individuals per million of population.

### Definition

Characterizing pain in cancer survivors is challenging for a number of reasons. Firstly, the definition of a cancer survivor is ambiguous. Statutory agencies such as the American Cancer Society tend to use broadly inclusive definitions that capture anyone living with, through, and beyond cancer. By these broad definitions, cancer survivorship begins at diagnosis and includes people who continue treatment to reduce the risk of recurrence or to manage chronic disease so it could include patients right up until they enter a hospice.

Another definitional challenge is that not all pain in cancer survivors is due to cancer or its treatment. Patients with cancer frequently have painful comorbidities. A recent survey of patients attending oncology outpatient clinics in the USA found that approximately half the patients reported pain that was unrelated to cancer or its treatment. Approximately a quarter of the patients reported only non-cancer pain [42].

To overcome these challenges, this section will focus on pain caused by cancer treatment that persists after the usual time for healing, especially when the patient has early-stage disease and has completed definitive treatment and is hopefully are cured.

## Prevalence

Estimates of the prevalence of pain in cancer survivors reported in the literature vary widely, a result of the heterogeneity of the populations studied. To get a better picture of the extent and natural history of the problem, several longitudinal studies are underway to describe the prevalence of pain in survivors. The American Cancer Society has been undertaking the Studies of Cancer Survivors since 2000. This is a national, population-based, longitudinal study of quality of life, following 5000 survivors of 10 common cancers. It surveys their health behaviors and physical and emotional functioning at 1, 2, and 8 years post-diagnosis [43]. To date, only the year 1 data have been published, which found that greater than >90% of respondents reported symptoms related to cancer/treatment. One quarter were in the "high symptom burden" category. Pain, depression, and fatigue had the greatest impact on quality of life [44]. Also in the USA, the Childhood Cancer Survivor Study is following 10,000 US adult survivors of childhood cancer, meantime since diagnosis being 16.5 years. In this study, 21% reported pain in previous week which they related to their cancer or its treatment. Eleven percent reported medium or higher pain intensity [45]. In Australia, a random sample of a state cancer registry selected 1374 patients alive (any stage) 5–6 years post-diagnosis for heterogeneous cancer types. They were invited to complete the EORTC QLQ-30 quality of life questionnaire. Of 863 who returned the survey (63% response rate), 71% reported no physical symptoms, 11% reported one symptom, and 18% more than one. Overall, only 6% reported pain of "quite a bit or very much" intensity, but there was great variability according to primary site, the range being 2–21%. Patients with lung cancer had the highest percentage. Similarly, for pain interference, 4% rated it quite a bit—very much, the range being 1–14% depending on site, with lung worst [46].

The natural history of some cancer treatment-related pain syndromes are better established than others. Persistent pain after breast cancer (PPBCS) is an example of a well-studied syndrome. PPBCS is known to affect 25–60% women, may last for years, and can be permanent, interfering with physical function and causing poor QOL. In 10–15% cases, it is severe enough to require systemic opioids. Pain after colorectal surgery is an example of less well-described survivor pain syndrome. A recent Danish cancer registry study reported an incidence of 31%, with 12.5% experiencing pain daily. Median intensity was 4/10, moderate-severe in 55%. Incident pain very common, brought on by various routine activities including sitting, moving, walking stairs, urinating, defecating, and intercourse. The impact on quality of life was proportional to the severity. Fatigue, insomnia, and dyspnea were commonly associated symptoms [47].

Chemotherapy-induced peripheral neuropathy (CIPN) is another extensively studied complication of cancer treatment, but the extent to which it causes pain is unclear. Up to 60% of patients treated with taxanes, platinums, vincristine, and some newer agents (e.g., bortezomib) develop clinical and neurophysiologic evidence of CIPN, and half of them still have symptoms at 6 months [48]. However other neuropathic symptoms such as hypersensitivity to cold, reduction in tactile

sensation, loss of balance, and reduced fine hand-eye coordination seem to be more of a problem than pain [49]. In one study, 64% patients receiving paclitaxel experienced CIPN symptoms during treatment, but at a follow-up survey, only 27% of them were subsequently diagnosed with neuropathic pain [50]. In a prospective study of patients receiving oxaliplatin or docetaxel, pain symptoms were evaluated after treatment was finished and illustrated how challenging it is to assess CIPN-related pain. Some 45% and 55% complained of tingling/pins and needles in the upper and lower extremities, respectively, following oxaliplatin and 34% and 40%, respectively, following docetaxel. Similarly, 14% (for both upper and lower extremities) complained of burning pain/discomfort on exposure to cold following oxaliplatin and 1% and 3% in the upper and lower extremities, respectively, on cold exposure following docetaxel. However, burning pain/discomfort without exposure to cold was reported by only 6% and 8% in the upper and lower extremities, respectively, following oxaliplatin and 0% and 5% in the upper and lower extremities, respectively, following docetaxel [51].

## Risk Factors

Acute pain is a common complication of cancer treatment in cancer patients, but why some experience chronification of their pain is poorly understood. Studying risk factors is important for identifying high-yield modifiable targets or else subpopulations with non-modifiable risk factors who need a preventative intervention, and the impact of various demographic, disease, treatment, and other factors has been evaluated. The kind of treatment-related injury is relevant, as indicated in Table 42.1, but it is not the only factor. The transition from acute pain to chronic pain is now understood to be explained by genetics, environmental factors, and complex interactions between the two [52]. Preventing acute pain from becoming chronic pain is a major focus of pain research at the current time [53].

The risk factors for developing chronic pain following cancer treatment have been more extensively studied for some for some modalities than others. Many different kinds of surgeries are performed in the treatment of breast cancer, resulting in great variability in the kind of tissue damage sustained. A recent systematic review with meta-analysis of 77 variables across 30 studies involving almost 20,000 patients found that PPBCS is significantly associated with younger age, radiotherapy, axillary lymph node dissection, and greater acute postoperative pain and preoperative pain [54]. Axillary lymph node dissection provides the only high-yield target for a modifiable risk factor to prevent the development of PPBCS. No subpopulations with non-modifiable risk factors were identified. Psychological factors including depression and stress were significantly associated but not able to be pooled for meta-analysis.

## Management

### Assessment

Recommendations for managing pain in cancer survivors have been developed by other organizations, such as the National Comprehensive Cancer Network (NCCN) and most recently the

**Table 42.1** Variations in the incidence of chronic pain in various medical conditions, including post-treatment pains

| Acute pain | Chronic pain (>3 months duration) (%) |
|---|---|
| Limb amputation | 60–80 |
| Shingles | 25–50 |
| Spinal cord injury | 25–50 |
| Mastectomy | 40 |
| Guillain Barre syndrome/chronic idiopathic demyelinating polyneuropathy | 33 |
| Multiple sclerosis | 22 |
| Common post-surgical pain | 10–20 |
| Stroke | 8 |
| Cancer treatment | 5–10 |
| Back pain | 5–10 |

Siddall P. Neuropathic pain. In: Armati P, Chow R (eds). *Pain. The person the science, the clinical interface*. Melbourne: IP Communications, 2015, p. 132–3, with permission

American Society for Clinical Oncology (ASCO) [55, 56]. Such documents begin with advice to screen for pain at each encounter, just like when the patient had active cancer. The difference with survivors with pain is that clinicians should evaluate and monitor for recurrent disease, second malignancy, or late-onset treatment effects in any patient who reports new-onset pain. Screening for pain should be documented using a quantitative or semi-quantitative tool, such as a numerical rating scale (NRS). If pain is identified on screening, an in-depth interview that explores the multidimensional nature of pain should occur, documenting the associated psychosocial distress, comorbid conditions, and treatment history. The assessment should characterize the pain, clarify its cause, and make inferences about pathophysiology. A physical examination should accompany the history, and diagnostic testing should be performed when warranted. Clinicians should be aware of chronic pain syndromes resulting from cancer treatments (Table 42.2), the prevalence of these syndromes, risk factors for individual patients, and appropriate treatment options.

**Table 42.2** Examples of chronic pain syndromes following various modalities of cancer treatment

| |
|---|
| *Surgery* |
| Post-mastectomy pain |
| Other persistent pains following breast cancer surgery: pain related to breast implants/reconstruction, lymphedema, axillary webs, and cording |
| Phantom limb pain |
| Postsurgical neck dissection pain |
| Post-thoracotomy pain |
| *Chemotherapy* |
| Chemotherapy-induced peripheral neuropathy |
| *Radiation* |
| Radiation-induced plexopathies |
| Radiation-induced myelopathy |
| Enteritis/proctitis, cystitis; GI, abdominal, other adhesions in the radiation field |
| Fibrosis of skin or myofascia |
| Fistula formation |
| Osteoradionecrosis, pelvic insufficiency fractures |
| *Hormonal therapy* |
| Aromatase inhibitor-induced musculoskeletal syndrome |
| Other arthralgias/myalgias |
| Bone pain flare from tamoxifen |
| Carpal tunnel syndrome |
| Trigger finger |
| *Steroids* |
| Osteoporosis; osteonecrosis (avascular necrosis; typically femoral head, knee, humeral head) |
| *Bisphosphonates* |
| Osteonecrosis of jaw |
| *Hematopoietic stem-cell transplantation* (*chronic graft*-versus-*host disease*) |
| Skin infection, inflammation/edema |
| Contractures with pain and decreased range of motion |
| Fibrosis/scleroderma with contractures, pain, and decreased range of motion |
| Mucous membrane inflammation/thinning/ulceration/strictures, ulcers |
| Esophageal structures and ulcers |
| Abdominal adhesions or chronic biliary infection |
| Cystitis |
| Peripheral neuropathy |
| Arthralgia/myalgia |

## Treatment

The approach to treating pain in cancer survivors is currently evolving. In the past pharmacotherapy, with strong opioids utilized for moderate-severe pain, was the mainstay of treatment for survivor pain. This was based on the fact that pharmacotherapy is usually effective in cancer pain, patients were often already on them, there was usually identifiable tissue damage as basis of their pain (not unlike cancer patients and different to non-cancer patients) albeit that the mechanism is frequently neuropathic, and there was a high risk of recurrence. But now that more than 40% of people with cancer live at least 10 years after diagnosis, the concerns regarding the safety and effectiveness of long-term opioid therapy apply as much to survivors as to other patients with chronic pain [57]. Increasingly, multimodal interventions and other management strategies utilized in multidisciplinary pain clinics are being considered for cancer survivors, with a primary aim of restoring functionality rather than providing comfort. The ASCO guideline for survivorship pain proposes avoiding opioids if possible [55], but there is currently not a lot of data to support the use of other approaches in the survivorship population.

In the absence of data on the long-term safety and efficacy of opioids in cancer survivors, the ASCO guideline allows for a trial of opioids in

carefully selected patients who do not respond to more conservative management and who continue to experience distress or functional impairment. In that situation, the risks of adverse effects of opioids should be assessed, and if absent then a trial is warranted. A recent systematic review of the risks of long-term opioid therapy for chronic pain found that up to 20% patients will develop substance use disorder, 10% of them will be truly addicted, and the risk of death is dose-related [58]. Universal precautions to minimize abuse, addiction, and adverse consequences are recommended, e.g., screening for risk factors, real-time prescription monitoring, documentation of outcomes, and urine toxicology screening when appropriate. Tapering and/or referral to drug rehab programs is indicated when opioid use becomes problematic. In terms of harms, other potential risks of chronic opioid therapy exist in cancer survivors and include deleterious effects on the immune system and promotion of tumorigenesis [59].

Survivors with complex pain management needs may require assessment and/or treatment by other health professionals who provide comprehensive pain management care. Psychological distress and the unhelpful thoughts that are common in patients with chronic pain may also be occurring in cancer patients [60], and these may be amenable to cognitive behavioral approaches [61, 62]. Oncologists and primary care providers following survivors may prescribe these directly or refer their patients to other professionals to provide psychological therapies. Other non-pharmacologic modalities include physical medicine and rehabilitation and integrative therapies (e.g., massage, acupuncture, music therapy). Interventional techniques such as neurostimulatory therapies may have a role in cancer survivors [63].

## Return to Work

It is estimated that 40–50% of cancer patients are under the age of 65, and the absolute number who are working age is increasing, thanks to earlier diagnosis, better treatment and supportive care, and a societal trend to delay retirement. Because of the physical effects of cancer treatment described above, as well as the other burdens and inconveniences, cancer patients who were in paid employment prior to diagnosis usually take at least some time off work. The good news is that most survivors can expect to return to work (RTW), or maintain their employment, during the 18 months following completion of their primary treatment [64, 65]. A recent systematic review estimated that 64% of cancer survivors eventually RTW. Seamless reintegrating back into the workforce is therefore an important and growing issue for cancer survivorship.

Most research on employees with cancer—and other chronic diseases—has focused on documenting work outcomes such as productivity, absenteeism or work loss [66], and the predictors for these outcomes. There has been less research evaluating interventions to improve the chances of a successful RTW [67]. Studying RTW in people who have been out sick is methodologically complex. Working is not synonymous with being employed, especially for people who are on sick leave that may be paid or unpaid or those who receive disability benefits that are being provided through their employer versus a governmental agency. “Sick leave” is further complicated by the fact that in some jurisdictions, e.g., the USA, access to paid sick leave is dependent on organizational issues such as the number of employees in the workplace. Changes from traditional work practices to more flexible work arrangements and “telecommuting” could also affect survey results [68].

### Why Return to Work Is an Important Issue in Cancer Survivors

Financial issues are certainly a major consideration. A UK study reported that while approximately 83% of cancer survivors returned to work, over half of those returning were off work for 6 months or more, a scenario that may have caused a degree of income loss [69]. The vast majority of people affected by cancer report some degree of economic hardship resulting from extra

costs due to cancer, and much has been written lately about the financial toxicity of cancer treatment [70]. Studies of the costs of cancer care also need to incorporate costs pertaining to transport, eating away, "health food," special diets and supplements, special clothing, telephone calls, etc. [71].

Human beings also like to work for other reasons than money. Working provides socialization and a sense of meaning and purpose in life. These subjective experiences have been called "quality of working life" (QWL), and they are influenced by job and organizational characteristics, factors in the social environment, and individual work perceptions [72]. Having a high QWL is associated with higher levels of employee engagement and lower levels of quitting.

There has been little research on QWL in workers with chronic diseases, but it can be anticipated that they evaluate their QWL differently to healthy co-workers. For example, the impact of the disease or the treatment is going to be relevant to QWL for them. Working-age people with chronic diseases like to be in paid employment 10if possible, because it provides an improved quality of life and helps them regain a sense of normality, self-concept, and identity [73, 74].

## Returning to Work After Completing Treatment

There are long-term physical and mental health problems occurring as a result of cancer diagnosis and treatment. Fatigue, pain, and cognitive problems may impact adversely on cancer survivors' daily functioning and quality of life [75, 76] thereby reducing their chances of participation in work [77]. As a result, cancer survivors experience lower employment rates and higher rates of disability and work limitation, making cancer survivors 1.4 times more likely to be unemployed than healthy persons [78]. Lack of worthwhile advice regarding the appropriate time to go back to work has been identified as a barrier to a successful RTW [79].

While surveys show the majority of cancer survivors manage to eventually RTW, workers in temporary employment—an increasing labor market trend—may experience more job loss after being diagnosed with cancer, as employers are generally not inclined to prolong the temporary employment contracts of sick individuals [80]. Due to the increase in flexible employment in Western economies, workers on long-term sick leave, including cancer survivors, are more vulnerable to job loss. For cancer survivors who experience job loss, the process of RTW can be more complicated compared to cancer survivors who still have an employment contract. They face a large distance to the labor market, potential employer stigmatization during job interviews, and no access to support from employer and colleagues [80]. Therefore, cancer survivors who have experienced job loss may be in need for tailored RTW support.

A recent Cochrane review of interventions aimed at enhancing RTW in cancer survivors identified 15 randomized controlled trials over the past 30 years that included 1835 cancer patients [67]. Five types of interventions were evaluated: psychoeducational interventions, in which participants learned about physical side effects, stress, and coping and took part in group discussions; physical interventions, in which participants took part in exercises such as walking; medical interventions, including cancer drugs and surgery; and multidisciplinary interventions involving vocational counseling or physical training or both, in combination with patient education or counseling or both.

The main findings were that multidisciplinary interventions involving physical, psychoeducational, and vocational components led to more cancer patients returning to work than when they received care as usual, RR 1.11 (95% CI, 1.03–1.16) [67]. Quality of life was similar. When studies compared psychoeducational, physical, and medical interventions with care as usual, they found that similar numbers of people returned to work in all groups.

Compared to care as usual, RTW rates were higher for multidisciplinary interventions involving physical, psychoeducational, and vocational components and similar for psychoeducational interventions alone and physical training alone.

Less radical cancer treatments had similar RTW rates as more radical treatments. The four multidisciplinary interventions that were evaluated consisted of:

- A nursing intervention in breast cancer patients advised on exercise, examined arm movements, checked exercises, and encouraged RTW and becoming socially active [81].
- A group rehabilitation program teaching coping skills regarding RTW combined with psychical activity exercises [82].
- A program of physical exercise combined with behavioral biofeedback to decrease post-prostatectomy incontinence [83].
- A case manager working in a multidisciplinary team referred women with breast cancer after surgery to physical, occupational, or psychological support services [84].
- An oncology nurse or medical social worker working in a multidisciplinary team provided female cancer patients with vocational support, counseling, education, and RTW advice [85].

## Remaining at Work in the Longer Term

Although most cancer survivors RTW eventually, many struggle with it. One survey found that more than 50% of cancer survivors became unemployed, either by job loss or quitting work, in the first 6 years after diagnosis [86] Therefore attention must be paid to preventing survivors from becoming unemployed against their will. Experiences such as support, benefits, and ability to cope with their illness are factors that have been found to enable employees with a chronic physical disease to continue working [87].

The work experiences of cancer patients may be influenced by various medical and nonmedical factors. These include the type of cancer and its treatment modalities, the type of occupation, and the workplace environment [88, 89]. In a survey of 100 patients typically 3 years post-diagnosis who were attending pain and palliative care clinics at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, occupational factors were not significant predictors of being employed [90]. The odds ratios for working favored managers or professionals, working in flexible jobs in industries that were not very physically demanding and in organizations with the protection of ADA and FMLA legislation.

The adverse consequences of disease and its treatment on physical function and overall well-being may mitigate against one remaining in the workforce [91]. In the MSKCC study, being in pain reduced participants' chances of remaining at work. Therefore, symptom management is a very important supportive care priority in working-age patients. However, devising a pain management regimen that does not impair work ability through sedation or the need for frequent office visits does create an additional challenge for clinicians caring for advanced cancer patients who are trying to work.

## Working While on Cancer Treatment

Paid employment is an important supportive care topic and not just an issue for disease-free survivors. It is assumed most patients will take some time off work after diagnosis and won't work through treatment, but some treatments are now very prolonged, continuing for years. The challenge of keeping cancer patients in the workforce while on treatment is likely to grow in the future as chemotherapies and other cancer treatment modalities become more effective at extending survival, less toxic, and more convenient in terms of administration. Data from the MSKCC survey indicate that work is important to patients with cancer, and many would like to be able work more than they currently do [90]. Oncologists and palliative care clinicians should routinely discuss work issues with their patients, if appropriate given the clinical scenario, in order to adequately address this aspect of supportive care.

Few studies have addressed the issue of remaining in the labor force while on treatment [92–97]. The employment rate fell from 76–100% working before diagnosis to 15–56% while on treatment [92, 93, 95, 97]. Receiving chemother-

apy was a predictor for ceasing work [94], while the other showed working while on treatment is more challenging than working immediately after diagnosis and after treatment has finished [98].

## Work and Patients with Advanced Disease

As the prognosis of metastatic cancer improves, the opportunities and challenges for working in the face of metastatic disease are coming into sharper focus. Less is known about the work experiences of patients with advanced disease. In the past, work was given a low priority by palliative care patients [99]. A systematic review of 28 studies evaluating predictors of work outcomes in cancer patients [89] found only 5 studies which evaluated advanced disease as a risk factor [100–104]. All five studies found that patients with advanced disease were much less likely to be working than patients with earlier stage disease, with odds ratios typically around 0.2, although different endpoints were used across studies, making it difficult to compare them. None of the studies looked at the specific work-related issues of patients with advanced disease.

Disease as well as treatment effects may cause pain, fatigue, and other symptoms that can interfere with work ability. A recent study of the predictors of working or not in 683 patients with metastatic breast, colon, lung, or prostate cancer—of whom 34% were currently working—showed race, performance status, symptom burden, and cancer treatment to be associated with working or not [93]. That study did not address granular details of employment history, attitudes to work, and the work environment which are presented here. As cancer patients continue to live longer and receive prolonged courses of palliative systemic therapy, these issues can be expected to become more common. Almost half the patients who completed the MSKCC survey were currently employed, with a quarter of them working full time. Work was important to these patients, not just for the salary and benefits but because it formed an important part of their identity. They had often taken little or no time away from the workplace since diagnosis, and many even wanted to work more than they currently were or to return to work if they were not employed. Pain and pain medicine were the predictors.

The work issues faced by patients on treatment extend beyond those of the disease-free survivor and include issues which fall within the scope of palliative care, such as the management of pain and other symptoms, the side effects of narcotics, and coping with the risk of progression of disease, incurability, and death. Moreover, many of these issues also may apply to patients treated with curative intent, some of whom remain on therapy for years after a diagnosis (e.g., adjuvant endocrine therapy in breast cancer). It is possible employment-related issues facing patients with active disease on treatment are likely to extend beyond those of the disease-free survivor and may include the impact on work ability of pain and other symptoms, the side effects of narcotics, frequent medical appointments, coping with the risk of progression, and the development of uncontrollable disease. For those with advanced cancer, there is also the prospect of death.

More research is warranted on topic, including studies of larger and more diverse samples in which self-reported data are combined with clinical data obtained from the medical record to overcome some of the limitations listed above. Clinical trials of pain and symptom management (e.g., fatigue) that focus on work outcomes are needed. Interventions to help patients who are able to work to advocate for themselves in the workplace should be designed and evaluated. Finally, a multidisciplinary team including a palliative care specialist and a social worker could assist patients with cancer who are struggling with the need and desire to work when it is no longer feasible.

## Conclusions

Surviving cancer can be accompanied by a range of symptoms. The physical symptoms can be residual effects of the cancer or late effects of the

therapy. If anticipated some of these can be treated early. Symptoms like pain may be managed by lifestyle changes but may also require specific treatment. Anxiety and depression should be identified early and treated. Adjustment disorders can be short term but highlight the need for continued monitoring after cancer treatment. A range of social and economic supports may be required. All aim to maximize a patient's quality of life after treatment, beyond the assumption that just the absence of cancer will suffice.

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