Cancer Chemotherapy in the Elderly Patient

By Timothy L. Gillison, MD [2] and Gurkamal S. Chatta, MD [3]

The management of older patients with cancer is historically challenging because of a lack of prospective data regarding the appropriate management of this population. In this review, we address some of the issues and challenges surrounding the treatment of older cancer patients, including the withholding of medically appropriate treatment based on chronologic age, the historical omission of elderly from clinical trials, and the impact of geriatric assessment, and age-related changes in pharmacokinetics and pharmacodynamics. Finally, we conclude by discussing the existing evidence related to cancer treatment in the elderly, focusing primarily on the malignancies most commonly seen in older patients, and making general treatment recommendations where applicable.

Geriatric Oncology, the systematic examination of the treatment of elderly patients with cancer, is a relatively new field of study.[1] Before the National Cancer Institute and the National Institute on Aging released the sentinel document “Perspectives on Prevention and Treatment of Cancer in the Elderly” in 1983, most of the patient populations in clinical trials were relatively young and healthy, and older patients were frequently excluded.[2,3] Cancer is a disease that disproportionately affects older patients. However, it is important to draw the distinction between chronologic and biologic age in order to provide the best care for individual patients.

A number of retrospective data and clinical trials focusing on treatment and supportive care of older patients with cancer are ongoing or have been completed. Some differences in pharmacokinetics and natural history of disease do exist between older and younger patients, but for the most part, healthy elderly patients, with minimal comorbidities, like their younger counterparts, benefit from and are able to tolerate standard chemotherapeutic regimens across a broad spectrum of malignancies. In this review, we discuss the unique challenges and the many opportunities associated with the treatment of elderly cancer patients.

Cancer Burden in the Elderly

FIGURE 1

US Incidence of Various Cancers by Age, 2002–2006 (per 100,000 persons)

FIGURE 2

US Mortality Rates, 2002–2006 (per 100,000 persons)

The population of the United States continues to age: 12.3% of the population was aged 65 or older in 2008, and by 2030, this figure will be over 20%.[4] Between 2002 and 2006, 54.7% of newly
diagnosed cancers and 69.7% of all deaths from cancer occurred in patients aged 65 or older.[5] Across various types of cancer, older persons remain more likely to develop and die from cancer (see Figures 1 and 2). Estimated costs for cancer care in the US in 2004 were over $72 billion.[6,7] The staggering cost of cancer care underscores the importance of developing evidence-based guidelines for treating older cancer patients.

**Chronologic vs Biologic Age: Evaluation of the Elderly Cancer Patient**

Traditionally, age 65 years and above has been used as a cutoff to define the elderly. However, it is increasingly recognized that biologic age is more important than chronologic age alone in predicting the tolerance and efficacy of standard chemotherapy in the elderly. Thus, there is a shift toward further risk stratification of elderly cancer patients based on their functional status and the presence or absence of comorbidities. Extensive efforts have been made to develop assessment tools for predicting the efficacy:toxicity ratio of chemotherapy in the elderly. The Comprehensive Geriatric Assessment (CGA) is a valuable tool in the assessment of older patients and focuses on several domains, including functional status, comorbidity, cognitive function, nutrition, psychological and social support, and medications. The results of a CGA are useful in directing care and identifying needs in this population.[8,9] When evaluating an elderly cancer patient, other than the standard Eastern Cooperative Oncology Group (ECOG) performance status and Karnofsky scales, the Charlson Comorbidity Index (CCI, Table 1) and the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) are examples of tools that may be incorporated into the routine evaluation of elderly patients.

**TABLE 1**

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<th>The Charlson Scale for Evaluation of Age-Related Comorbidities</th>
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| An exhaustive discussion of these tools is beyond the scope of this review. However, it is clear that a CGA, although useful, is time-consuming and only indicated in select patients.[8,9] Furthermore, advanced age alone does not portend a poor outcome. Much more sensitive predictors of outcome include the functional status of the patient, the presence of organ dysfunction, and the presence of other comorbidities. The National Comprehensive Cancer Network (NCCN) has developed useful guidelines for managing older cancer patients, and these can be readily accessed at [http://www.nccn.org](http://www.nccn.org). Nevertheless, some of the challenges that remain are (1) developing and validating low burden–high frequency instruments that can be administered more frequently during the treatment course, and (2) developing and validating biomarkers of occult hematopoietic and renal dysfunction.

**Pharmacokinetics and Pharmacodynamics of Anticancer Agents in the Elderly**

A comprehensive review of the pharmacokinetics of anticancer agents in the elderly has been the subject of several recent excellent articles, and is beyond the scope of this review.[10-12] In general, most of the data in the elderly have been derived from a few prospective studies (eg, in taxanes) and a large number of retrospective analyses. A solid theoretical basis exists for abnormal pharmacokinetics for both oral and intravenous agents in the elderly. Potential factors include decreased absorption because of delayed gastric emptying and reduced gastrointestinal motility; changes in body composition resulting from increased fat content, decreased water content, and increase in volume of distribution; decreased metabolism caused by changes in liver blood flow; decreased excretion resulting from age- and disease-related decline in glomerular filtration rate; and the potential for drug-drug interactions caused by polypharmacy. However, prospective studies of young and elderly cancer patients with normal organ function have shown no appreciable differences in pharmacokinetics for taxanes and platinum agents. The age-related differences in pharmacokinetics, when observed, are subtle and characterized by extreme heterogeneity.
Most of the age-related differences in cancer patients are in the realm of pharmacodynamics, and manifest as decrements in end-organ function, which in turn leads to either dose reductions or a delay in administration of chemotherapy, changing the risk-benefit ratio in treating elderly cancer patients. Thus, the principal challenge in addressing the efficacy-tolerance balance of treatment in the elderly is the development and validation of biomarkers predictive of renal and hematopoietic dysfunction in the setting of cytotoxic chemotherapy.[13,14]

**Inclusion of Elderly Patients in Clinical Trials**

One of the major barriers to determining the appropriate treatment for older patients is the lack of prospective clinical data focusing on older patients. Elderly patients are often underrepresented in clinical trials.[2,7] In addition, few clinical trials are designed to focus specifically on older patients. Furthermore, older patients are much more likely to be undertreated than their younger counterparts.[6] Much of the data that do exist are extrapolated from unplanned retrospective or pooled analyses. The National Institutes of Health and other organizations have specifically identified the need to increase the participation of older patients in clinical trials.

One area in which these issues have been closely examined is breast cancer. Despite a 5-fold increase in incidence and 10-fold increase in mortality in patients with breast cancer over the age of 65, these patients are often undertreated and underrepresented in clinical trials. One study found that the proportion of patients age 65 and older, age 70 and older, and age 75 and older among all patients with breast cancer was 60%, 45%, and 31%, respectively.[15] The proportion of patients in these three age groups included in clinical trials was 36%, 20%, and 9%, respectively, suggesting that older patients were routinely excluded from participation. Another study showed women over the age of 70 with early-stage, node-negative invasive breast cancer were less likely to receive both definitive locoregional therapy and adjuvant chemotherapy, compared with women aged 50 to 69.[16] Multivariate analysis also shows that an age of 75 years or older was independently associated with treatment that deviated from accepted guidelines, even after adjusting for comorbidities, marital status, race, educational background, tumor characteristics, and clinical stage.[15]

**Treatment of Older Patients With Cancer**

**TABLE 2**

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<th>Recommendations for Treatment of Older Patients With Common Malignancies</th>
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Although there is a dearth of prospective phase III data to drive evidence-based decision-making in the elderly cancer patient, we review here the current standards of care and some of the important studies germane to the cancers commonly seen in the elderly (Table 2).

**Non–Small-Cell Lung Cancer**

Medical treatments for non–small-cell lung cancer (NSCLC) can be divided into two groups: adjuvant and palliative. The mainstay of both is platinum-based chemotherapy. Unfortunately, these agents present a unique set of challenges when used in the elderly, primarily because of hematologic, neurologic, and renal toxicity. No significant prospective phase III studies of platinum regimens have been done in older patients, and some evidence suggests that older patients do worse than younger patients when treated with these drugs.[17] However, some retrospective data also suggest that older patients may be able to tolerate platinum-containing regimens, but this remains an area of controversy.[17-19]

In the adjuvant setting, cisplatin can be combined with any number of agents, including vinorelbine, etoposide, gemcitabine (Gemzar), and docetaxel (Taxotere).[20-22] For patients with comorbidities such as renal dysfunction or neuropathy, carboplatin may be a more reasonable option than
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Hormonal therapy is tamoxifen, which reduces the odds of recurrence and death by 39% and 31% survival benefit when treated with tamoxifen or an aromatase inhibitor. The most well-established have breast cancers that express estrogen or progesterone receptors, and these women receive a proliferation rates. Furthermore, older patients tend to present with less advanced disease than younger patients. Unfortunately, older women who receive equivalent therapy seem to be more outcomes compared to patients younger than 70 but also demonstrated significantly higher toxicity.

Although elderly patients have frequently been excluded from oncologic clinical trials, some notable prospective studies have addressed the issue of elderly patients with NSCLC. Thus, the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) group published a phase III randomized trial comparing single-agent vinorelbine to best supportive care for patients greater than age 70 with advanced NSCLC, showing a median survival of 28 weeks for those treated with vinorelbine compared to 21 weeks in the control arm.

Gemcitabine is another agent that has been shown to be useful in older patients. A trial comparing vinorelbine plus gemcitabine vs single-agent vinorelbine in patients 70 years of age or older with advanced NSCLC revealed a survival advantage for the combination arm compared to single-agent vinorelbine (29 and 18 weeks, respectively). However, the much larger Multicenter Italian Lung Cancer in the Elderly Study (MILES) comparing single-agent gemcitabine, vinorelbine plus gemcitabine, and single-agent vinorelbine in patients aged 70 or older with advanced NSCLC found no statistical difference in overall survival between the three arms.

Other agents, such as taxanes, are the subject of ongoing investigation for use in older patients. Taxanes have also been shown to be effective in the treatment of elderly lung cancer patients in early-phase trials. A randomized phase II trial comparing docetaxel to vinorelbine in patients 65 or older with advanced NSCLC suggested a survival benefit in fit patients. In 2006, the Western Japan Thoracic Oncology Group (WJTOG) trial 9904 compared docetaxel to vinorelbine in older patients (age > 70) with advanced NSCLC. This trial showed that patients who received vinorelbine had a superior overall median survival compared to those receiving docetaxel (14.3 and 9.9 months, respectively). A phase III trial of docetaxel and gemcitabine vs single-agent gemcitabine in patients aged 70 to 85 with advanced NSCLC is ongoing. Thus, based on current evidence, we recommend that elderly patients with advanced NSCLC and an ECOG performance status of 0 or 1 be offered treatment with standard platinum-based doublet regimens. However, in the oldest-old and in frail patients, single-agent regimens such as vinorelbine or a taxane may be most appropriate. Newer biologic agents, particularly bevacizumab, should be used with caution until more data exist to support their routine use in this population.

Breast Cancer

Like many malignant neoplasms, breast cancer has a disproportionate impact on older patients. In general, breast cancer is a more indolent disease in older patients. This can be explained by observed biologic differences: Older women have a higher expression of estrogen and progesterone receptors, lower expression of human epidermal growth factor receptor 2, and lower tumor proliferation rates. None of these combinations has demonstrated a clear superiority, even when directly compared. Hence, carboplatin remains a reasonable alternative for those with comorbidities. The use of biologic agents has likewise been studied, but primarily in a retrospective manner. Like cytotoxic chemotherapy, these agents can be effective in older patients, but do carry the risk of higher toxicity. Bevacizumab (Avastin) is now approved for use as a first-line agent in combination with chemotherapy in stage IIIB/IV NSCLC.

Cetuximab (Erbitux), pemetrexed (Alimta), and erlotinib (Tarceva) all are approved for use in specific patient populations. Unfortunately, no trials of biologic agents have focused on older patients in a preplanned, prospective manner. In the subset analysis of ECOG trial E4599, a phase III study combining bevacizumab with standard therapy, patients aged 70 or older showed no significant improvement in overall survival, but patients did demonstrate a significant increase in toxicity with the addition of bevacizumab to carboplatin and paclitaxel. Subset analysis of patients aged 70 or older from the National Cancer Institute of Canada Clinical Trials Group study BR.21, a randomized placebo-controlled phase III trial of single-agent erlotinib as second-line for metastatic NSCLC, showed that older patients had similar outcomes compared to patients younger than 70 but also demonstrated significantly higher toxicity.

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respective, regardless of age.[38] Subsequent trials of aromatase inhibitors appear to show a survival advantage compared with tamoxifen, but this result has not been replicated in every trial.[39–42] Nonetheless, aromatase inhibitors have become the preferred first-line hormonal treatment for postmenopausal estrogen receptor- or progesterone receptor-positive patients. The current recommendations of the NCCN for postmenopausal women are to treat with an aromatase inhibitor for 5 years (preferred), tamoxifen for 2 to 3 years followed by an aromatase inhibitor to complete 5 years total, or tamoxifen for 5 years alone for patients who are intolerant of or decline aromatase inhibitors.[43]

The issue of bone loss associated with aromatase inhibitors is particularly relevant for older patients, who have a higher incidence of osteopenia and osteoporosis at baseline. As such, careful monitoring and early intervention with bisphosphonate therapy is recommended.

For patients with more advanced or hormone-negative disease, the addition of neoadjuvant or adjuvant chemotherapy to surgery and radiation can improve survival. Unfortunately, definitive therapy and adjuvant chemotherapy have often been withheld from older patients. However, the preponderance of evidence supports the concept that fit and willing older patients benefit from definitive surgical resection and do not suffer from excessive surgical morbidity.[44,45]

The role of adjuvant chemotherapy in elderly patients has been less well studied. Retrospective analyses have concluded that older patients, particularly those with hormone receptor-negative, node-positive disease, do have improved survival when treated with adjuvant cytotoxic chemotherapy.[46,47] In fact, a recently concluded prospective study by the Cancer and Leukemia Group B (CALGB) reported that standard chemotherapy (either CMF [cyclophosphamide, methotrexate, and fluorouracil (5-FU)] or AC [cyclophosphamide plus doxorubicin]) was superior to single-agent capecitabine (Xeloda) in the adjuvant setting in women greater than 65 years of age with node-positive or node-negative stage I to stage IIIC invasive breast cancer.[48]

One of the barriers to inclusion of older patients in these trials has been the issue of congestive heart failure (CHF) in older patients receiving anthracycline-based chemotherapy. Observational studies of older patients treated with anthracyclines suggest an increased rate of CHF compared to younger patients. This conclusion led to a study of adjuvant low-dose anthracycline-based chemotherapy, which found that patients with node-positive disease who received low-dose weekly epirubicin and tamoxifen had improved disease-free survival compared to those receiving tamoxifen alone.[49–51]

The role of low-dose anthracycline regimens, pegylated liposomal doxorubicin (Doxil), and non–anthracycline-based regimens has yet to be determined in a prospective manner. A number of ongoing trials are examining the issue of adjuvant chemotherapy in this population. Collectively, these trials will further our understanding of the optimal treatment of older breast cancer patients in the adjuvant setting.

Likewise, few prospective data exist for the treatment of older patients with metastatic breast cancer. A trial comparing gemcitabine to epirubicin as first-line treatment of metastatic disease in women aged 60 or older found that both regimens were relatively well tolerated, but epirubicin produced a better response rate, time to progression, and overall survival.[52] A study of low-dose capecitabine also showed this agent to be effective with acceptable toxicity.[53] Other phase II trials have shown the combinations of vinorelbine plus pegylated liposomal doxorubicin as well as capecitabine with vinorelbine, docetaxel, or paclitaxel, to be effective in the first-line setting for metastatic disease in patients.[52–54] Currently, the treatment of elderly breast cancer patients with an ECOG performance status of 0/1 should be no different than the treatment of younger patients. However, in the setting of comorbidities, there will invariably continue to be modifications in both dose and regimens pending definitive phase III data.

**Prostate Cancer**

Prostate cancer is almost exclusively a disease of older patients, with more than 90% of the patients being over 60 years old at diagnosis.[55] Because this disease is often quite indolent, it remains unclear which patients will benefit from treatment, and the utility of routine screening in older patients is uncertain.[56] Many prostate cancer patients will die from other causes before they become symptomatic from their prostate cancer. The Centers for Disease Control and Prevention (CDC) currently recommends that the question of whether or not to screen for prostate cancer should be an informed decision made by the patient as part of a discussion between the patient and his health-care provider.[57] The current consensus is against screening patients aged 75 or older.[58]

Given the demographics of disease burden in prostate cancer (it primarily impacts men less than 65 years of age), it is reasonable to develop recommendations for elderly patients from the available
phase III data. The initial treatment of localized prostate cancer is surgery or radiotherapy, with the former modality demonstrating a survival benefit only in men less than 65 years of age.[59] In the setting of low-risk prostate cancer, active surveillance may be reasonable, particularly in men with a life expectancy of less than 15 years.[60]

The cornerstone for the treatment of both locally advanced and metastatic disease continues to be hormonal therapy (ie, androgen deprivation therapy [ADT]), with the goal of treatment being to lower serum testosterone levels.[55,61] ADT is any treatment that blocks the interaction of androgens with the androgen receptor (AR). Testosterone and dihydrotestosterone (DHT) are the two major androgens in men, with testosterone present mainly in circulation, and DHT the primary androgen in prostatic tissues. The current evidence-based indications for hormonal therapy include (1) newly diagnosed metastatic disease; (2) adjuvant therapy of node-positive disease discovered at prostatectomy; and (3) in combination with radiotherapy in patients with intermediate- or high-risk disease. In practice, ADT is employed much more widely, and its use in the setting of biochemical progression alone is controversial. In the metastatic setting, ADT is palliative and not curative. Thus, there continues to be debate about the optimal timing of its use.

ADT has a wide variety of side effects, all of which increase with time. These include hot flashes, decreased libido, erectile dysfunction, weight gain, insomnia, osteopenia, sarcopenia, and the risk of cardiovascular disease.[62] Eventually, all patients with metastatic prostate cancer on ADT develop androgen independence, with the mean time to progression being 12 to 30 months. This process is primarily driven by disease biology. Thus, androgen independence, hormone resistance, or castrate resistance is defined as evidence of disease progression (prostate-specific antigen levels, measurable disease, or both), in the face of castrate serum testosterone levels. Recent data suggest that the intratumoral levels of androgens are persistently high, and hence, the appropriate term for this disease state is castrate-resistant prostate cancer (CRPC).[63]

Multiple potential mechanisms foster CRPC: upregulated enzymes of steroidogenesis within the tumor (primary and metastatic); increased tissue production of androgens; persistent AR signaling despite low serum androgens; AR mutations; and AR signaling via alternate ligands. The end result of all these phenomena is persistent AR-dependent signaling in the tumor.[64,65] Elucidation of the above mechanisms of CRPC has led to the development of new agents that are currently in trials, including a new generation of AR blockers (MDV3100) and agents that block intratumoral steroidogenesis (abiraterone).

CRPC was once labeled “chemotherapy resistant.” However, new agents show great promise in both palliative and survival endpoints. Mitoxantrone with prednisone was the first combination to be approved for the treatment of CRPC based on a palliative benefit in patients with painful bone metastases. Docetaxel is the first chemotherapeutic agent with demonstrated survival benefit in prostate cancer and has become standard of care for first-line therapy in CRPC. Compared with mitoxantrone, docetaxel in combination with prednisone improved median survival from 16 to 18.5 months (a 24% increase) in the TAX-327 trial.[66] Currently, a number of trials are ongoing for regimens combining cytotoxic agents with drugs targeting the angiogenesis pathway.

The majority of men with prostate cancer eventually develop bone metastases, which may be associated with pain, spinal cord compression, pathologic fractures, and reduced marrow reserve. As such, pain control, intravenous bisphosphonates, palliative radiation, radioisotopes, and blood product support are an integral part of care for patients with metastatic CRPC. As discussed, prostate cancer is primarily a disease of older men. At every stage of the disease, from screening to treatment, controversy exists regarding the optimal approach to therapy in the elderly. Given the heterogeneity of older patients, the trade-off between efficacy and side effects needs to be evaluated on an ongoing basis, and treatment should be individualized.[67]

**Colon Cancer**

The mainstay of therapy in localized colon cancer is surgical intervention, but neoadjuvant or adjuvant chemotherapy also have well-defined roles. Chemotherapeutic regimens of 5 FU/leucovorin; FOLFOX (capecitabine, 5-FU/leucovorin, and oxaliplatin [Eloxatin]); and FOLFIRI (5-FU/leucovorin and irinotecan) have all been successfully employed in this setting as well as in patients with unresectable or metastatic disease.[68,69] Recently, these regimens have been combined with bevacizumab, and with cetuximab in patients with wild-type KRAS gene.[70]

Most of the evidence for treatment of elderly patients comes from retrospective analyses. A pooled analysis from seven large prospective trials supported the use of adjuvant chemotherapy in elderly patients.[71] The use of 5-FU has also been validated in a retrospective manner for fit elderly patients with metastatic disease, but carries with it the increased risk of toxicity.[72,73]
was confirmed in a prospective observational trial.[74] Regimens containing oxaliplatin or irinotecan also appear to be equivalent in efficacy in older patients compared with younger patients, but hematologic toxicity is more common.[75,76] Prospective validation of these findings does exist, primarily in the form of phase II trials. Single-agent 5-FU and capecitabine were shown to be efficacious in older patients.[77,78] Combination chemotherapy is also effective and safe in fit older patients. The FOLFIRI regimen was shown to have reasonable efficacy and acceptable toxicity in two phase II studies.[79,80] The FOLFOX regimen was also examined and produced similar results.[81] The oral version of 5-FU (capecitabine) has been shown to be equivalent with 5-FU when combined with irinotecan or oxaliplatin.[78,82]

**Leukemias**

The incidence of acute myeloid leukemia (AML) increases with age, with the median age at diagnosis in the United States being over 65 years of age.[83] Senescent changes in hematopoiesis favor myeloid dominance in the marrow, perhaps contributing to an increase in AML in the elderly.[84] The treatment of AML in older patients presents a number of challenges. Older patients are more likely to die as a result of treatment, have comorbidities (including chronic illnesses and organ dysfunction, particularly kidney, liver, and hematologic disorders), and have decreased performance status, which correlates more strongly with poorer outcomes as opposed to age alone.[85,86] Older patients also are more likely to have unfavorable cytogenetics and have an increase in chemotherapy resistance mechanisms such as increased levels of MDR1 and multiple internal tandem duplications of the FLT3 gene.[87] Cumulatively these factors are associated with worse outcomes.[86,88]
<table>
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<tr>
<th>Drug</th>
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<tr>
<td>Mitoxantrone</td>
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<td>Oxaliplatin (Eloxatin)</td>
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<td>Paclitaxel</td>
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<td>Vincristine</td>
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<td>Vinorelbine</td>
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Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

Allogeneic stem cell transplant is the only therapy that may cure some AML patients with unfavorable cytogenetics. Although the majority of elderly AML patients have cytogenetic abnormalities, stem cell transplant is not a reasonable option, with the rates of graft failure and fatal
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graft-vs-host disease being unacceptably high. As such, elderly patients with AML are often treated with the standard induction regimen for AML, employing cytarabine and an anthracycline given intravenously for 7 and 3 days, respectively (commonly referred to as 7 + 3). This regimen seldom results in cure in the elderly AML patient and, in fact, is associated with a significant amount of toxicity and treatment-related deaths. Even if induction is successful, no consolidation regimen (including high-dose cytarabine) has been shown to confer a survival advantage in AML patients over age 60.

Attempts to treat older patients with less toxic regimens have produced some favorable responses, but no survival advantage. Thus, in the typical elderly AML patient with multiple comorbidities and unfavorable cytogenetics, the goals of treatment are purely palliative and focused on hematopoietic support and mitigation of infections.[89] Treatment with 7 + 3, low-dose cytarabine, or supportive care remains the standard, and clinical outcomes have remained essentially unchanged for over 2 decades. The NCCN currently recommends clinical trials for elderly AML patients where feasible, and low-intensity therapy or supportive care for all other patients over the age of 60 who are not participating in a trial.[90]

Because a significant proportion of AML cases in the elderly evolve from an underlying myelodysplastic syndrome (MDS), cytogenetic abnormalities are relatively common. Historically, the treatment of MDS in the elderly has primarily been supportive. However, recent advances based on a better understanding of the molecular basis of MDS have led to the use of hypomethylating agents. Thus far, azacitidine (Vidaza) and decitabine (Dacogen)—both hypomethylating agents—have been US Food and Drug Administration (FDA)-approved for the treatment of MDS. They appear to improve the outcome for patients with poor-risk MDS and can ameliorate the cytopenias of MDS as well as decrease the percentage of blasts in the bone marrow. Aberrant methylation of cytosines within CpG promoter regions by DNA methyltransferases may silence critical components of the normal cell growth and differentiation programs. Hypomethylating agents promote myeloid differentiation in vitro, and these effects are seen at doses much lower than those needed for their maximal cytotoxic effect. Immunomodulatory agents like lenalidomide (Revlimid) are also currently being evaluated for higher-risk MDS patients, especially those with a 5q– abnormality.[91]

**Chronic Lymphocytic Leukemia and Multiple Myeloma**

Chronic lymphocytic leukemia (CLL), monoclonal gammopathy of undetermined significance (MGUS), and multiple myeloma are B-cell dyscrasias, which also have a predilection for the elderly.[92-94] They are often diagnosed incidentally, and the clinical course can be extremely variable. When diagnosed early, the clinical course is indolent (ie, years), and standard treatment is observation. However, stage IV CLL and stage III myeloma have a more aggressive clinical course, with a median survival of 2 to 3 years and 5 to 7 years, respectively. Treatment for both CLL and myeloma continues to evolve, with a number of recently approved agents available, including nucleoside analogs (fludarabine) and monoclonal antibodies (rituximab [Rituxan], alemtuzumab [Campath]) for CLL; proteasome inhibitors (bortezomib [Velcade]) and immunomodulatory agents (thalidomide [Thalomid], lenalidomide) for multiple myeloma. In the elderly, the challenge is to maintain a balance between treatment-related morbidity and mortality and favorable disease-related outcomes.

**Lymphomas**

Over half of patients diagnosed with lymphoma in the US each year are over age 60, and the majority of these patients have diffuse large B-cell lymphoma (DLBCL).[95] Older patients also have lymphocytic/lymphoplasmocytic lymphoma and peripheral T-cell lymphoma in greater frequency than other subtypes. Although no significant genetic or morphologic differences exist between younger and older patients diagnosed with aggressive lymphomas, older patients typically have worse outcomes.[96]

The standard therapy for DLBCL is cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP). The addition of rituximab to CHOP has been shown to improve survival in older patients.[96] For patients who have stage I/II nonbulky disease, the NCCN recommends R-CHOP for three cycles plus locoregional radiation therapy or six to eight cycles with or without radiation.[97] For bulky stage I/II disease, six to eight cycles of R-CHOP plus radiotherapy is recommended, and for patients with stage III/IV disease, eight cycles of R-CHOP or a clinical trial are recommended. For patients with relapse or poor prognostic features, high-dose chemotherapy with autologous stem cell transplant is recommended. While R-CHOP may be curative in many patients, it is also associated with a high incidence of toxicity and mortality in older patients. Low-intensity therapy with dose-reduced R-CHOP is less toxic, but outcomes are inferior to those of standard therapy.[98]
R-CHOP is normally given every 3 weeks, and a phase II trial to determine whether this regimen could be given weekly in divided but equivalent dosages showed that weekly R-CHOP resulted in significantly lower progression-free and overall survival.[99]

Relapse generally portends a poor outcome for older patients.[100] For patients with recurrent disease, several other reasonable options can be employed. A recent trial using a variety of acceptable regimens in patients aged 60 to 80 showed a 2-year survival of 25% to 31%.[101] High-dose chemotherapy with autologous stem cell transplant is feasible in a select population of fit older patients.[102]

In summary, R-CHOP is reasonably well tolerated in older patients and remains the standard of care for first-line treatment. Older patients, in general, have a greater susceptibility to hematologic toxicity, so aggressive support with growth factors is indicated.[103] Older patients who experience relapse have a particularly poor prognosis, and they often may not be able to easily tolerate high-dose chemotherapy followed by autologous stem cell transplant. The optimal treatment for other less common subtypes of lymphomas in older patients is less well defined.

Conclusions

We are obligated to provide older patients with appropriate care that achieves the best outcomes and avoids unnecessary or ineffective treatments. In order to achieve this, we need to continue to improve our understanding of the best practices for caring for elderly patients through increased enrollment in clinical trials. Unfortunately, older patients have historically been omitted from trials. In addition, patients with comorbidities are often excluded, resulting in a study population that is healthier and more fit and thus not representative of typical older patients.

While differences may exist in disease biology for certain cancers in older patients, the more relevant issues while treating elderly cancer patients tend to be functional status and comorbidities. Screening of older adults to determine the appropriate level of care is underutilized and should be a routine part of treatment planning for these patients. While some specific treatment recommendations for the elderly do exist, most treatment decisions are extrapolated from data based on younger, more fit patients, further emphasizing the need for more prospective data on the treatment of older patients. In addition, further exploration of simple and effective screening tools for assessment of older patients is needed.

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