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Key Words. Elderly • Pharmacology • Toxicity • Chemotherapy

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe pharmacokinetic changes associated with aging.
2. Describe concepts of geriatric assessment.
3. Describe the treatment of common malignancies in the elderly with emphasis on pharmacokinetic change.

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ABSTRACT

Persons over the age of 65 years are the fastest growing segment of the U.S. population. In the next 30 years, they will comprise more than 20% of the population. Fifty percent of all cancers occur in this age group, and therefore, there is an expected rise in the total cancer burden. Data are becoming available that will better guide the use of chemotherapy in the older patient population. In this paper, information regarding age-related physiologicchanges and their relationship to pharmacology, functional status, and hematopoiesis is presented. The adjuvant treatment of breast and colon cancer, as well as the primary therapy of aggressive non-Hodgkin lymphoma is reviewed. The treatment of more advanced breast, ovarian, and non-small cell lung cancer is also discussed. ***The Oncologist*** 2005;10:602–612

INTRODUCTION

Persons over the age of 65 years are the fastest growing segment of the U.S. population [1]. Cancer is a disease of aging, with a steep increase in cancer cases after the age of 60 years [2]. Therefore, there will be an increasing number of older patients who will need effective cancer care. Aging is an individualized, heterogeneous process, and therefore, chronologic age does not always predict physiological decline. There are varying levels of vulnerability and declining functional reserve. This requires that cancer therapy be prescribed on an individual basis, and the phases of aging and comorbidity should be taken into consideration [3].

Clinical Pharmacology

Aging can affect the pharmacokinetics and pharmacodynamics of antineoplastic therapy. Pharmacokinetics is the interaction between the drug and the body in terms of its absorption, distribution, metabolism, and excretion.

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Absorption can be reduced by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy [4]. Oral therapy is increasing in importance [5]. Compliance with oral therapy is an important factor and a major obstacle, and may influence survival [6]. Factors evaluating compliance and potential remedies have been studied [7–9]. The volume of distribution (Vd) of drugs is a function of body composition and the concentration of plasma proteins [4, 10]. Fat content can double in the elderly and intracellular water decreases. This leads to a decreased Vd of drugs that primarily distribute to body water, while the Vd of lipid-soluble drugs increases. This can lead to changes in peak concentration and the prolongation of the terminal half-life [4, 10]. Aging is often associated with a decreased serum albumin level and anemia. Anemia can be relevant for treatment with drugs that are heavily bound to red blood cells. The correction of anemia is beneficial, and anemia is the only component of Vd that can be easily adjusted [11]. The liver is the main site of drug metabolism. Phase 1 metabolism occurs primarily via the cytochrome P450 (CYP) microsomal system, consisting of a number of isoenzymes. The CYP system enzymes are heme-based enzymes that are located in the liver, small bowel, kidneys, lungs, and brain. Genetic variability accounts for differing levels of enzyme activity, which may lead to clinically important pharmacodynamic differences among individuals [12]. The potential for drug interactions is high, particularly with the CYP3A4 enzyme [13]. This enzyme is inhibited by a variety of common medications and is involved in the metabolism of a variety of anticancer agents [14–16]. Renal excretion is affected by the gradual decline in function with age. There is a decrease in the glomerular filtration rate (GFR) by approximately 1 ml/minute for every year over the age of 40 [17]. The reduction in GFR is not reflected by an increase in serum creatinine because of the simultaneous loss of muscle mass. Various equations are available to calculate clearance. The most common are the Cockcroft-Gault and Jellife equations [18, 19]. They are less accurate with severe renal failure, decreased muscle mass, and the elderly. The Wright equation may provide more accurate estimates in the elderly [20]. Dosing modifications have been suggested to avoid toxicity in older patients with renal impairment [21].

Comorbidity, Functional Status, and Geriatric Assessment

Comorbidity is one key factor in the overall survival of patients and in the benefits as well as the toxicity of therapy. The number and severity of comorbid illnesses can predict survival in general medical patients [22]. In cancer patients, increases in the comorbidity index result in stepwise increases in the cumulative mortality [23, 24]. In addition, the degree of dependency and geriatric functional scores can also help predict survival [25]. Functional status is also a significant issue. Comorbidity and functional status are independent in older cancer patients, and they both need to be assessed [26]. Traditional oncological measures of function, such as the Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance status scales are not good predictors in the elderly [27, 28].

The "fit elderly" group can often tolerate the standard dose and schedule of chemotherapeutic medications with no significant side effects and obtain the same benefit as younger patients. The patients may still have age-related changes (Vd, pharmacodynamic differences), which may result in increased toxicity. The "frail elderly," which can be defined as those with an excess decrease in lean body mass, and mobility, poor tolerance to therapy and fatigue may be good candidates for palliative treatment, which can provide a better quality of remaining life [29].

Comprehensive geriatric assessment has been used very effectively in general geriatrics to benefit elderly in the community setting, patients under home care programs, and those admitted on geriatrics services [30, 31]. Its use in caring for oncology patients lacks any data from randomized clinical trials at the present time, although such a use seems logical and several observations have been reported to support that notion [28]. There are ongoing efforts by the Cancer and Leukemia Group B (CALGB) (Hurria, personal communication) and the International Society of Geriatric Oncology (SIOG) [32] to develop validated scales that can help clinicians make treatment decisions by recognizing which patients will benefit from aggressive treatments and which patients are more appropriately treated with palliative therapy.

Hematopoiesis

Stem cell reserve appears to be compromised with aging in humans and animal models and may be responsible for relatively increased hematological toxicity [33–35]. The incidence of anemia increases significantly with age, both in men and in women [36]. It is much more so in the frail elderly compared with the fit elderly. The adverse effect of anemia on survival and functional status has been evaluated [36–38]. Recent guidelines have stressed the need for early and adequate treatment of anemia in older patients to maintain a hemoglobin level of approximately 12 g/dl [39]. Chemotherapy-induced neutropenia also appears to be more common, more severe, and associated with a higher rate of infectious complications, more hospitalizations, and a higher mortality in elderly individuals [40–42]. It has

been proposed that the elderly be considered as a special population and that granulopoietic growth factors be used as primary prophylaxis after chemotherapy because many of the infectious and life-threatening complications occur early in the course of therapy [43–45]. Because of toxicity concerns, lower and likely less effective doses of chemotherapy in potentially curable settings, such as adjuvant chemotherapy for breast cancer, colorectal cancer (CRC), and non-Hodgkin lymphomas (NHL), have been used. This may be responsible, at least in part, for the poorer outcome of treatment in the elderly reported in some studies [46–49]. This was particularly evident in a trial of the Southwest Oncology Group (SWOG), in which patients over the age of 65 years had an arbitrary dose reduction for the first cycle of chemotherapy for aggressive lymphoma. This resulted in a poorer outcome for the older patients [49].

Treatment for Common Tumors

Treatment of Early Breast Cancer

Breast cancer is the most common cancer in women, and its incidence increases with age. Despite the fact that it is a very common disease among women >65 years of age, the enrollment of these women in clinical trials, particularly involving chemotherapy, has been negligible [50]. Reports indicate that elderly women receive less optimal surgery and less dose-intense chemotherapy, although data suggest that there is a benefit to chemotherapy, albeit less than in patients <50 years of age [51, 52]. Because of the lower number of women over the age of 70 years in these trials, there are no definitive data that they benefit from adjuvant therapy. Many clinicians extrapolate the data showing benefit in younger women as a rationale for adjuvant therapy in fit, highly functional, older women. In one study, women >80 years of age were less likely to undergo axillary nodal dissection or radiation after lumpectomy for stage I breast cancer than women aged 75–79 years [53]. A randomized study questioned the benefit of radiation therapy after lumpectomy in stage I, receptor-positive women >70 years old [54].

Adjuvant chemotherapy is underutilized in older women, and the relative dose intensity is low. Yet there was no difference found in the pharmacokinetics and clearance of either cyclophosphamide or doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com) in older women [55]. Pharmacodynamic differences may be age-related [56]. There was a higher incidence of mucositis in elderly patients receiving CMF (cyclophosphamide, methotrexate, 5-fluorouracil [5-FU]) chemotherapy [57]. Paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) is commonly employed in node-positive women and is well tolerated in older women as a single agent [58, 59]. From the above evidence, it appears that older women can tolerate adjuvant chemotherapy relatively well and should not be denied treatment based on age alone. With the recent publication of a study in which a sequential dose-dense approach was found to be equally effective, with the concurrent use of doxorubicin and cyclophosphamide followed by paclitaxel, it may be even better to use single agents sequentially to lessen the toxicity associated with combined doxorubicin and cyclophosphamide [60]. The use of hematopoietic growth factors in the dose-dense approach may also be a benefit in delivering the required relative dose intensity.

Hormonal treatment with tamoxifen (Nolvadex®; AstraZeneca Pharmaceuticals, Wilmington, DE, http://www.astrazeneca-us.com) for receptor-positive breast cancer is relatively well tolerated, although complications, including endometrial cancer, are seen in postmenopausal women [61]. With the emerging evidence that the aromatase inhibitor anastrozole (Arimidex®; AstraZeneca Pharmaceuticals) may be better in efficacy and tolerability than tamoxifen, the use of agents in this class will increase. Chronic toxicity with these agents, such as their effect on bones and a potentially greater cardiac risk than with tamoxifen, will require longer follow-up [62]. Anastrozole and letrozole (Femara®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com) are active agents in the adjuvant treatment of breast cancer in newly diagnosed patients [63, 64]. Postmenopausal patients with receptor-positive tumors who have finished 5 years of tamoxifen are now being offered the continuation of hormonal treatment with another aromatase inhibitor, letrozole [64]. Exemestane (Aromasin®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com) is also an important agent [65].

Metastatic Breast Cancer

For medical treatment purposes, metastatic breast cancer (MBC) can be divided into three categories: (a) hormone-receptor–positive (HRP) MBC, (b) Her-2-neu–overexpressing MBC, and (c) hormone-receptor–negative and Her-2-neu–negative MBC. For HRP cases, initial treatment with hormonal agents, such as aromatase inhibitors, tamoxifen, megestrol acetate, and a newer estrogen receptor modulator fulvestrant (Faslodex®; AstraZeneca Pharmaceuticals), is the preferred treatment strategy unless a rapid response is desired. There are phase III studies that have shown the superiority of aromatase inhibitors over tamoxifen in the first-line treatment of breast cancer [66, 67]. As mentioned previously in the section on the treatment of early breast cancer, these agents are relatively safe, but monitoring for thromboembolic disease and endometrial cancer should be

done when using tamoxifen, and close monitoring for bone loss should be done when using aromatase inhibitors.

For MBC patients with overexpression of Her-2-neu, single-agent trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com) or a combination of this humanized monoclonal antibody with either single-agent or combination chemotherapy are all reasonable choices depending on disease activity and the patient's performance status [68]. Monitoring for cardiac side effects of this agent, which otherwise is well tolerated, should be done, and there are no known age-related contraindications. It has been shown that response rates and overall survival are improved when this agent is combined with paclitaxel [69]. It has also been shown to produce very high response rates when combined with docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com), vinorelbine (Navelbine®; GlaxoSmithKline, Philadelphia, http://www.gsk.com), and gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, http://www.lilly.com), among other chemotherapeutic agents and combinations [70, 71]. However, it should not be given in combination with anthracyclines because of an unacceptably higher rate of cardiotoxicity [69].

MBC patients who are hormone-receptor negative and do not overexpress Her-2-neu need to be treated with chemotherapy. Chemotherapy is also needed to treat those receptor-positive patients who have progressed on hormonal agents. Single-agent chemotherapy is preferred, but for some patients with aggressive tumors, combinations may be appropriate. Anthracyclines, taxanes, capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.rocheusa.com), vinorelbine, gemcitabine, and combinations thereof can be used, depending on the prior therapy received by the patient. For most of these agents, there are no specific contraindications in the elderly. Capecitabine needs dose adjustment for renal dysfunction, and close monitoring is necessary when patients are on this medication [72, 73]. Renal dysfunction leads to increased exposure to capecitabine metabolites, which correlates with toxicity. Based on safety results in patients with severe renal impairment, a dose modification cannot be recommended for these patients, and they should not be treated with capecitabine. Additional data from the clinical safety database and pharmacokinetic results support the recommendation that patients with moderate renal impairment be treated with 75% of the recommended standard starting dose to achieve systemic exposure comparable with that in patients with normal renal function [74]. The dose of 1,000 mg/m^2 twice daily is equal to the classic dose of 1,250 mg/m^2 twice daily but is better tolerated and can be considered acceptable in the elderly [75]. Taxanes can be given weekly, and this seems to be better tolerated than regular doses every 3 weeks, with greater efficacy [76, 77].

CRC: Adjuvant Therapy

CRC is the third most common type of cancer in both sexes and is the second most common cause of cancer-related death in men. Two thirds to three quarters of these occur in the population >65 years old. The standard adjuvant chemotherapy for some stage II and all stage III patients has been 5-FU and leucovorin. It is clear that adjuvant therapy is underutilized in elderly patients despite the fact that they can benefit [78–80]. The data on the use and toxicity of 5-FU–based treatments in older individuals are conflicting [57, 81–83]. Some studies suggest a higher incidence of toxicity (mucositis, leukopenia, and diarrhea) in older patients, whereas others contradict these findings. In a pooled analysis of 3,351 patients from seven randomized trials, toxicity was not significantly greater with increasing age [81]. The standard of adjuvant therapy is changing as new data are available from the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer trial, in which 3-year progression-free survival was significantly superior in the arm in which oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us) was added to 5-FU and leucovorin [84]. Oxaliplatin has been shown to be safe in elderly patients [85–87]. Capecitabine has been approved for the adjuvant treatment of stage III colon cancer [88].

Metastatic CRC

Chemotherapy for metastatic CRC has changed rapidly in the past 5 years. Until recently, 5-FU/leucovorin as a bolus regimen was the standard; now, infusional 5-FU, either in combination with irinotecan (Camptostar®; Pfizer Pharmaceuticals) (FOLFIRI) or oxaliplatin (FOLFOX), is being used because of a survival advantage over 5-FU/leucovorin or bolus irinotecan/5-FU/leucovorin (IFL) [89–91]. Oxaliplatin is a third-generation platinum agent and does not share the renal toxicity of cisplatin (Platinol®; Bristol-Myers Squibb). In metastatic disease, there are data showing that the drug is tolerable in the elderly [85]. In patients with varying creatinine clearance >20 ml/minute, there was no excess toxicity, and dose modification is not necessary [92]. In one recent study, elderly patients with metastatic colon cancer were treated with the addition of either oxaliplatin or irinotecan to 5-FU/leucovorin [87]. The median age was 78; dose reductions were needed in 35% of patients, and grade 3 or 4 toxicity occurred in 42% of patients. There were no deaths secondary to drug toxicity. In the Tournigand et al. [90] study, there was no difference in toxicity between patients <65 and those >65 years of age. In that

randomized trial, patients were given infusional 5-FU in combination with either irinotecan or oxaliplatin and were switched over to the opposite arm upon progression.

In the original Saltz et al. [93] trial of bolus ILF (irinotecan, leucovorin, 5-FU), age was not a factor for either excess toxicity or poor outcome. In practice, most clinicians use a modified Saltz regimen (2 weeks on and 1 week off) that appears to be tolerated better than the original 4 weeks on and 2 weeks off schedule. Special precautions should be taken when irinotecan is used in patients with hepatic or renal dysfunction [94]. The early institution of aggressive supportive measures and treatment of diarrhea and neutropenia may help decrease the mortality from complications associated with irinotecan [95, 96]. Bevacizumab (Avastin®; Genentech, Inc.) is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). In a randomized study, it was combined with bolus ILF. Patients receiving the antibody had a 5-month survival advantage over those who did not. Based on these data, it has been approved for use in metastatic CRC in combination with fluorouracil-based chemotherapy. Fit elderly patients should be offered these treatments with close monitoring for hypertension, proteinuria, thromboembolic complications, bleeding, perforations of the gastrointestinal tract, and wound healing [97].

Capecitabine is active in metastatic CRC and is superior to bolus leucovorin/5-FU [98]. Phase II data have shown that the combinations of irinotecan plus capecitabine (Capiri) or oxaliplatin plus capecitabine (Capox, Xelox) have tolerable toxicity. Capecitabine needs dose adjustment in patients with impaired renal function [86, 99, 100, Szatrowski, personal communication].

The chimeric monoclonal antibody cetuximab (Erbitux®; ImClone Systems, Inc., New York, http://www.imclone.com) has been approved for use in epidermal growth factor receptor (EGFR)-expressing metastatic CRC, either as a single agent or in combination with irinotecan in patients refractory to irinotecan-based therapy, and as a single agent in patients who are intolerant to irinotecan-based therapy [101]. EGFR is overexpressed in the majority of patients with CRC, and in some studies has been correlated with poorer outcome [102–104]. Cetuximab is relatively well tolerated, and the most common side effects are skin rash, diarrhea, and allergy [105].

Aggressive NHL

NHL accounts for 4% of all invasive cancers, and its incidence is increasing, much faster in people >65 years old. Aggressive lymphomas are potentially curable with adequate chemotherapy regimens that include an anthracycline. However, age influences outcome; in the International Prognostic Index (IPI), age >60 is an independent variable [106]. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) has been the standard chemotherapy regimen based on the comparison of this regimen with MACOP-B, m-BACOD, and Pro-MACE-CytaBOM) in a SWOG study [107]. There have been very few randomized trials in the elderly to guide us in the treatment of these patients. A review of various trials has been published and supports the use of CHOP in those elderly who do not have any comorbidities [108, 109]. There are patients with significant comorbidities in which alternative regimens are required [109]. A chimeric monoclonal antibody directed against the surface antigen CD20 was made available in the late 1990s [110]. CD20 is expressed on the surface of normal as well as malignant B cells, and most (~ 90%) NHLs are of the B-cell type. In the pivotal study of this antibody, rituximab (Rituxan®; Genentech, Inc.), a response rate of approximately 45% was reported in relapsed, heavily pretreated patients with follicular lymphomas [111]. In a randomized phase III study, CHOP versus CHOP plus rituximab was compared in patients of 60–80 years of age with diffuse large-B-cell lymphoma (DLBCL). There was no additional or excessive toxicity observed other than infusion-related reactions. The complete response rate (76% versus 63%; $p = .005$), event-free survival at 2 years ($p = .001$), and overall survival ($p = .007$) were all significantly better in the antibody arm, and the current standard for DLBCL is rituximab plus CHOP [112]. An ECOG/CALGB trial confirmed the added benefit of rituximab [113].

A dose-dense approach used to treat high-grade NHL in the elderly (69–75 years) has been studied. Patients received CHOP or CHOEP (with the addition of etoposide [Etopophos®, VePesid®; Bristol-Myers Squibb]), given either every 2 weeks (CHOP-14 or CHOEP-14) or every 3 weeks (CHOP-21 or CHOEP-21), and G-CSF. The highest rates of complete remission and overall survival were seen in the CHOP-14 arm. The delivered dose was >90% in all but the CHOEP-14 arm, in which it was 87%. These data indicate that elderly patients with NHL can tolerate the CHOP regimen in the dose-dense fashion. The efficacy of combining CHOP-14 with rituximab is not known at this time [114].

Chemotherapy for Ovarian Cancer: Primary Therapy

Ovarian cancer is the leading cause of death from a gynecologic cancer. The vast majority of epithelial ovarian cancers are diagnosed in postmenopausal women, and the median age at diagnosis is 63 years. Age-specific incidence and mortality rates of ovarian cancer increase with age among women 80–84 years of age. Treatment rates among elderly women are significantly lower than those of younger

women. Chemotherapy is used less among patients over the age of 65, especially those who are non-white or in the oldest age groups [115].

The most commonly used chemotherapeutic agents in ovarian cancer are platinum and taxanes [116, 117]. The half-life is dependent on normal renal function because of a 90% renal elimination for cisplatin. The major toxicities include renal insufficiency, magnesium wasting, nausea, vomiting, peripheral neuropathy, auditory impairment, and myelosuppression. Severe nausea and vomiting is considerably reduced with the use of serotonin-receptor-type-3 antagonists and steroids as premedication. The nephrotoxicity of cisplatin is approximately 5% with current supportive care measures. Amifostine (Ethyol®; MedImmune, Inc., Gaithersburg, MD, http://www.medimmune.com) may provide some protection against cisplatin-induced nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression. Cisplatin can be safely used in well-selected elderly patients [118, 119]. Age is an important and significant predictor of the area under the concentration versus time curve (AUC). [120, 121].

Carboplatin (Paraplatin®; Bristol-Myers Squibb) has a similar mechanism of action to cisplatin. It is completely eliminated through the kidneys, and currently has one of the most unique methods of dosing chemotherapy. The combination of a calculated GFR and Calvert formula allows for accurate dosing, taking into account renal function changes with age and a targeted AUC [122]. Carboplatin exhibits biphasic elimination, with an initial half life of 1.1–2 hours and final half life of 2.6–5.9 hours for patients with creatinine clearance greater than 60 ml/minute. The combination of carboplatin and paclitaxel is currently the standard of care for the first-line therapy of ovarian cancer [123]. This combination has been shown to be safe in fit elderly patients [124].

Ovarian Cancer: Recurrent

Despite the high response rate to front-line therapy, the majority of patients with ovarian cancer relapse and ultimately die of progressive disease. The options for treatment of recurrent disease have increased with the identification of several active second-line agents. However, no second-line agents are curative [125]. The treatment-free interval has been shown to be predictive of response to retreatment with carboplatin [126]. Patients not responding or who progress on carboplatin require other options. There are a number of agents that have favorable toxicity profiles in elderly patients. In relapsed ovarian cancer, liposomal doxorubicin (Doxil®; Alza Pharmaceuticals, Mountain View, CA; http://www.alza.com; Rubex®; Bristol-Myers Squibb) and gemcitabine are particularly tolerable. Weekly paclitaxel and docetaxel has been studied in elderly patients and is a reasonable option [127, 128]. Treatment with topotecan (Hycamtin®; GlaxoSmithKline) is difficult for older patients because of the 5-day schedule. Alternative schedules, including weekly administration, are being evaluated as more tolerable alternatives [129, 130]. Oral etoposide can be used safely if doses are adjusted appropriately [131]. In some patients, the pharmacokinetics are very unpredictable, especially with the oral formulation. Doses should be adjusted according to serum bilirubin levels as well as renal function [121].

Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related death, and approximately 60% occurs in people >65 years of age. Almost one third of patients presents with stage IV disease, and the majority of all non-small cell lung cancer (NSCLC) patients are not able to undergo potentially curative surgical resection. In general, the elderly have been enrolled in small numbers in clinical trials. The CALGB found that, despite no age restrictions, no patient >80 years of age was enrolled in two studies, and only 20% of the patients were 71–79 years. The elderly experienced more grade 3 toxicity, but infectious complications were not more frequent, and there was no difference in overall outcome compared with patients <70 years of age [132]. There is a higher incidence of hematological toxicity with standard chemotherapy in patients >65 years of age than in younger patients [41, 133, 134].

That chemotherapy improves survival and quality of life in elderly patients with advanced disease was established with single-agent vinorelbine in the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) trial [135]. The combination of vinorelbine and gemcitabine may not better than single-agent vinorelbine alone (the Multicenter Italian Lung Cancer in the Elderly Study [MILES] trial) [136]. Platinum-based chemotherapy doublets are considered the standard in advanced stage NSCLC, even in older patients [137, 138]. Comparisons of various doublets by ECOG and other investigators, in which carboplatin plus paclitaxel was compared with various cisplatin-containing doublets, have revealed no significant differences in response or survival [139]. In patients with advanced NSCLC (stage IIIB and IV) treated with a combination of carboplatin and paclitaxel, there was no difference in toxicity or survival between patients >70 years of age and those <70 years of age [133]. There were similar findings in the ECOG 5592 study using cisplatin [118]. From these data, it appears that platinum-containing doublets may be used in the elderly for the first-line treatment of advanced NSCLC. It should be mentioned that the cooperative group trials may have had a

selection bias. Most likely only the fit elderly were selected, and therefore, the results may not reflect those of greater than 70-year-old patients as a whole. Effective single-agent second-line treatment with docetaxel is available and offers a marginal survival advantage over best supportive care (BSC) or other chemotherapy medications [140]. Pemetrexed (Alimta®; Eli Lilly and Company) is a novel, multitargeted antifolate chemotherapeutic agent that is active in many tumor types, including mesothelioma and NSCLC. Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Folate and vitamin B_{12} nutritional status affect the toxicity of pemetrexed, including rates of neutropenic fever. Treatment with pemetrexed without vitamin supplementation results in significantly higher incidences of hematologic and nonhematologic toxicities. Therefore, supplementation with folic acid at 350–1,000 mg orally daily and vitamin B_{12} at 1,000 μg i.m. every 9 weeks is essential to control the toxicity of pemetrexed [141]. In a randomized trial of previously treated patients, pemetrexed and docetaxel had similar efficacies, but pemetrexed had a superior safety profile, particularly in terms of neutropenia and its sequelae [142]. The pharmacokinetics data show that it is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70%–90% of the dose recovered unchanged within the first 24 hours following administration. Clearance decreases and exposure (AUC) increases as renal function decreases. No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26–80 years. Pharmacokinetic analyses in patients with creatinine clearances of 45, 50, and 80 ml/minute had 65%, 54%, and 13% greater, respectively, pemetrexed total systemic exposure (AUC) than patients with creatinine clearances of 100 ml/minute. No dosage adjustment is needed in patients with a creatinine clearance >45 ml/minute. Insufficient numbers of patients have been studied with a creatinine clearance <45 ml/minute to give a dose recommendation. The manufacturer recommends that pemetrexed not be administered to patients whose creatinine clearance is <45 ml/minute [143].

Gefitinib (Iressa®; AstraZeneca Pharmaceuticals) and erlotinib are approved for use as third-line agent [144, 145]. It is a small molecule inhibitor of tyrosine kinase directed against EGFR type I. It is well tolerated and has a response rate of 10% but improves symptoms and quality of life in approximately 40% of patients. Acneiform rash and diarrhea are the main side effects [146, 147].

The International Adjuvant Lung Trial showed a significant survival advantage in patients with stage I to stage III NSCLC given platinum-based chemotherapy after definitive surgery. An absolute difference of 4% was reported. High-risk patients are being offered adjuvant chemotherapy with a platinum-containing doublet [148].

Conclusion

The elderly, who represent an increasing proportion of the population, are a heterogeneous group at high risk for developing cancer. The instruments and methodologies for identification of those elderly who are at high risk for developing toxic side effects from chemotherapy remain underdeveloped. Fortunately, there are clinical trials within various cooperative groups directed toward the development of effective and safe treatment strategies for this special population. Chemotherapy for several common malignancies, both in the adjuvant setting and for metastatic disease, are changing rapidly; however, it remains a challenge to tailor and deliver the most beneficial treatment for those over the age of 65, taking into account comorbidities and physiologic reserves. Several biological agents targeting specific receptors or molecules have entered and will continue to enter clinical practice. So far, several of these agents, such as rituximab, trastuzumab, imatinib (Gleevec®; Novartis Pharmaceuticals Corporation), bevacizumab, cetuximab, and gefitinib, are approved for use and have a relatively good therapeutic index. Tests are being developed that may aid in the prediction of response [149]. With the use of hematopoietic and other active supportive interventions, we may be able to treat cancer in the elderly more effectively. Perhaps the most important objective remains the development and conduct of clinical trials that include statistically significant numbers of participants over the age of 65 as well as trials that specifically address the relevant cancer treatment issues among the elderly.

Disclosure of Potential Conflicts of Interest

Dr. Lichtman has received research support from Glaxo SmithKline and Amgen.

Online Supplemental Data

Since the writing of this article, several newer developments have taken place. While it is not possible to include all of them, the online supplemental data section describes some of them.

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