Aging and Cancer: What Oncologists Need to Know

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Cancer is a disease associated with aging. Approximately 60% of cancer diagnoses and 70% of cancer mortalities occur in patients age 65 or older. By 2011 in the United States, the "Baby Boomer" generation will be turning 65. The aging of these baby boomers, along with a rise in the overall life expectancy, is leading to a rapid growth of the older U.S. population. By 2030, one in five Americans will be age 65 or older. These demographics, along with the known association between cancer and aging, will contribute to an enormous rise in the number of older adults with cancer. Incorporating geriatric principles of care will be increasingly essential to cancer treatment.

Planning cancer therapy in older adults can be complex for several reasons. First, the very biology of cancer may differ from younger to older adults. For some cancers, such as breast cancer, older age is associated with a more indolent biology [1, 2], while for other cancers, such as acute myelogenous leukemia, older age is associated with an aggressive biology that is more likely to be refractory to standard therapy [3]. Understanding the tumor's biological characteristics is essential to treatment planning.

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A. Hurria, L. Balducci (eds.), *Geriatric Oncology*,
DOI 10.1007/978-0-387-89070-8_1,

In addition to considering disease-related biology, the clinician must weigh host-related factors that may influence both life expectancy and treatment tolerance. These include physiologic changes that accompany aging, as well as factors traditionally captured in a geriatric assessment, such as functional status, comorbid medical conditions, psychological state, social support, and cognitive function.

Perhaps the most important part of planning cancer therapy is to understand the individual's wishes for treatment and acceptance of the side effects he or she will endure in order to achieve a cancer cure or remission. One of the greatest barriers to providing optimal care for older adults with cancer is the underrepresentation of older adults in clinical trials, which set the standards for oncology care [4–6]. Because older adults, particularly those at the extremes of age, rarely take part in clinical trials, the benefits and risks of cancer therapy for them are extrapolated from a younger patient population, which generally experiences a lower incidence of side effects to cancer therapy [7]. This makes therapy planning a challenge in the older adult.

This chapter summarizes the key principles of geriatric medicine, principles that oncologists can incorporate into their care of an older adult. Subsequent chapters will examine each of these topics in detail.

Physiologic Changes with Aging: Practical Considerations in Prescribing Cancer Therapy in Older Adults

The aging process is characterized by a progressive loss in physiologic reserve [8, 9]. Declines in organ function that occur with aging can affect the dosing and side effects of cancer therapy. In particular, with increasing age, renal function decreases. Renal blood flow diminishes by 1% per year after age 50, and renal mass goes down by 25%–30% over a lifespan [10]. Beginning around age 40, the glomerular filtration rate ebbs at an estimated

0.75 ml/min/yr [11]. At the same time, age-related declines in renal and hepatic function are not typically evident in standard blood work. For example, serum creatinine is a poor reflection of renal function with increasing age because of an age-related loss in muscle mass [12]. Therefore, only a creatinine clearance can quantify an older adult's renal function in order to accurately prescribe cancer therapy that is renally metabolized.

With increasing age, hepatic mass and blood flow decrease [8, 13]; however, the impact of this decline on hepatic organ function is not certain [14–16]. Liver biopsy studies have shown a decrease in cytochrome p450 content with aging [17]; however, age-related changes do not show up in serum liver function tests. Surrogate measures of liver function are still being studied [14].

Age-related changes in gastrointestinal absorption can influence the bioavailability of oral cancer therapy and supportive medications. For example, with increasing age, there are splanchnic blood flow decrease, mucosal atrophy of the gastrointestinal system, and a decrease in gastric motility and enzyme secretion [18, 19]. In addition, age-related changes in body composition can influence the volume of distribution of medications. With increasing age, there is an increase in total body fat, leading to an increase in the volume of distribution of drugs that are lipid-soluble [10]. Conversely, with increasing age, total body water decreases, leading to a diminution in the volume of distribution for hydrophilic drugs. Malnutrition and hypoalbuminemia also alter the distribution of drugs that are heavily bound to albumin [10].

Perhaps one of the most significant changes with aging is the diminished response to hematopoietic stress, placing older adults at greater risk for myelosuppression [7, 20–23]. Age >65 is a risk factor for febrile neutropenia [21, 24], and myelosuppression-associated complications occur most frequently during the first cycle of therapy [25]. Early initiation of white blood cell growth factor can help to decrease the risk of febrile neutropenia and decrease the risk of hospitalization resulting from neutropenia-associated complications [26].

Cancer treatment can also cause anemia, which may contribute to fatigue and functional decline [27, 28].

Domains Other Than Chronological Age That Affect Life Expectancy and Treatment Tolerance

Aging and Functional Decline

Aging is associated with a progressive loss in physical function. The need for assistance with daily activities is predictive of morbidity and mortality in older adults [29, 30]. Older patients with cancer are also more likely to require assistance with daily functioning than those without cancer [31]. Furthermore, this increased need for assistance persists in cancer survivors [32]. Among patients with cancer, the need for functional assistance is also predictive of survival, chemotherapy toxicity, and post-operative complications [31–33]. From a practical standpoint, understanding someone's functional status is essential in order to determine if an individual can seek medical attention if he or she develops cancer symptoms or therapy side effects. For example, can he use the telephone without assistance, or take transportation to clinic visits or to an emergency room? If he is unable to perform these tasks, then a support system (such as a family member, visiting nurse, or lifeline) must be enlisted to ensure that the patient can get help if he notices warning signs of toxicity.

ADLs and IADLs

The assessment of functional status should also include an evaluation of the ability to complete activities of daily living (ADLs) or instrumental activities of daily living (IADLs). ADLs are basic self-care skills required to maintain independence in the home, such as the ability to bathe, dress, transfer, maintain continence, and feed oneself. The need for assistance in ADLs is common among hospitalized patients with cancer.

In one study, 45% of older adults with cancer who were admitted to the hospital required assistance with ADLs. In another study of cancer survivors, patients with a history of cancer were more likely to continue to require assistance with ADLs than patients who had no history of cancer [32].

IADLs are activities required to maintain independence in the community, such as the ability to do housekeeping, take transportation, do laundry, use the telephone, manage finances, and take medications. Among patients with advanced non-small lung cancer, the need for assistance with IADLs has been associated with poorer survival [34]. Among patients with ovarian cancer, the need for assistance with daily functioning has also been associated with increased risk of chemotherapy toxicity [35].

These observations highlight the importance of evaluating functional status in older adults with cancer in order to estimate both the tolerance to cancer therapy and mortality. In addition, it is critical to evaluate a patient's social support, which may compensate to some degree for a patient's functional impairment.

Age and Comorbidity

The Role of Comorbidity in Treatment and Prognosis

The number of competing comorbid medical conditions rises with increasing age. Comorbid medical conditions have an impact on life expectancy [36–40] as well as on treatment tolerance [37, 41, 42]. In addition, certain comorbid medical conditions such as diabetes or obesity may play a role in cancer prognosis [43–47]. A thorough understanding of a patient's coexisting medical conditions is necessary in order to weigh the impact of the cancer on life expectancy versus other comorbid medical conditions. In addition, the impact of comorbid medical conditions on cancer treatment tolerance must be considered.

Comorbidity Scales

Several validated scales have measured comorbidity. Karampeazis and Extermann provide a thorough review of comorbidity scales in their chapter (Chapter 5). In addition to comorbidity scales, other authors have recommended prognostic indexes that include factors other than comorbidity (such as age, functional status, and gender). The comorbidity index utilized will depend on the question being considered. For example, Lee and colleagues developed a prognostic index for the risk of four-year mortality, which includes comorbid medical conditions, functional status, and age [48]. Charlson and colleagues developed an index that ranks and weighs conditions that increase the risk of one-year mortality among patients hospitalized on an inpatient medicine service, and includes the age of the patient [49]. Walters and colleagues developed a prognostic index for the risk of one-year mortality among older adults who are hospitalized, which includes comorbid conditions (including a diagnosis of cancer), gender, functional status, and laboratory values [50].

Aging and Changes in Social Support

Among older adults, a lack of social support is an independent predictor of mortality [51]. Older adults are particularly vulnerable in this regard because the aging process is associated with losses in the social support system: the loss of a spouse, the loss of family members, and the loss of friends. In addition, adult children often live far from their parents and are consumed with daily work and their own activities. A lack of social support can be particularly problematic for older adults undergoing cancer therapy, which can require frequent doctor or hospital visits. Treatment-related side effects can require immediate attention, making an adequate support system crucial.

The Role of Social Support After Therapy

Social support also plays an important role following the completion of cancer therapy. A lack of social support is associated with poorer psychological adjustment in cancer survivors. Among breast cancer survivors, a mean of nearly seven years after therapy, having less social support, being divorced, or being separated were significant predictors of increased psychological distress [52]. In another study of breast cancer survivors, 20 years after adjuvant therapy, a lack of social support was associated with a higher prevalence of posttraumatic stress disorder [53].

On the other hand, while social support may benefit patients, emerging literature details the burdens experienced by their caregivers. In a study of 101 patients with advanced cancer, 39% of the spouse caregivers reported symptoms of depression. In contrast, only 23% of the patients reported significant symptoms of depression [54]. In another study of 310 Korean caregivers of patients with cancer, 67% of the caregivers reported high depression scores. The most significant predictor of depression was the feeling of care burden. Other predictors of caregiver depression included caring for a spouse with a poor performance status, being female, being a spouse of the patient, having poor health, adapting poorly, and being unable to function normally [55]. These findings suggest that a significant proportion of caregivers are at risk for depression, and attention should be paid to minimizing caregiver burdens.

Aging and Psychological State

Approximately one third of patients with cancer experience psychological distress. The prevalence of clinically significant depression in the older population with cancer is estimated to be 3-25% [56]. Depression in the older person is associated with an increased risk of subsequent functional decline and increased resource requirement [57]. For example, in a survey of 6,649 patients over

the age of 70, the presence of depression was associated with the need for increased hours of informal caregiving [58].

While some studies report that older patients with cancer experience similar or less psychological distress than younger patients, other studies are now identifying older age as a psychological risk factor [56, 59]. In a study of 2,924 patients with cancer, 8% reported thoughts of hurting themselves or feeling that they would be better off dead. In multivariate logistic regression, risk factors included age > 65 ($p = 0.29$), clinically significant emotional distress ($p < 0.001$), and substantial pain ($p < 0.001$).

Other studies have reported that older adults who are more vulnerable to psychological distress are those with inadequate social support. For example, in a study of breast cancer survivors, older age was associated with less distress; however, patients with less adequate social support experienced greater distress [53]. A case-control study of suicide risk in older adults revealed that the risk of suicide is higher among older adults with cancer than among older adults with other illnesses [60].

Aging and Cognitive Decline

With increasing age, there is an increased risk of cognitive decline. A diagnosis of dementia is associated with shortened survival [61]. Patients with cancer who have a diagnosis of dementia are likely to be diagnosed with cancer at a more advanced stage and are less likely to receive curative therapy [62, 63]. This was illustrated in two studies from the SEER Medicare database, which reported that older adults with either breast or colon cancer and a diagnosis of dementia were less likely to receive curative therapy.

While cancer or cancer therapy may have an impact on general cognitive function, few studies have focused on the impact of cancer therapy on the cognitive function of older adults. In a study of older adults receiving adjuvant chemotherapy for breast cancer, half of these patients described a decline in cognitive function from before therapy to six months after chemotherapy [64]. Other studies in a general population,

however, suggest no differences in the self-reported cognitive status of cancer survivors and controls [32].

Cognitive Status Related to Treatment Choices

Older adults report that the impact of a therapy on cognitive status is an important part of the informed-consent process. In one survey of older adults, 88% stated that they would forego life-saving treatment if the outcome was survival with cognitive decline [65].

From a practical standpoint, an understanding of someone's cognitive status is required prior to prescribing cancer therapy in order to determine whether the person understands the risks and benefits of cancer therapy and is able to provide informed consent. In addition, the treating oncologist needs to determine whether the patient can remember the complex instructions regarding therapy, supportive medications, and the indications for seeking medical attention.

Understanding Treatment Goals

Perhaps the most important part of an oncologist's care in an older adult is understanding his or her treatment goals. Clinical trials to date have utilized traditional endpoints of disease-free and overall survival as measures of efficacy. While these endpoints are important for patients of all ages, additional endpoints may be considered equally as relevant by the geriatric population. The quality of survival and the impact of therapy on daily function and cognition have been highlighted as factors of concern in an older adult's decision-making process [65], and these factors are rarely studied in clinical trials.

The principle of "prolongation of active life expectancy" is especially relevant to the geriatric population with cancer, where the goal of treatment is to control or prevent disease in order to allow the person to maintain daily function and cognitive capacities. This process involves assessing the impact of

therapy on daily life and exploring whether the trade-offs of cancer or therapy-associated loss of function or cognition are worth the prolongation of survival. An evaluation of the longitudinal impact of therapy on function and cognition should be considered a relevant endpoint for clinical trials in older adults in order to guide decisions involving the risks and benefits of cancer therapy.

Conclusions

Cancer is a disease associated with aging. This chapter highlighted the key factors to consider when treating an older adult with cancer. First, determine whether age-related changes in tumor biology will impact either the risk of cancer on life expectancy or the treatment efficacy. Second, consider age-related changes in physiology that may affect dosing and the tolerance to cancer therapy, including age-related declines in renal and hepatic function, changes in the absorption and volume of distribution of medications, and decreased bone marrow reserve. Third, evaluate factors other than chronological age that may impact life expectancy and tolerance to cancer therapy. These include functional status, comorbid medical conditions, psychological state, social support, and cognitive function. Fourth, understand the patient's goals with therapy, and prescribe treatment with these goals in mind.

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