Quality Care

Treating elderly cancer patients: what you need to know about their physiology and specific medical needs

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By 2030, more than 20% of people in the United States will be aged 65 years or older. Approximately half of all cancers occur in this population. Because life expectancy has increased tremendously over the past century and further increases are projected, the study of cancer and aging has emerged as a critical topic in oncologic care. This article outlines key issues in caring for the older adult with cancer and offers practitioners a better understanding of the differences in physiology of these patients and their specific medical needs. **For information on treatment guidelines from the National Comprehensive Cancer Network, see the Resources box on page 732.**

Americans aged 75 years or older will triple in number by 2030; the number of people over age 85 will double. This poses a tremendous challenge for healthcare professionals, in particular oncology practitioners, as cancer is the most common cause of death in the elderly.[1]

KEY POINTS

- The number of older Americans is growing rapidly, and that is posing a huge challenge for healthcare professionals, particularly oncology practitioners.
- Aging can affect pharmacokinetics in various ways, which can alter drug absorption, distribution, metabolism, and excretion.
- Better understanding the physiology of the geriatric patient—as well as differences within the aging population—can lead to more finely calibrated care.
- Designing a treatment plan should take into account patients' goals for therapy and the expectations of both patients and family members.
- A number of resources are offered, including National Comprehensive Cancer Network guidelines.

Aging at different rates

Because aging is a complex, heterogeneous, and highly individualized process, a person's age alone does not always predict his or her physiological decline. This is due in part to the effect of comorbidity on aging. It has been suggested that the process of aging is a functional continuum-running from independence to frailty and pre-death.[2] In the primary healthy stage, there are no significant limitations in activity and minimal reduction in functional reserve. Many individuals then become somewhat vulnerable, with functional reserve critically reduced, causing some functional limitations and less resilience to treatment toxicity. The final stage of frailty is characterized by severe limitations with no significant recovery of functional reserve.[3] As such, cancer chemotherapy needs to be tailored to the individual, taking into consideration these phases, to optimize therapeutic benefit, minimize toxicity, and preserve function and independence.

Yet despite the increased incidence of cancer and the burden of mortality in the elderly, they have

Manuscript received May 31, 2006; accepted October 16, 2006.

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Commun Oncol 2006;3:730–734

consistently been underrepresented in clinical trials.[4,5] And despite the fact that elderly patients are the largest users of pharmaceuticals, there have been few studies on the pharmacology of anticancer drugs in older patients. This had made evidence-based dosing decisions difficult, perhaps contributing to the increased incidence of drug toxicity with age. In fact, toxicity differences with aging are likely due to the result of age-related changes in pharmacokinetics and pharmacodynamics of chemotherapy.

However, the data that are available from clinical trials show variable degrees of toxicity among the older patients enrolled. These differences may reflect disparities in clinical trial eligibility or the heterogeneity in terms of comorbidity, functional and performance status, or other parameters of the older enrolled population. Only a few studies have addressed tolerance to cancer therapy in the frail older patient, those with organ dysfunction or with poor performance status.[6,7]

Pharmacokinetics

Aging can potentially affect the various components of pharmacokinetics:

Absorption

A number of changes in the digestive system can affect drug absorption. They include decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.[8,9] All these factors can result in reduced absorption rate. Since most chemotherapy drugs are administered parenterally, absorption abnormalities do not usually affect treatment. However, the increased use of oral antineoplastic therapy makes adherence to a drug regimen especially important.[10,11]

Distribution

The volume of distribution of drugs is a function of body composition and the concentration of circulating plasma proteins, such as serum albumin and red blood cell concentration.[9,12,13] Fat content doubles in the elderly from 15% to 30% of body weight. The average 75-year-old has 33% intracellular water, compared to 42% in the average 25-year-old. This decrease can change the volume of distribution of drugs, which ultimately can lead to changes in peak concentrations and the terminal half-life.[9,12] Aging is also associated with a decrease in plasma albumin levels by 15%–20%. Anemia is also common, which can lead to changes in the volume of distribution of drugs that are bound to red blood cells, such as anthracyclines, taxanes, and epipodophyllotoxins. Anemia is a risk factor for the development of neutropenia during treatment.[14]

Metabolism

Hepatic mass and blood flow decrease with age, but the impact of this decline on hepatic enzyme function is controversial.[9,15] In a study of 226 patients, the cytochrome P450 content in liver biopsy samples decreased by approximately 30% in patients over the age of 70.[16] Phase I metabolism occurs primarily via the cytochrome P450 microsomal system and exhibits genetic variability.[17] (Cytochrome P450 are heme-based enzymes located primarily in the liver, as well as the small bowel, kidneys, lungs, and brain.)

Genetic variability accounts for differing levels of activity across the spectrum of enzymes, through various pathways that may lead to clinically important pharmacodynamic differences among individuals.[18–20] The potential for drug interactions is relatively high in the elderly due to polypharmacy. This is important with the CYP3A4 enzyme, which is inhibited by a variety of commonly prescribed medications and is involved in the metabolism of a variety of anticancer agents. Cyclophosphamide, ifosfamide (Ifex), paclitaxel, etoposide, teniposide (Vumon), vincristine, vinblastine, and tamoxifen are all substrates of CYP3A4 and may be significantly affected by common enzyme inhibitors of this enzyme.[21]

With age come changes in excretory function, a gradual loss in renal mass and clearance. Glomerular sclerosis leads to a loss of capacity to perform ultrafiltration of plasma, which in turn leads to a decrease in the glomerular filtration rate (GFR) by approximately 1 mL/min for every year over 40 years of age.[22–25] The reduction in GFR is often not reflected by an increase in serum creatinine lev-

TABLE 1

Dose adjustments for chemotherapeutic agents based on renal dysfunction

	Creatinine clearance		
Drug	**> 60 mL/min**	**30–60 mL/min**	**< 30 mL/min**
Bleomycin	0.70	0.60	NR
Carboplatin		Calvert formula	
Carmustine	0.80	0.75	NR
Cisplatin	0.75	0.50	NR
Cytarabine	0.60	0.50	NR
Dacarbazine	0.80	0.75	0.70
Fludarabine	0.80	0.75	0.65
Hydroxycarbamide	0.85	0.80	0.75
Ifosfamide	0.80	0.75	0.70
Melphalan	0.65	0.50	NR
Methotrexate	0.85	0.75	0.70

NR = not recorded

Resources

Recently, the National Comprehensive Cancer Network (NCCN) formulated guidelines for the treatment of older patients with cancer. You can access these guidelines at www.nccn.org/professionals/physician_gls/PDF/senior.pdf to provide appropriate treatment of elderly patients, avoid significant toxicity, and maintain their quality of life. NCCN has included geriatric assessment as well as therapeutic guidelines.

els because of the simultaneous loss of muscle mass that occurs with age. Serum creatinine is often not an adequate indicator of renal function in elderly patients.[26]

To estimate glomerular clearance, various equations have been evaluated to calculate creatinine clearance based on serum creatinine levels and other factors. The two most common equations used clinically are the Cockcroft-Gault and Jelliffe equations.[27,28] These equations are less accurate in populations with severe renal failure; in patients with decreased muscle mass, cachexia, and obesity; and in the elderly. A comparison of the accuracy of various formulae has been performed.[29,30] A number of review articles and guidelines discuss the dosing modifications that are recommended for patients with renal impairment to avoid toxicity (Table 1).[31]

Comorbidity and functional status

The role of comorbidity in survival has been evaluated by Charlson et al,[32] who found that the number and severity of comorbid illnesses can predict survival in general medical patients admitted in an inpatient unit. The effect of comorbidity on survival of patients with colorectal cancer and breast cancer has also been extensively evaluated, looking at conditions such as heart disease, hepatobiliary disease, and renal dysfunction. The increase in the degree of comorbidity is an independent predictor of survival.[33,34]

Another significant consideration in the elderly is functional status,[35] which is usually determined by two common geriatric scales: Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). The ADL scale is a measure of simple functions (transfer, bathing and grooming, toileting, dressing, feeding, behaving appropriately). The IADL scale requires more complexity and interaction with the external environment (cooking, cleaning, laundering, using the telephone, using transportation, managing money, taking medications).

Comorbidity and functional status are independent factors in older cancer patients and need to be assessed independently. Traditional oncology measures such as the Karnofsky score and Eastern Cooperative Oncology Group performance scale are not always effective predictors in the elderly. The degree of dependency and geriatric functional scores can predict survival in older patients.[35–38] These factors are important in clinical trial design, and treatment planning in the elderly. The National Comprehensive Cancer Network (NCCN) guidelines and the International Society of Geriatric Oncology recommend some form of geriatric assessment.[39] Although traditional assessments are too time-consuming for a busy outpatient office, abbreviated assessments are being developed to make it more practical for oncologists to evaluate older patients.[40]

Hematopoiesis

Stem cell reserve appears to be compromised with aging and may be responsible for increased hematologic toxicity.[41–43] The incidence of anemia increases significantly with age, both in men as well as in women,[44] and much more so in the "frail elderly" as compared with the "fit elderly." The adverse effect of anemia on survival and functional status has been evaluated.[44–46] To maintain a hemoglobin level of approximately 12 g/dL, recent guidelines stress the need for early and adequate treatment of anemia in older patients.[47]

Chemotherapy-induced neutropenia also appears to be more common and more severe in elderly individuals, and more highly associated with infectious complications, hospitalizations, and mortality.[48–50] Some authors propose that clinicians consider the elderly as a special population and use granulopoietic growth factors as primary prophylaxis after chemotherapy, since many of the infectious and life-threatening complications occur early in the course of therapy.[51–53] Because of toxic-

Preventing toxicity caused by drugs excreted predominantly by the kidneys

- Optimize hydration and evaluate renal function to establish the possible need for dose adjustment.
- Note that serum creatinine levels alone are insufficient for evaluating renal function. Formulae for calculating, creatinine clearance such as Cockcroft-Gault, are available and generally provide accurate indices of a patient's renal function status. However, in elderly patients, these equations are not as precise as in a younger population.
- When dealing with extremes of obesity and cachexia, or very high and low creatinine values, no single tool is completely accurate.
- Within each drug class, preference may be given to agents that are less likely to be influenced by renal clearance.
- Within each drug class, preference may be given to agents that are less toxic to the kidneys or for which there are ways to prevent renal toxicity.
- Co-administration of known nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, should be avoided or at least minimized.
- Future trials should be designed to allow for the evaluation of renal function and its effect on toxicity and efficacy.

TABLE 2

Publications that offer guidance on treatment of elderly patients

Cancer type	Reference	Treatment
Breast	Muss et al[58]	Older patients derive same benefit from adjuvant therapy as younger patients with lymph-node–positive breast cancer
Colon	Sargent et al[59]	Older patients derive same benefit from adjuvant therapy as younger patients (< 70 years) with similar toxicity profiles
Lymphoma	Feugier et al[60]	Rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) are standard of care for older patients with aggressive non-Hodgkin's lymphoma
NSCLC	Gridelli et al[61]	Platinum-based therapy for advanced NSCLC; single agents for less-fit patients

NSCLC = non-small cell lung cancer

ity concerns, lower—and likely less effective—doses of chemotherapy have been used in potentially curable settings such as adjuvant chemotherapy for breast cancer, colorectal cancer, and non-Hodgkin's lymphomas. This approach may be at least partly responsible for the poorer outcome of treatment in the elderly reported in some studies.[54–57]

Conclusion

Treatment guidelines, such as those offered by the NCCN, can help minimize toxicity. The most important aspect of these guidelines is the individualization of cancer therapy. When making treatment decisions, it's crucial to define the goal of therapy, whether it be prolonging survival, remission, cure, or palliating symptoms. Defining the goal allows patient and family to calibrate their expectations and make short- and long-term plans.

Of course, the aggressiveness of the tumor, the patient's overall condition, and the availability of effective treatment will help drive treatment decisions. Choices made by a frail, elderly patient with metastatic melanoma for which no significant effective therapy exists would certainly differ from those of an elderly woman with asymptomatic bone metastases from a hormonally responsive breast cancer.

Effectively managing cancer in geriatric patients requires medical oncologists to be aware of new data and ideas about the biology of aging and treatment programs for older patients. To optimize treatment for older patients, geriatricians and oncologists must form a partnership, prospective clinical trials in the elderly need to be conducted, and guidelines should be assessed. A number of publications that offer disease-specific guidance are available (Table 2).

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