Chemotherapy Toxicity: Focus on the Older Cancer Patient

Edited by

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Monograph

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About the Activity

The CME activity is based on the information learned from reading this monograph, Chemotherapy Toxicity: Focus on the Older Cancer Patient. It was developed from an identified educational need for information about practical management issues in the practice of medical, surgical, and radiation oncology.

This activity has been developed and approved under the direction of the CME LLC.

Activity Learning Objectives

After reading Chemotherapy Toxicity: Focus on the Older Cancer Patient, participants should be able to:

• Gain a greater awareness of geriatric assessment, which will aid in appropriate drug selection and dosing based on pharmacology and physiology, allowing a greater number of older patients with colorectal, breast, lung, head and neck, and prostate cancer to benefit from treatment.

• Understand that the standard therapies available (i.e. FOLFOX, fol-firi, and biologics) can be safely given to older colorectal cancer patients, with appropriate assessment, monitoring and supportive care.

• Attain a better understanding of the biology of breast cancer in older patients, which will lead to improved outcomes and less therapy-related toxicity.
• Understand that lung cancer patients have increased comorbidity and are particularly vulnerable to drug toxicities.
• Discuss assessment/rational dosaging/drug selection in head and neck and prostate cancer patients.

Target Audience
This activity targets physicians in the fields of oncology and hematology.

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Dr. Lichtman serves as a speaker for Amgen, Merck, and sanofi-aventis, U.S. Dr. Dreicer serves as a consultant for Lilly and AstraZeneca and has received honorarium from sanofi-aventis, U.S. Dr. Murphy receives research funds from sanofi-aventis, U.S. Drs. Balducci, Bond, and Budman have no financial relationships to disclose.

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Colorectal cancer is the world's third most common cancer and predominantly affects older people. The world's population is aging; it is estimated that the number of Americans older than age 65 will double by the year 2030 and will account for 20% of the total population (1). The average 65-year-old person can expect to live another 15 years and remain functionally independent. Similarly, 75- and 85-year-olds will have a life expectancy of 10 and 6 years, respectively, and often remain functionally independent for the majority of that time (2). Thus, the number of older cancer patients is expected to increase. It is estimated that 50% of all cancers and 70% of cancer mortality occur in this age group (3). In 2008, it was predicted that 148,810 new cases of colorectal cancer would be diagnosed in the United States, with 52,180 deaths attributable to the disease and between 67% and 75% of all patients being 65 years old or older (4). The current median age of a colorectal cancer patient is 71 years (4). Oncologists will therefore increasingly see older patients with colorectal cancer. Management of this distinct patient group is of paramount importance.

Clinical Trials and the Elderly

The development of oral fluoropyrimidines, oxaliplatin, irinotecan, and monoclonal antibodies (e.g., bevacizumab, cetuximab, and panitumumab)
has resulted in significant improvements in response rate and progression-free, disease-free, and overall survival in the metastatic setting (5–9). These advances have resulted in the investigation of new regimens in the adjuvant setting. The Intergroup 0089 study was reported by Haller et al. with a 10-year follow-up and 3,561 patients confirmed the benefit and durability of 6 months treatment with 5-fluorouracil (5-FU) and leucovorin (LV) (10). Further improvements in relapse-free and overall survival have been seen with the addition of oxaliplatin to FU/LV (11). A serious concern with adjuvant data, however, is that many of the trials have not included significant numbers of elderly patients; hence, extrapolation of response, progression, survival, and toxicity data to the age group most representative of colorectal cancer patients may not be valid. Underrepresentation of patients older than age 65 years in cancer clinical trials is not a new finding. Hutchins found that compared with patients younger than 65 years, significantly fewer patients 65 years and older (63% vs. 25%, respectively) were entered into Southwest Oncology Group trials (12). Potosky et al. found that only 65% of patients aged 65–74 years, 47% aged 75–79 years, and 24% aged 80 years or older received adjuvant therapy, compared with 78% of patients aged 55 years or younger (13). This trend has persisted in 2006 (14). Shrag and colleagues also confirmed that age at diagnosis directly correlates with the use of adjuvant chemotherapy (15). Despite the fact that clear evidence demonstrates the effectiveness of adjuvant chemotherapy for resected colorectal cancer in geriatric patients, many of the adjuvant studies underrepresent the elderly. The MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study is a case in point (11). The median age in this study was 61 years, more than a decade younger than the median age of people with colorectal cancer in the general population. Reasons for this trend include physician or patient preference, concern about comorbidities, poor social support, unwillingness of third parties to pay for clinical trials, and perhaps simple ageism.

Age-Related Changes

Aging is a very heterogeneous process with physiologic, sociologic, and psychological changes (16). A hallmark of aging is a gradual diminution of physiologic reserve that especially manifests when the body is exposed to stressors—for example, infection, cancer, surgery, and chemotherapy. Physiologic changes affect all organ systems—for example, the cardiovascular, gastrointestinal, pulmonary, renal, and immune sys-
Physiologic Changes and Clinical Pharmacology in the Aging Patient

Physiologic changes that occur with increasing age affect the pharmacokinetic characteristics of chemotherapy in a number of ways. Changes within the gastrointestinal system can result in reduced drug absorption,
decreased gastrointestinal motility, reduced splanchnic blood flow and digestive enzyme secretion, and mucosal atrophy (29). Aging also affects body composition; fat content can double in the elderly and intracellular water levels decrease. Because the volume of distribution (Vd) of drugs is a function of body composition and the concentration of plasma proteins (29), these changes can result in a decreased Vd of water-soluble drugs and an increased Vd of lipid-soluble drugs (29). The Vd of drugs can also be affected by anemia, which often occurs in aging patients, along with an associated decrease in albumin levels. The liver is the main site of drug metabolism. There are no significant age-related changes in liver function and drug metabolism. Phase 1 metabolism occurs primarily via the cytochrome P450 microsomal system and exhibits genetic variability (30). Due to the large number of drugs elderly patients use, the potential for drug interactions is high, particularly with the CYP3A4 enzyme (31,32). Renal function also gradually declines with age, as evidenced by a reduced glomerular filtration rate in elderly patients. This reduced renal excretion, however, does not result in increased serum creatinine levels because of the simultaneous loss of muscle mass. Therefore, serum creatinine is a poor measure of renal function in older patients. Various equations, such as the Cockcroft-Gault, Jelliffe, and Wright equations are used to calculate renal clearance in patients of all ages (33–35). There are reviews that discuss the dosing modifications that are recommended for older patients with renal impairment to avoid toxicity (36). Table 1 summarizes some of the pharmacokinetic changes that occur with aging.

Therapy-Related Toxicities

Most publications describing chemotherapy in older patients are retrospective subset analyses in which older patients make up a fraction of patients. Patients reported generally do not have significant comorbidity and may not be truly representative of the average patient seen in practice. There have been a number of publications regarding end-organ dysfunction (37,38). Although end-organ dysfunction trials are not specifically for the elderly, the data can be used for this purpose, as older patients have a higher incidence of comorbidity and end-organ dysfunction. Because of the overall lack of data, particularly for patients older than 80 years, the clinician will continue to have the task of extrapolating data to fit the individual patient. Modification of toxicity and dosing will also be affected by the use of hematopoietic growth factors (39). The NCCN guidelines for the management of older cancer patients are an important resource (40).
### Table 1. Pharmacokinetic changes that occur with aging

<table>
<thead>
<tr>
<th>Absorption</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Controllable</td>
<td>Concomitant medication (e.g., H₂ blockers, antacids)</td>
</tr>
<tr>
<td></td>
<td>Compliance</td>
</tr>
<tr>
<td>Not controllable</td>
<td>Reduced gastric secretion, gastric emptying, gastrointestinal motility</td>
</tr>
<tr>
<td></td>
<td>Diminished splanchnic blood flow</td>
</tr>
<tr>
<td></td>
<td>Decreased absorption surface</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in body composition</td>
<td>Increased fat content (Fat content doubles)</td>
</tr>
<tr>
<td></td>
<td>Decreased intracellular water</td>
</tr>
<tr>
<td></td>
<td>Reduced albumin concentrations (etoposide, taxanes are highly protein-bound)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Increased volume of distribution</td>
</tr>
<tr>
<td></td>
<td>Lower peak concentration and prolonged terminal t₁/₂</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced liver flow</td>
<td>Decreased liver size</td>
</tr>
<tr>
<td></td>
<td>Possible related changes in P450 microsomal systems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polypharmacy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P450 inhibitors: grapefruit juice</td>
<td>P450 inducers: phenobarbital</td>
</tr>
</tbody>
</table>

| Drug interactions leading to adverse events |

<table>
<thead>
<tr>
<th>Excretion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in glomerular filtration rate (one of the most predictable changes associated with aging)</td>
<td></td>
</tr>
<tr>
<td>Additional effect of comorbid conditions on renal function</td>
<td></td>
</tr>
</tbody>
</table>

Surgery

Surgery is integral to the curative and palliative treatment of colorectal cancer. Accurate surgical staging is critical to proper evaluation and survival. The recommendations from the American College of Pathologists suggest that 12 or more lymph nodes (LNs) should be examined from a colorectal cancer specimen. Baxter and colleagues used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program between 1988 and 2001 to determine the proportion of colorectal cancer patients in the United States who receive adequate LN evaluation (41). More than 116,995 patients were analyzed, and only 37% received adequate LN evaluation. Older patients (71 years or older) were less likely to receive adequate LN sampling than younger patients (odds ratio [OR] = 0.45, 95% confidence interval [CI] 0.44–0.47). Also, patients operated on at NCCN centers are much more likely to have at least 12 LNs sampled (89% of cases) than those in population-based samples (45%) (42).

As expected with increasing age, the operative mortality increases, but not significantly in most studies. Furthermore, morbidity and mortality in older patients are often related to more advanced disease, emergency operative conditions, and comorbidities. A large review of colorectal surgery in elderly patients showed that the median mortality rate for each group increased with age (3% for the youngest, 6.4% for the 65–74 group, 8.6% for the 75–84 group, and 19.4 for the 85 or older group). However, when studies of only elective surgery were examined, the mortality rates declined to 1.7%, 0%, 1.0%, and 2.0%, respectively. These data underscore the fact that many of the operations in older patients were performed as an emergency, raising the morbidity and mortality considerably. This study, like so many others, showed that cancer-specific survival was similar among the elderly and younger patients; age alone should not be used to deny a patient curative surgery (43,44).

Minimally invasive surgery has been used in the treatment of colorectal cancer. A case-matched control study on laparoscopic versus open colectomies in octogenarians showed an open conversion rate of 6.1% and that the operative time was 49 minutes longer in the laparoscopy group (P = .001), with a low perioperative mortality (2.4%), which did not differ significantly from the younger patient cohort. The morbidity rate was 21.5% in the laparoscopy group and 31.1% in the open group (P = .30), with patients in the laparoscopy group experiencing faster recovery of bowel function, (P = .01) and a significant reduction in the mean length of hospital stay (9.8 vs. 12.9 days; P = .001). Laparoscopic colectomy permitted an improved scale of postoperative independence when compared with the
open group \( (P = .02) \) (45,46). Various methodologies are being studied to properly evaluate elderly patients to minimize operative and postoperative complications and to aid in the selection of procedures (45,47-49).

Resection of hepatic metastases should be considered in well-selected, fit older patients evaluated at specialized centers with significant experience. There are very few data on the short- and long-term outcomes of older patients who have surgery for metastatic colorectal cancer to the liver. One of the largest studies to date was published by Fong et al. in 1995, showing that older patients can undergo adequate resection without excessive risk (50). Since that time, many things have changed, particularly the improvement in medical therapy for the disease, which allows patients the opportunity to potentially benefit from surgery. It is interesting to note that when meta-analyses of risk assessment have been performed, age is not an adverse prognostic factor. However, these reviews did not rigorously describe the experience of older patients in any detail (i.e., adverse events, length of stay, long-term follow-up) (51,52).

Chemotherapy Toxicity

The choice of chemotherapy for an elderly patient is dependent on a number of clinical factors. This includes disease-related factors—primarily the availability of effective therapy. Patient factors include the patient’s physiology, comorbidity, functional status, and performance status. The accumulated patient factors lead to a prediction of tolerance. It is critical, in devising a treatment plan, to assure the patient that he/she will be able to complete the prescribed regimen. Toxicity is often difficult to predict. Data are available in the literature; however, much of these are based on patients 10–15 years younger than the \( \geq 70 \)-year-olds discussed in this chapter. Extermann et al. have developed a methodology to help predict toxicity. The MAX2 index is a convenient and reproducible way of comparing the average per-patient risk for toxicity from chemotherapy across several regimens. The index was developed from the literature on patients age 70 and older. It is being incorporated prospectively into trials to validate its clinical usefulness (53).

Chemotherapy for Colon Cancer

The chemotherapeutic agents used in colorectal cancer are the fluoropyrimidines (5-FU with/without LV), capecitabine, oxaliplatin, and irinotecan. Table 2 is an overview of other agents and their toxicities.
Table 2. Pharmacokinetic parameters of chemotherapeutic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common applications</th>
<th>Elimination of active compounds</th>
<th>Dose adjustment</th>
<th>Toxicities</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Breast cancer</td>
<td>Renal</td>
<td>Yes</td>
<td>Mucositis, diarrhea, hematologic</td>
<td>Decreased CrCl, effusions, ascites</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Breast, lung, ovary, pancreas, and biliary cancers</td>
<td>Yes</td>
<td>NA</td>
<td>Mucositis</td>
<td>Marked hepatic dysfunction or renal insufficiency</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Breast and colorectal cancers</td>
<td>Cellular and hepatic</td>
<td>No</td>
<td>Mucositis, diarrhea, hematologic</td>
<td>DPD deficiency</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Leukemia</td>
<td>Cellular and hepatic</td>
<td>Yes (decreased CrCl; age &gt; 60 yrs)</td>
<td>Diarrhea, hematologic, central nervous system toxicity</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>CLL, lymphoma</td>
<td>Renal</td>
<td>Yes</td>
<td>Immune suppression, hematologic</td>
<td>Marked renal insufficiency</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Lymphoma</td>
<td>Renal</td>
<td>?</td>
<td>Hematologic</td>
<td>NA</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Mesothelioma, lung cancer</td>
<td>Renal</td>
<td>No</td>
<td>Neurotoxicity</td>
<td>Marked renal insufficiency</td>
</tr>
<tr>
<td>Alkylation agents</td>
<td>Lymphoma, breast cancer</td>
<td>Hepatic and renal</td>
<td>Yes</td>
<td>Hematologic, bladder</td>
<td>NA</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------</td>
<td>------------------</td>
<td>-----</td>
<td>---------------------</td>
<td>----</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>CLL, lymphoma</td>
<td>Hepatic and renal</td>
<td>NA</td>
<td>Hematologic</td>
<td>NA</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Multiple myeloma</td>
<td>Hepatic and renal</td>
<td>Yes</td>
<td>Hematologic</td>
<td>NA</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Brain tumor</td>
<td>Hepatic</td>
<td>NA</td>
<td>Hematologic</td>
<td>NA</td>
</tr>
<tr>
<td>Platinum analogs</td>
<td>Lung, germ cell, and gastrointestinal cancers</td>
<td>Inactivated in the circulation</td>
<td>Yes</td>
<td>Renal, neurotoxicity</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Ovary and lung cancers</td>
<td>Renal</td>
<td>Yes</td>
<td>Hematologic</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Colon cancer</td>
<td>NA</td>
<td>NA</td>
<td>Neurotoxicity</td>
<td>NA</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Breast cancer, lymphoma</td>
<td>Biliary</td>
<td>Yes</td>
<td>Hematologic, mucositis, cardiac</td>
<td>Left ventricular dysfunction</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Myeloid leukemia</td>
<td>Renal</td>
<td>NA</td>
<td>Cardiac</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetic parameters of chemotherapeutic drugs
### Table 2. Pharmacokinetic parameters of chemotherapeutic drugs (Continued from page 9)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common applications</th>
<th>Elimination of active compounds</th>
<th>Dose adjustment</th>
<th>Toxicities</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin</td>
<td>Breast cancer</td>
<td>NA</td>
<td>NA</td>
<td>Cardiac</td>
<td>NA</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Lymphoma, prostate cancer</td>
<td>Hepatic and renal</td>
<td>Yes</td>
<td>Hematologic</td>
<td>NA</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>Bladder cancer</td>
<td>Hepatic and renal</td>
<td>No</td>
<td>Hematologic, renal</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Plant derivatives**

<table>
<thead>
<tr>
<th>Etoposide</th>
<th>Lung cancer, lymphoma</th>
<th>Mixed hepatic and renal</th>
<th>Yes (decreased CrCl)</th>
<th>Hematologic</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinca alkaloids</td>
<td>Lung and breast cancers, lymphoma</td>
<td>Biliary</td>
<td>Yes</td>
<td>Neurotoxicity</td>
<td>NA</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Lung and breast cancers</td>
<td>Hepatic</td>
<td>Yes</td>
<td>Hematologic, neurotoxicity</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Notes:**
- CLL = chronic lymphocytic leukemias, CrCl = creatinine clearance, DPD = dihydropyrimidine dehydrogenase, NA = not applicable.
Fluoropyrimidines

There is marked variability in plasma levels of the parent drug and metabolites, and toxicities can vary. Arbitrary dose reductions occur in the elderly, but there is no pharmacokinetic basis for dose modification based on age alone.

Studies Suggesting an Effect of Age on Toxicity

Increased toxicity with age was shown in a trial of metastatic colorectal cancer (54). These conclusions are also supported by data derived from a meta-analysis comparing infusional 5-FU with bolus 5-FU (55). Older patients and poor performance status had higher rates of diarrhea, mucositis, nausea, and vomiting, with older female patients having the highest incidence. Grade 3 or greater hematologic toxicity was almost eightfold more common with bolus 5-FU (31% vs. 4%) (55).

Studies Suggesting That Age Is Not a Determinant of Toxicity

An overview of trials involving 5-FU with either LV or levamisole showed no interaction between age and outcome except for the occurrence of treatment-related leukopenia (56). In a retrospective analysis of clinical trials testing FOLFOX-4 (5-FU, LV, oxaliplatin), older age was not associated with increased overall incidence of grade 3 toxicity or higher or 60-day mortality; however, there was a higher incidence of grade 3 neutropenia and thrombocytopenia. The benefit of FOLFOX-4 did not differ by age (7). In an Intergroup study with adjuvant 5-FU for high-risk stage II and stage III colon cancer, an analysis of this trial demonstrated that the elderly are as likely to benefit and tolerate adjuvant chemotherapy as are younger patients (10). In an evaluation of the SEER-Medicare linked database for resected stage III colorectal cancer, adjuvant 5-FU was well tolerated, even among the very old patients without a major comorbidity (15). A retrospective analysis of European trials showed that benefit and toxicity were equivalent in “fit” elderly patients and younger patients (57).

A significant determinant of this difference in toxicity profile is the schedule used. Weekly bolus 5-FU and infusional regimens are better tolerated than the monthly regimen (10,57). The data suggest no reason to dose reduce intravenous therapy based on age alone.
Capecitabine

The pharmacokinetics of capecitabine are not affected by age in patients with normal renal function (58). Studies have compared capecitabine with 5-FU in patients with a median age over 60 years (59). Capecitabine at 1,250 mg/m$^2$ twice daily on days 1–14 every 21 days is better tolerated than 5-FU administered as per Mayo schedule (425 mg/m$^2$ on days 1–5 every 28 days). Studies in elderly breast cancer patients showed that the dose might be reduced from 1,250 mg/m$^2$ to 1,000 mg/m$^2$ with equal efficacy but with reduced toxicity. A study in advanced colorectal cancer (age older than 70 years) was done with doses adjusted based on creatinine clearance. Only 12% of patients experienced grade 3 or 4 treatment-related adverse events such as diarrhea, hand-foot syndrome, and thrombocytopenia. The median dose intensity was 88% (60). Some toxicities may be due to declining renal function with aging. In another study, patients with moderate renal impairment at baseline (estimated creatinine clearance 30–50 mL/min) experienced a higher incidence of grade 3 or 4 toxicities. This resulted in a recommendation of a lower starting dose with moderate renal impairment (calculated creatinine clearance 30–50 mL/min) and a contraindication in patients with severe renal dysfunction (less than 30 mL/min). The dose of capecitabine should be adjusted to creatinine clearance, and a starting dose of no greater than 1,000 mg/m$^2$ twice daily should be strongly considered.

Compliance is an important issue with capecitabine, particularly because older patients may take a large number of medications (61,62).

Oxaliplatin

Single-agent oxaliplatin is not used in colorectal cancer. Therefore, the toxicity issues are in combination with fluoropyrimidines. The kidneys eliminate approximately 30%–50% of the drug. In studies of patients with mild to moderate renal impairment (glomerular filtration rate of more than 20 mL/min), no increased toxicity was seen (63). Clearance of ultrafilterable platinum after administration of oxaliplatin is not influenced by impairment of hepatic function, sex, or age.

The previously mentioned retrospective meta-analysis of patients receiving FOLFOX did not find increased neurotoxicity with age. A retrospective review of patients with a median age of 78 years showed manageable toxicity (64). However, neurotoxicity is still a significant problem. Many older patients have comorbid conditions such as diabetes that may exacerbate neurotoxicity. In the NASPB C-07 trial, 26%
had hand/foot numbness, some of which was long-lasting (65). This may have significant functional consequences for older patients. The combination of oxaliplatin/capecitabine has been studied in patients age 70 and older. No relationship was seen between response and patient age, Eastern Cooperative Oncology Group performance status, or the ability to perform activities of daily living or instrumental activities of daily living (66). There are no data supporting dose reduction based on age alone. Patients with a severe decrease in glomerular filtration rate should have dose reduction.

Irinotecan

Irinotecan can be given as a weekly and every-3-week dose (67). Age of 70 or older independently predicted occurrence of grade 3/4 diarrhea. Treatment with the every-3-week schedule was associated with a lower rate of diarrhea (67). Delayed diarrhea was increased in patients with advanced age. Pharmacokinetic parameters in patients 65 years or older were similar to those in younger patients. In addition, response rates did not vary based on age. It is recommended that patients older than age 70 years, patients with prior pelvic irradiation, or patients with poor performance status start at reduced doses (67).

A multicenter study reported by Rothenberg et al. showed increased toxicity in elderly patients older than age 65 years who had been treated with weekly irinotecan. This is reflected in the package insert, in which dose modification is recommended for patients older than 70 years (68). However, data from a number of trials, including a meta-analysis, indicate that patients 70 years of age and older derive the same benefit with similar toxicities as younger patients (6,69). It needs to be emphasized that patients who are entered into these trials have performance scores with less comorbidity and fewer functional impairments than most patients seen in practice. There are virtually no data on patients older than 80 years of age. Therefore, extrapolation of the data must be done with care. The potential for grade 3 and 4 diarrhea and its consequences need to be always kept in mind.

In 2005, Souglakos et al. reported a phase II trial of FOLFIRI (irinotecan/leucovorin/5-FU) in patients older than age 70 years (70). Overall response rate was 33.3%, with 36% having stable disease and a disease control rate of 69%. The median time to disease progression was 7.0 months. Grade 3 and 4 neutropenia in 20% of patients was observed, and grade 3 to 4 diarrhea was observed in 17% of patients. Similar data have been seen in the results of a study published by Sastre et al. in 2005.
evaluating the efficacy and safety profile of irinotecan and 5-FU in 86 patients who were older than 72 years of age (71). These patients were treated with irinotecan at 180 mg/m² followed by 5-FU 3,000 mg/m² continuous infusion for 48 hours. These two drugs were given every 2 weeks. A total of 68% of patients obtained disease control, and the median duration of response was 7.0 months (95% CI, 4.2–9.9 months). The grade 3 and 4 neutropenia and diarrhea were seen in 21% and 18% of patients, respectively. Two deaths were reported; one died of grade 4 diarrhea resulting in renal failure, and the other died of intestinal hemorrhage. However, diarrhea remains the most threatening side effect. In the original trial of bolus ILF (irinotecan, LV, 5-FU), age was not a factor for either excess toxicity or poor outcome (72). In the adjuvant trial, increased toxicities were seen, and this regimen is now rarely used (73). When it is used in practice, most clinicians use a modified regimen (2 weeks on and 1 week off) that appears to be tolerated better than the original schedule. Special precautions should be taken when irinotecan is used in patients with hepatic or renal dysfunction (38). The combination of capecitabine and irinotecan (XELIRI) has shown activity. There is significant hematologic and gastrointestinal toxicity. If this regimen is used in patients older than age 65 years, doses should be modified for the first cycle, and it should be used with caution (74,75). The early institution of aggressive supportive measures and treatment of diarrhea and neutropenia may help decrease the morbidity from complications associated with irinotecan. A meta-analysis demonstrated that there were no age-related changes in efficacy and safety. Patients older than 70 years of age who were selected for inclusion in phase III trials derived similar benefits as younger patients from irinotecan-containing chemotherapy, and the risk of toxicity was similar (6).

Biologic Therapy

Cetuximab, bevacizumab, and panitumumab are part of the therapy for metastatic disease. Bevacizumab has been approved for use in the metastatic setting in combination with FU-based chemotherapy (8). Fit elderly patients should be offered these treatments, with close monitoring for hypertension, proteinuria, thromboembolic complications, bleeding, perforation of the gastrointestinal tract, and poor wound healing (8). In elderly patients, bevacizumab has also been combined with 5-FU/LV and FOLFOX, with proven efficacy (76). As many geriatric patients have hypertension, coronary artery disease, and history of stroke, the decision on the safety of bevacizumab in the elderly is a difficult one.
There is a clear increased risk of an arterial thromboembolic event in older patients (77). In patients with neither baseline risk factor (age and arterial thromboembolic event), the rate of arterial thromboembolic events per 100 person-years of follow-up was 1.9 in control patients and 2.6 in bevacizumab-treated patients (hazard ratio = 1.39, 95% CI = 0.48–3.99; P = .544). The subgroups with the strongest trend toward an increased rate of arterial thromboembolic events per 100 person-years in the bevacizumab-treated group were patients aged 65 years or older (4.7 in control group patients vs. 10.0 in bevacizumab-treated patients, hazard ratio = 2.1, 95% CI = 0.91–4.89; P = .082); patients with a history of an arterial thromboembolic event (5.9 in control patients vs. 24.4 in bevacizumab-treated patients, hazard ratio = 4.18, 95% CI = 0.95–18.4; P = .060); and patients with both risk factors (3.6 in control patients vs. 27 in bevacizumab-treated patients, hazard ratio = 7.6, 95% CI = 0.99–58.7; P = .052). Some of the analyzed patients were on aspirin, but the beneficial effect of aspirin could not be determined. However, there was no increase in bleeding. These toxicities need to be taken into account when making a decision about using bevacizumab. This is particularly important in light of the 2008 paper showing that the addition of bevacizumab to FOLFOX increased progression-free survival but not overall survival or response rates (78).

Cetuximab, a chimeric monoclonal antibody against the epidermal growth factor receptor, has also been approved for metastatic colorectal cancer either as a single agent or in combination with irinotecan in patients refractory to irinotecan-based therapy (5). Given the side effect profile of skin rash, diarrhea, and allergy, it appears that cetuximab is well tolerated in geriatric patients, with no significant life-threatening toxicity. In a safety analysis, cetuximab was well tolerated, but when used as a single agent, 20% of patients over 70 years developed grade 3 and 4 diarrhea (79). Older patients are given this treatment as palliative therapy, and this degree of potential toxicity should be anticipated. In 2005, the N0147 study was redesigned to accrue 2,400 patients with stage III colorectal cancer, and patients are randomized to receive modified FOLFOX-6 with or without cetuximab. A potential role for cetuximab in the adjuvant setting may result from this study. Panitumumab, a fully humanized monoclonal antibody against epidermal growth factor receptor, has been approved for third-line use in progressive metastatic colorectal cancer. Its side effect profile is similar to cetuximab (80). In single-agent trials with a median age of approximately 60 years, the incidence of grade 3 and 4 diarrhea was less than 5% (80–82). There is a growing body of evidence that wild-type Kras is required for these agents to have activity (83).
Rectal Cancer and the Elderly

The current standard of care for all stage II (T3/T4N0) and stage III (TanyN1/N2) rectal cancer is combined modality therapy including chemotherapy, radiation, and surgery. The 2001 German trial of 823 patients with resectable rectal cancer concluded that preoperative and not postoperative chemoradiation was superior in terms of local recurrence rate (6% vs. 13%; P = .006) after 5 years. Preoperative treatment was associated with an impressive decrease in toxicity (grade 3 or 4 toxic effects 27% vs. 40% postoperative). The median age in this study was 62 years (range of 30–76 years). There was no difference, however, in the frequency of distant metastases and overall survival (84). Preoperative chemoradiation has therefore been adapted as the standard of care accepted by the NCCN guidelines. The median age of 62 years reported in this study is at least a decade younger than the average age of a rectal cancer patient, and extrapolation of this data to an elderly population should be done with caution. In rectal cancer treatment, there is much debate in the recent literature regarding the need for neoadjuvant radiation, with its attendant short- and long-term morbidity. Many patients present to specialist centers having had upfront surgery for their rectal cancer (stage II and III). There are data to support combined chemoradiation in patients older than age 65 years in the adjuvant setting. Neugut et al. report that elderly patients with stage III rectal cancer derive as much benefit from adjuvant chemoradiation (29% increase in 5-year survival) as those observed in randomized trials (85). However, SEER-Medicare database populations and other analyses show that as age at diagnosis increases, the use of combined chemoradiation decreases (86,87). Elderly patients in the adjuvant setting should be referred for chemoradiation, as the literature does not support increased toxicity or lack of benefit in the elderly. Advances in both rectal surgery (e.g., total mesorectal excision) and systemic chemotherapy (e.g., oxaliplatin and fluorouracil) have together advanced the case for neoadjuvant chemotherapy without radiation (88,89). Some studies have indicated that total mesorectal excision may not improve survival in older patients, particularly those with significant comorbid illness, as operative complications and noncancer conditions may affect survival (90,91). As discussed previously, oxaliplatin combined with capecitabine in the adjuvant colon setting is similarly tolerated in older and younger patients, and age should not be a barrier to its use in an elderly population (92). It is imperative that elderly patients are included in future trials incorporating modern systemic chemotherapies and targeted therapies in both the neoadjuvant and adjuvant setting for rectal cancer. Analysis of quality of

The Older Colorectal Cancer Patient
life and adaptation of older patients to colostomies and rectal function needs to be further studied (93).

References


Aging, Breast Cancer, and Toxicity

Daniel R. Budman, MD, FACP

Breast cancer continues to be a significant public health problem in the developed world, with more than 1 million women in the 50- to 69-year-old age group and another million older than 70 years of age currently having the diagnosis of breast cancer (1). In addition, although the annual incidence of diagnosis of this disease has recently dropped (http://seer.cancer.gov), the population older than 65 years of age with breast cancer is expected to climb over the next 50 years as the population ages (Figure 1) (1). The aggregate of this disease in the United States shows a tendency to be more prevalent in the elderly population based on Surveillance, Epidemiology, and End Results (SEER) data (Figure 2), which has led to recent concerns about the management of elderly patients with this disease (2). Fortunately, the majority of postmenopausal patients are estrogen receptor–positive, with an increasing proportion of patients having estrogen receptor-positive disease with advancing age (3,4). In addition, new molecular data indicate that the pathways driving tumor proliferation in the young patient with breast cancer are different than those of patients 65 years of age or older (5). These favorable biologic characteristics (6) were examined in a retrospective review of SEER and San Antonio breast cancer data in 206,578 patients aged 55 years or more, with the findings demonstrating that the more elderly patients had larger tumors but more indolent disease (4).
These findings have been confirmed with a more recent study of the SEER database (7). As a consequence, recent reviews of "elderly" patients with breast cancer have devoted little space to cytotoxic chemotherapy (8). However, a retrospective survey at the Jules Bordet Institute of 2,723 consecutive patients also noted that 19% of breast cancer patients older than 50 years had a luminal B phenotype associated with a more aggressive course (9). Hence, a significant number of elderly female patients with breast cancer may be exposed to chemotherapy at some time during their disease course.

**Methods**

A retrospective review of the literature using the terms "breast cancer," "elderly," "chemotherapy," and "toxicity" yielded 3,149 potential refer-
ences on this subject. Articles were then manually scored for relevance, with only a proportion retained for this chapter to limit size and redundancy. Prospective, retrospective, and review articles were evaluated.

**Problems with the Database**

Age criteria for the label of “elderly” vary from 50 to 70 years depending on the investigators, and there is not apparent uniformity in the definitions used to identify the “elderly” oncology patient. Age alone is not a measure of physiologic age (10,11). In addition, most clinical trials include or exclude patients on the basis of performance status. Age and performance status are not equivalent to a “geriatric assessment,” which is a better measure of fitness for a given treatment (10,12,13). A 2002 European report of cancer patients older than 65 years of age noted that 13% of such patients with a normal performance status had two or more comorbid conditions, and 38% had impairment of daily living (14). The frail patient must also be distinguished from the healthy elderly patient (15). The frail patient is obviously at higher risk to develop complications from cancer treatment (16), and cytotoxic drugs are generally not recommended (17). The majority of trials include only performance status.
Clinical investigators in 1989 identified the problem of selection bias for trial entry (Table 1) causing a paucity of elderly patients to enter oncology trials (18). Elderly patients with cancer may not be referred to an oncology center for treatment (19). Investigators in the Cancer and Leukemia Group B (CALGB) did a case-control analysis of breast cancer patients and pair-matched controls interviewing the patients and their physicians as to why they did or did not participate in a breast cancer clinical trial. The principal barrier to trial accrual was reluctance by the treating physician to offer the study (20,21). An analysis of the Oxford overview analysis evaluating the effect of adjuvant chemotherapy noted “[f]ew women older than 70 years of age, and very few women older than 80, were randomized into these chemotherapy trials” (22). As a result, the error bars for treatment effect in patients older than age 70 are very wide. Investigators at the U.S. Food and Drug Administration did a retrospective analysis by age of 28,766 cancer patients entered in 55 registration trials active from 1995 to 2002. Study patients were partitioned into cohorts of 65 years of age or older, 70 years of age or older, and 75 years of age or older and compared with the corresponding

Table 1. Difficulties in interpreting published literature

<table>
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<tr>
<td>Small numbers of elderly patients in a larger trial</td>
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<td>Inclusion of selected populations in trials by exclusion criteria</td>
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<td>Comorbid conditions not always reported</td>
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<td>Polypharmacies not reported</td>
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<td>Compliance with treatment not usually reported</td>
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<tr>
<td>Inadequate toxicity reporting</td>
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<td>Inadequate follow-up</td>
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<td>Publication bias</td>
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<tr>
<td>Lack of a geriatric assessment</td>
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<td>Entry criteria selection bias</td>
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<tr>
<td>Lack of a younger age control group for the given therapy</td>
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<tr>
<td>Comorbid conditions not reported</td>
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<td>Compliance not reported</td>
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<td>Polypharmacies not reported</td>
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<td>Short-term follow-up</td>
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oncology patients identified in the national SEER database. Patients older than age 70 were less likely to be in a study than the proportion of patients with neoplastic disease seen in the United States (23). A retrospective review by the National Cancer Institute (NCI) of supported clinical trials indicated that the majority of screened patients were rejected as not meeting entry criteria, and a major concern was potential excessive toxicity in participants and desire to have a homogenous patient population. The authors suggested that such restriction would make extrapolation to other patient populations problematic (24).

Clinical therapeutic trials may assume a continuum of disease manifestations, response to toxicity, and outcome. Based on this reasoning, the investigators would then include all eligible patients regardless of age. The advantage of this approach is that the outcome and toxicities of various age groups can be compared in a randomized prospective trial. This approach is favored by the Food and Drug Administration, as comparisons between cohorts can be robust. However, this approach has led to an exclusion of the majority of patients older than age 60 years, probably in part due to a bias of oncologists not to treat aging patients with cytotoxic therapy (24). In contrast, the age-specific trial has recently been in vogue, as it allows large numbers of protocol patients who are “elderly” to be evaluated in a prospective fashion, thus allowing sufficient participants to get statistically meaningful results. The drawbacks of both approaches are seen in Table 1.

Evaluation of toxicity from reported trials or the SEER database is also problematic. Underreporting of toxicity is common and occurs both in population studies such as the SEER database and in prospective trials. In retrospective studies using the SEER database linked to Medicare to identify patients older than 65 years of age, large numbers of patients can be examined, which allows sufficient numbers of patients with an “elderly” label to be evaluated. For example, a University of Texas study of the SEER database identified 35,060 patients with breast cancer older than age 65 years from 1991 to 1996 who were hospitalized for adverse reactions to chemotherapy (25). Women who received chemotherapy compared with those patients not exposed to these agents were 14 times more likely to require hospitalization; comorbidity increased the risk, and anthracycline-containing treatments more than doubled the risk (25). However, investigators from the CALGB compared the data in their cooperative group registry of patients with either breast or lung cancer with an average age of 71 (±4.5) years versus Medicare reporting and found that Medicare toxicity reporting was of very limited value, as major toxicities were not registered and procedure codes not valid (26). Investigators from the NCI came to the same conclusion and suggested
validation studies were necessary to confirm retrospective findings (27). Underreporting of toxicities also occurs in prospective trials. Investigators from the New England Medical Center retrospectively analyzed 192 randomized drug trials in noncancer patients, with a total sample size of 130,074 patients. Safety reporting of adverse events were found lacking, with only 29% of trials having adequate reporting of laboratory determined toxicities and 39% of trials having adequate reporting of clinical adverse events (28).

The Issue of Comorbid Conditions

Breast cancer patients do not develop their disease in a vacuum. As the patient ages, other medical conditions occur that can influence the quality and longevity of life. A Medline search on “comorbid conditions” and “age” led to 16,493 potential citations. Further screening this search with the parameter “breast cancer” led to 337 articles. The influence of other medical conditions on the management of the breast cancer patient has been long recognized (11,29–32) and intuitively practiced by the physician in selecting treatment (33). An early report from Detroit noted that women with breast cancer with three or more significant other medical conditions had a fourfold increase in mortality compared with patients without comorbid conditions (34). Using retrospective SEER data, Canadian researchers analyzed 784,378 cancer patients from 1984 to 1993. A total of 136,515 breast cancer patients, with a median age of 62 years at diagnosis and median follow-up of 128 months, were available for evaluation. Competing causes of death from other medical conditions were noted to surpass cancer-related death by age 70 (35). A retrospective review of 2,999 patients seen at the European Institute of Oncology (Milan) indicated that comorbid conditions could be identified in 45% of breast cancer patients aged 50–64, compared with 72% of patients aged 75 years or older (P <0.01) (36). The presence of comorbid conditions led to physician reluctance to prescribe systemic therapy for such patients (36). Similar findings have been seen in the Danish experience of retrospectively looking at patients with breast cancer and comorbidities (37). A 2008 report from NCI-Canada of the MA-17 extended hormone adjuvant therapy trial also noted that, with a median follow-up of 3.9 years, non-breast cancer deaths accounted for 60% of deaths, with the majority occurring in patients older than age 70 years (38). A visual effect of the influence on comorbidity to guide treatment can be seen with the use of the non-genomic prognostication of outcome offered by Adjuvant! (http://
www.adjuvantonline.com), which was developed with the SEER database. Patients older than age 70 are scored by using the proportional risk reduction seen in the average breast cancer patient between 50 and 69 years of age (39). A visual representation can be seen in Figure 3. For a breast cancer patient aged 75 years with an estrogen receptor-negative tumor, stage II disease, and comorbid conditions, the best adjuvant chemotherapy available changes outcome (assuming manageable toxicity) in only 3% of cases, and the patient has a threefold chance of dying of a disease other than breast cancer (see Figure 3A). Figure 3B is the identical patient without comorbid conditions who is more apt to die of her tumor and receives significant benefit from third-generation adjuvant chemotherapy.

**FIGURE 3.** (A) A 75-year-old patient with significant comorbidities.

<table>
<thead>
<tr>
<th>Age: 75</th>
<th>General health: Poor</th>
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<tbody>
<tr>
<td>Estrogen receptor status: Negative</td>
<td>Histologic grade: Undefined</td>
</tr>
<tr>
<td>Tumor size: 1.1–2.0 cm</td>
<td>Nodes involved: 1–3</td>
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<tr>
<td>Chemotherapy regimen: Third-generation regimen</td>
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**Decision: no additional therapy**
- 14 out of 100 women are alive in 10 years.
- 22 out of 100 women die because of cancer.
- 64 out of 100 women die of other causes.

**Decision: hormonal therapy**
- Fewer than 1 out of 100 women are alive because of therapy.

**Decision: chemotherapy**
- 3 out of 100 women are alive because of therapy.

**Decision: combined therapy**
- 3 out of 100 women are alive because of therapy.
chemotherapy. Investigators at the University of South Florida have used Markov analysis of the available literature to determine at what point adjuvant therapy makes a reasonable impact on mortality, defined as a 1% absolute gain in survival. For receptor-negative disease, the database for the elderly patient was so sparse that the model was unstable, and numerous assumptions were required to attain a result (40). Race may also add to competing causes of death (41). However, at least in the CALGB 8541 trial, when other risk factors were accounted for in the model, this effect was not seen (42). Quantification of the risk of the comorbid condition remains in its infancy, which might allow more
accurate analysis of the risk and/or benefit of treatment. In general, trials do not report toxicity data by comorbid conditions, which would strengthen the database.

The Issue of Dose and Schedule, Pharmacology, and Pharmacokinetics

The currently available cytotoxic anticancer drugs have a small therapeutic window between benefit and unacceptable toxicity (43–47). The majority of adjuvant studies were done in younger women and are assumed to hold true for an older cohort of estrogen receptor-positive breast tumors. This may not hold true for receptor-positive disease (48). However, if such drugs are to be used, both dose and schedule are important, with higher dosages or more intensive regimens leading to higher toxicity (49–51). Dose as a surrogate measure of pharmacologic effect in the patient depends on dose absorbed, distribution of the agent, metabolism, and excretion. The majority of therapeutic studies of breast cancer patients have not tried to quantify whether or not the study patients took their oral medication, which is one reason why the CALGB dose-intensity study employed intravenous agents (44). In noncancer patients, lack of knowledge, polypharmacies, and confusion were identified as factors leading to noncompliance (52). Adherence to medical dosing is not a trivial issue, as a recent study of the relatively well-tolerated drug tamoxifen in breast cancer patients indicated a dropout rate of 35% by 3.5 years (53). In this study, 1,453 breast cancer patients older than age 65 years were identified in the Irish Health Services Executive Primary Care Reimbursement Services database. Patients older than age 70 years are automatically entered into this database, which covers one-third of the Irish population. Patients older than age 70 years were especially apt to discontinue treatment medication (53). A decline in the quality of life on treatment, and to a much lesser extent age (hazard ratio = 1.15; P <.001), also correlates with discontinuing therapy in the Eastern Cooperative Oncology Group trials (54). A recently reported CALGB breast adjuvant trial (49907) of patients older than age 65 with performance scores of 0–2 had a subtrial study of adherence to oral medication with 161 patients. Twenty-four percent of patients were nonadherent with the dosing, but no age effect could be discerned (55). Hence, toxicity prevalence in a study may be underestimated by nonadherence, which is rarely documented.

Polypharmacies used by elderly patients are additional problems in interpreting the degree of toxicity induced by a given regimen (56). Much
of the available information about this confounding factor is found in the noncancer literature. A recent report from the Karolinska Institute noted that polypharmacies in the elderly are increasing to a mean of 4.4 agents in Swedish patients 77 years of age or older, with the increase greater in the less educated patients (57). These investigators warned that drug–drug interactions could be a major cause of toxicity. An additional study by the Swedish researchers evaluated 630,743 patients 75 years of age or older who were registered in the Swedish Prescribed Drug Registry from October to December 2005. Potential clinically relevant drug interactions were found in 26% of the cohort, with severe interactions documented in 5% (58). A Veterans Affairs Hospital study of 167 geriatric patients taking five or more drugs noted that 35% had self-reported adverse reactions (59). Overuse of psychotropics, which also may obscure the true cause of drug toxicity, was also noted in the elderly population (60). Suggested risk factors for adverse drug events in this population included age 85 years or older, depression, female gender, low body weight, use of five or more drugs, use of multiple pharmacies, dementia, and renal impairment (61). These issues are rarely accounted for in oncology clinical trials except by exclusion criteria.

Pharmacologic properties and pharmacodynamic properties change with age and have been the subject of numerous articles, with the findings of alteration in drug absorption, distribution, metabolism, and clearance all noted (62–65). Pharmacodynamic responses also change with age so that the effect of a given drug on an organ system may be vastly different in an elderly patient (61). Pharmacologic studies of anticancer drugs in the elderly have recently been reviewed, with the majority of studies not showing an age-related influence on measured parameters (66,67). The International Society of Geriatric Oncology formed a task force to look at the use of cytotoxics in the elderly patient with cancer (68). Because of a paucity of prospective data, extrapolation from younger patients to the elderly was necessary, and the conclusions were a consensus opinion. End-organ dysfunction and myelotoxicity were identified as a major risk factor and as a consequence of treatment of this patient population (68).

Estimations of end-organ reserve to withstand noxious chemotherapy and of the end-organ function to eliminate the cytotoxic agent remain painfully inexact. At the present time, surrogate markers for liver reserve and ability to metabolize a given agent do not allow accurate nomograms for dosing and are only a crude guide for withholding treatment. Renal function is usually measured by serum creatinine or calculated creatinine clearance. An International Society of Geriatric Oncology task force on renal insufficiency noted that serum creatinine is
not a sufficient measure of renal function to give reliable dosing for anti-
cancer agents cleared by the kidney (69). In addition, the task force
noted that at extremes of cachexia or obesity and at extremes of serum
creatinine values, the calculated creatinine clearance formulas were unreli-
able (69). The International Breast Cancer Study Group Trial VII selected
postmenopausal breast cancer patients with serum creatinine values of
1.5 mg/dL or less and compared the use of adjuvant CMF (cyclophosha-
mide, methotrexate, 5-fluorouracil) in the age groups younger and older
than age 65. The more elderly group had an increased risk of hemato-
logic toxicity (P <0.0002) (70). This result may reflect lessened renal
function and inability to clear the cytotoxic agent as muscle mass dimin-
ishes with age. A retrospective study of 1,405 patients aged 65 years or
more with breast cancer treated with CMF at Memorial Sloan-Kettering
Cancer Center between 1998 and 2000 identified that a calculated crea-
tinine clearance of less than 50 mL/min was associated with increased
toxicity (71). In noncancer patients, the Cockroft-Gault formula was
noted to underestimate creatinine clearance (72). This finding may be
also true of cancer patients. Using $^{51}$Cr-EDTA renal clearance as the
gold standard, 225 patients with median age 74 years (range of 70-89)
with the diagnosis of malignancy had their creatinine clearance calcu-
lated by the Cockroft-Gault, Jelliffe (used by the Gynecologic Oncology
Group), and Wright formulas. All three formulas significantly varied
from the gold standard, especially at the extremes of renal function.
The Wright formula was the most accurate in this cohort (73). Similar
findings were found in an Australian study that included younger
patients (74).

The Use of Chemotherapy in the
Elderly Population

With the previous caveats, the elderly patient with breast cancer can be
treated with manageable toxicity if the appropriate parameters are
appreciated (75). The side effects of the various agents are the same as in
the younger patient and described in summary form (66,76). Investiga-
tors at the H. Lee Moffitt Cancer Center treated 60 patients aged 70
years or older who had a variety of cancers; they conducted both base-
line geriatric assessments and quality-of-life measures, which they repeated
at the end of treatment. Only 63% completed both evaluations, with a
drop in physical function that correlated with toxicity from the chem-
otherapy. The investigators indicated that the side effects of cytotoxic
therapy were manageable in this patient population (77). An early study
of the Piedmont Oncology Group demonstrated that women 70 years of age or older meeting the criteria of normal functioning and normal end-organ function as measured by laboratory tests could be safely treated for metastatic breast cancer with cytotoxic agents without increased toxicity (78). The Hellenic Cooperative Group reported on their experiences for patients over age 65 years treated on their protocols. They retrospectively identified 250 breast cancer patients with a median age of 70 (range 65–84 years). Performance status was 0–1 in 87%, and comorbidity identified in 38% (79). In the breast cancer population, grade 3–4 neutropenia was the most common acute toxicity, with advanced age not predictive of increased toxicity. By multivariate analysis of the entire group (including patients with colon or lung cancers besides breast), excessive toxicity was associated with female sex, low serum albumin, and abnormal serum creatinine (79). An additional Hellenic Cooperative Oncology Group study of patients with metastatic breast cancer receiving non–anthracycline-based regimens also did not note an effect of age on toxicity (80). A nationwide study of 115 community oncology practices between 2002 and 2005 had 122 patients with breast cancer aged 70 years or older treated with cytotoxic chemotherapy. This report was mainly an observational study, and treatment protocol was not mandated. For the subgroup of breast cancer patients, which included both adjuvant and metastatic treatment, 4% developed febrile neutropenia in the first cycle of therapy, and 20% developed severe neutropenia in the first cycle. Across all treatment cycles, there was a total incidence of 12% febrile neutropenia. Thirty-two percent of breast cancer patients received less than the protocol-predicted dose intensity. Colony-stimulating growth factor reduced the neutropenia rate (81).

The Overview Analysis by the Oxford group demonstrated the usefulness of using cytotoxic chemotherapy in the estrogen receptor–poor population. A total of 3,965 women between 50 and 69 years of age were available for analysis, with a 10-year recurrence rate reduced from 52% to 42% with adjuvant chemotherapy. As noted previously, however, the few numbers of patients older than age 70 precluded definite conclusions for that older cohort (82). Fear of toxicity in this elderly population has been suggested as the primary reason why protocol accrual has been poor (83). The St. Gallen Consensus Conference has advocated cytotoxic treatment for the “fit” elderly patient with receptor-negative disease (84). Additional studies have been done in this age group. Memorial Sloan-Kettering Cancer Center investigators retrospectively looked at 1,405 consecutive patients aged 65 years or older who were evaluated for further therapy after primary surgery for localized
breast cancer (85). One hundred thirty-two patients with a mean age of 70 years (range of 65–79) and with a low comorbidity score by Charlson Comorbidity Index (86) were studied in a retrospective review, with the finding that the toxicity was linked to the regimen of drugs administered rather than the age of the patient (85). The French Adjuvant Study Group 08 Trial reported 6-year follow-up of operable breast cancer patients older than age 65 treated with either tamoxifen alone or epirubicin/tamoxifen. A total of 338 patients entered between 1991 and 2001 with a performance status of 0–2 and a normal cardiac ejection fraction greater than 50% were recruited. Approximately 40% of the patients were older than age 70. Disease-free survival was better with the epirubicin treatment, with mild acute events. Of note, 29% of patients stopped their tamoxifen treatment prematurely (87). A recent docetaxel/cyclophosphamide versus doxorubicin/cyclophosphamide breast adjuvant study by the U.S. Oncology Group demonstrated benefit for the docetaxel/cyclophosphamide arm over the control arm for patients older than age 50 years but did not separate the resultant toxicities by age (88). Perhaps the most interesting retrospective review was done by CALGB investigators, who analyzed four randomized breast adjuvant trials from 1975 to 1999 for the effect of age (89). Comorbidity was not an exclusion criterion. Of the total 6,487 study patients, only 542 (8%) were aged 65 years or older and only 2% over age 70. The incidence of treatment mortality increased linearly with increasing age but remained low (for ages 51–64: 0.7%; for ages 65 or older: 1.5%), leading the authors to suggest that age alone was not a contraindication to administration of effective adjuvant therapy (89). The CALGB investigators reported the initial findings of their most recent adjuvant trial (CALGB 49907) in elderly breast cancer patients at the 2008 meeting of the American Society of Clinical Oncology (90). The study patients were healthy, with a performance score of 0–2 and all older than age 65 years. Patients were randomized to “conventional therapy” with doctor’s choice of doxorubicin/cyclophosphamide or CMF versus capcitabine. The study was terminated early by the Data Safety Monitoring Committee when the combination therapy arm was determined to be statistically superior. A total of 614 patients were evaluable for toxicity. Grade 3–4 hematologic toxicity was seen in approximately 50% of the combination chemotherapy arm patients compared with 3% of the capcitabine patients. Nonhematologic toxicity at grades 3–4 occurred in approximately one-third of patients (90). Of note, these were selected elderly patients receiving standardized protocol therapy and had significant toxicities. The investigators deemed adjuvant therapy feasible with close follow-up.
Special Toxicity Issues

Toxicity evaluation must be partitioned into acute adverse events and delayed events. The acute events in the elderly entered into defined protocols mimic the younger patient, with a higher incidence of myelotoxicity in the elderly in some studies (85). Febrile neutropenia occurs in approximately 5% of breast cancer patients independent of age and can be lessened by the use of white cell growth factors (91). A European observational study of cancer patients included 444 patients with operable disease receiving chemotherapy. The mean age of the cohort was 54 years (range of 27–81). Grade 3–4 neutropenia was seen in 64% of breast cancer patients, with febrile neutropenia in 6% (92). Multivariate analysis revealed (a) performance status >1 (hazard ratio = 4.13), (b) age older than 65 years (hazard ratio = 1.73), and (c) febrile neutropenia during cycle 1 of chemotherapy (hazard ratio = 3.68) as the primary factors of dose reduction (92). The CALGB 49907 enrolled 633 fit patients for adjuvant cytotoxic treatment of breast cancer and noted 53% grade 3-4 hematologic toxicities with conventional therapy, as noted previously (90).

Acute myeloid leukemia and myelodysplasia are feared late complications of treatment with cytotoxic agents, with abnormalities of chromosome 5 and 7 being most common (93). An observational study of 64,715 female patients in the Medicare/SEER database identified 10,130 patients who had received adjuvant chemotherapy. These women had a 53% increase in the chance of developing acute myelogenous leukemia compared with patients who had not received chemotherapy. However, the absolute risk after 10 years of follow-up was only 1.8% compared with a control of 1.2%. The investigators could not find that the increased hazard was due to taxane or anthracycline exposure. A higher Charlson comorbidity score also increased the risk (94). Investigators from Columbia did a similar observational study of the Medicare/SEER database looking at women older than age 65 years with breast cancer in the time interval from 1991 to 1999. In their analysis, there was a hazard ratio of 2.14 for the association of colony-stimulating factor exposure and the development of acute myelogenous leukemia. The majority of these cases of leukemia were diagnosed within 48 months of adjuvant chemotherapy exposure (95). A case-control study from France with patients having a median age of 52 years (range of 27-86) suggested that mitoxantrone was an etiologic agent (95). The National Surgical Adjuvant Breast and Bowel Project investigators, not looking at age, noted that in their trials, more intense alkylating agent exposure or breast radiation increased the risk of secondary acute myelogenous leu-
Aging, Breast Cancer, and Toxicity

Hence, exposure to cytotoxic agents especially with growth factors might increase the risk of leukemia, but the risk remains very small. The M.D. Anderson investigators looked at the question of treatment-induced second malignancies in women with breast cancer older than age 65 in a retrospective review of 65 patients and did not note an increased risk (97). However, the sample size was small and thus may underestimate the risk.

Cardiotoxicity is a well-known cumulative side effect of anthracyclines. Congestive heart failure after exposure to anthracyclines or trastuzumab is therefore another major concern in the elderly population (98). The French Adjuvant Study Group did a retrospective review of eight trials with 3,577 patients and 7 years of median follow-up (99). Four hundred fifty of these patients were 65 years old or older. Age 65 years or older and body mass index of more than 27 kg/m² were risk factors for the development of cardiotoxicity. Both normal electrocardiogram and ejection fraction before treatment did not preclude such toxicity, but 24% of patients did not have an initial determination (99). The Southwest Oncology Group noted in Trial s8897 no increase in cardiotoxicity with doxorubicin exposure; however, the number studied was small, and the median age study was 56 years (100). Using the Medicare/SEER database for women older than age 65 years, M.D. Anderson investigators evaluated 43,338 women with breast cancer and noted an absolute increase in late cardiac toxicity (congestive heart failure) of 4.6% versus 1% for women who received anthracycline treatment compared with other agents or no adjuvant therapy. Being older (hazard ratio = 1.8), being black (hazard ratio = 1.4), having hypertension (hazard ratio = 1.5), having diabetes (hazard ratio = 1.7), and having coronary disease (hazard ratio = 1.6) were predictors of congestive heart failure (100). For the use of adjuvant trastuzumab, older age was also noted to be a risk factor (101).

Cognitive dysfunction, also known as “chemo brain,” is a particularly significant potential toxicity in the older patient, as loss of independence is a major issue even in the healthy elderly. The etiology of this process, methods to best measure its effect, and prospective studies are in their infancy (102,103). As a consequence, an International Workshop has formed a task force to prospectively study this problem. Some patients seem to develop cognitive dysfunction, possibly as a consequence of their malignancy. Tumor necrosis factor-α has been demonstrated in a rat model to damage old neurons, thus suggesting a potential paraneoplastic effect of tumor-released cytokines (104). Other cytokines may also be important (105). In a rat model, 5-fluorouracil caused delayed myelin destruction in the central nervous system (106).
Other agents may also have a central effect (107). Biologic modifiers may also affect cognition (108). Small uncontrolled studies in humans have suggested that chemotherapy has late effects, as measured by positron emission tomographic scans of the frontal cortex of the brain (109), and a longitudinal study of small numbers of patients suggested that high-dose chemotherapy had a delayed effect (110). A correlative problem, fatigue, also is a major problem in the elderly as well as in younger patients (111). In more than 90% of cancer patients, fatigue can be seen during and after therapy (112). However, a Korean study did not find a change in quality of life after adjuvant treatment, so the etiology and prevalence of this disorder need clarification (113).

**Conclusion**

The majority of information regarding the toxicity of classic chemotherapy agents in the elderly is based on retrospective reviews and databases that have elements of missing data. Prospective studies are now an area of active research as the population ages. At the present, there is a great need for better definition of organ function and organ reserve to judge whether or not a given patient is “fit” for cytotoxic chemotherapy. Age by itself is not a barrier to treatment, but frailty, comorbid conditions, polypharmacies, and organ function are critical factors in preventing toxicity. Many of the studies suggest that cytokine growth factors can at least lessen the risk of febrile neutropenia.

**References**


75. Ganz PA. Does (or should) chronologic age influence the choice of cancer treatment? Oncology (Williston Park) 1992;6:45–49.


111. Butt Z, Rosenbloom SK, Abernethy AP, et al. Fatigue is the most important symptom for advanced cancer patients who have had chemotherapy. J Natl Compr Canc Netw 2008;6:448-455.


The Role of Chemotherapy in the Management of Non–Small-Cell Lung Cancer in the Elderly

Lodovico Balducci, MD

During the last ten years, the issues related to the management of lung cancer in the elderly have become more relevant than in the past. This is the result of two factors. First, the median age of lung cancer patients has progressively increased and now is around 71 years (1), due to a progressive prolongation of life expectancy and increased incidence of lung cancer in past smokers (2). These patients develop lung cancer 10–20 years later than current smokers. Second, the development of new chemotherapeutic agents has improved the survival and the quality of life in patients with early, locally advanced, and even metastatic lung cancer (3). Ongoing studies explore the value of screening and early detection of lung cancer. If proved effective, early detection will mainly benefit aged ex-smokers and will further enhance the clinical relevance of lung cancer in the elderly (4).

Despite its importance, the management of lung cancer in the elderly has been studied only in a limited, albeit important number of trials (5,6) demonstrating the benefits of single-agent chemotherapy in individuals aged 70 and older with metastatic non-small-cell lung cancer (NSCLC), in terms of survival and quality of life. After a brief review of the clinical definition of aging, this chapter explores a number of impor-
tant open questions. Based on available data, the following questions are asked:

- Do older individuals benefit from adjuvant chemotherapy?
- Do older individuals with locally advanced NSCLC tolerate combined-modality treatment?
- Are platinum-based doublets superior to single-agent chemotherapy in older individuals with metastatic NSCLC?
- Are the effectiveness and tolerance of targeted agents affected by the age of the patient?

The chapter concludes by proposing a research agenda related to these questions.

**Definition of Age**

In this section, the physiology of aging and its consequences on cancer treatment and outcome are explored.

**Chronologic versus Physiologic Age**

Aging involves a progressive decline in the functional reserve of multiple organ systems and increased prevalence of chronic diseases (7). Together, these factors reduce life expectancy and tolerance of stress (7) and may impair the ability of the older person to live independently. Loss of independence is a landmark in the trajectory of aging. It may be considered a harbinger of more diseases and approaching death. Not surprisingly, preservation of independence, also referred to as “active life expectancy,” is a major goal of management of older individuals (8).

At this point, two concepts germane to independent living need to be highlighted. First, independence may be preserved by social interventions that prevent a disability from becoming a handicap (8). Disability refers to the impairment of a particular function; handicap refers to the inability to perform the activity related to that function. For example, a patient with paraplegia has a disability that may become a handicap only if the patient does not have access to a wheelchair, a ramp for climbing a flight of stairs, or an elevator for moving to different floors. A person with a disability is not necessarily dependent if appropriate social and environmental arrangements can be made.

The second concept is “frailty” (7). At least in the United States, the majority of geriatricians refer to frailty as a condition of enhanced sus-
ceptibility to stress. A minimal stress, such as elective hip surgery or cancer chemotherapy, may precipitate deconditioning of the frail person and trigger progressive and irreversible functional decline. Recognition of frailty before treatment is essential to prevent its complications. The diagnosis is problematic because frailty is a syndrome associated with multiple causes, a crossroad of different factors affecting the aging of a person (7). Currently, the criteria proposed by the Cardiovascular Health Studies (Table 1) are used for the diagnosis of frailty (9).

Although aging is universal, the rate of aging varies from one individual to the other. To interpret correctly the results of clinical trials, it is important to take into consideration the physiologic age of each person. For example, adjuvant chemotherapy of lung cancer is unlikely to benefit a 75-year-old with a life expectancy of less than 2 years, but it may definitely benefit an 85-year-old individual with a life expectancy of 5 years or longer. The assessment of physiologic age is currently based on a comprehensive geriatric assessment (CGA) that takes into consideration function, comorbidity, presence or absence of the so-called geriatric syndromes, nutrition, medications, living conditions, and social support. In addition to assessing a patient’s life expectancy and tolerance of treatment, a geriatric assessment unearths conditions that may complicate the administration of chemotherapy, including high risk of malnutrition, polypharmacy, and absence of a reliable home caregiver. Given its proven benefits, the National Comprehensive Cancer Network (NCCN) guidelines (10) recommend that a CGA be performed in all cancer patients aged 70 and older before the administration of cancer chemotherapy (Table 2).

Some biologic markers may be useful to estimate a person’s physiologic age. In particular, measurement of markers of inflammation in the circulation may identify patients at risk of dying and of functional decline in the following couple of years (11). This assessment was suggested by the mounting evidence that age is a chronic and progressive inflammation (12). The clinical application of these interesting findings has not been established yet.

At the end of this discussion, one may ask whether chronologic age is important at all. My answer is that chronologic age is a landmark, beyond which one finds most of the people who are physiologically old. In the Senior Adult Oncology Program of the H. Lee Moffitt Cancer Center, patients aged 70 and older are enrolled because previous studies established that the incidence of age-related changes increases steeply between age 70 and 75. Thus, the majority of physiologically old people are at least 70 years old. The converse is not true, however. Not all individuals 70 and older (perhaps not even the majority of them) are physiologically
Table 1. Evaluation of frailty according to the Cardiovascular Health Studies

1. Weight loss. Unintentional weight loss of ≥ 10 pounds in prior year, by direct measurement of weight
2. Grip strength < 20% below standard for BMI measured with Jamar Hydraulic Dynamometer (see below)
3. Walk time below a cutoff point for sex and height (see below)
4. Exhaustion, measured as two statements from the Center for Epidemiologic Studies Depression Scale (CES-D)
5. Physical activity, measured on the short version of the Minnesota Leisure Time activity (see below). Men, < 383 kcal/wk; women, < 270 kcal/wk

Grip strength by BMI

<table>
<thead>
<tr>
<th>BMI</th>
<th>Cutoff grip strength (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>≤ 24</td>
<td>≤ 29</td>
</tr>
<tr>
<td>24.1–26</td>
<td>≤ 30</td>
</tr>
<tr>
<td>26.1–28</td>
<td>≤ 30</td>
</tr>
<tr>
<td>28</td>
<td>≤ 32</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>≤ 23</td>
<td>≤ 17</td>
</tr>
<tr>
<td>23.1–26</td>
<td>≤ 17.3</td>
</tr>
<tr>
<td>26.1–29</td>
<td>≤ 18</td>
</tr>
<tr>
<td>&gt; 29</td>
<td>≤ 21</td>
</tr>
</tbody>
</table>

Walk time

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Cutoff point (second)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>≤ 173</td>
<td>≥ 7</td>
</tr>
<tr>
<td>&gt; 173</td>
<td>≥ 6</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>≤ 159</td>
<td>≥ 7</td>
</tr>
<tr>
<td>&gt; 159</td>
<td>≥ 6</td>
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</tbody>
</table>

(continued)
Exhaustion (score 2 or 3 on two questions of the CES-D)
A. I felt everything I did was an effort.
B. I could not get going.
Scores: 0 = never; 1 = 1–2 days a wk; 2 = 3–4 days a wk; 3 = most of the time.

Physical activity
Patients are asked whether they engaged in any of the following activities in the past 2 wks:

High-intensity activities
- Swimming
- Hiking
- Anaerobics
- Tennis
- Jogging
- Racquetball
- Walking for exercise for at least 1 hr at ≥4 miles/hr

Moderate- or light-intensity activity
- Gardening
- Mowing
- Raking
- Golfing
- Bowling
- Biking
- Dancing
- Calisthenics
- Exercise cycle
- Walking for exercise for at least 1 hr at a strolling pace

Patients who have not engaged in any of these activities over the past 2 wks are considered at low physical activity.

BMI = body mass index derived from height and body surface.
The Role of Chemotherapy

Age and the Treatment of Cancer

The management-related decisions of individuals aged 70 and older involve assessment of physiologic age to balance the risk and benefit of treatment. In addition, a number of pharmacologic changes are associated with chronologic age (Table 3). For this reason, the NCCN has recommended that the initial dose of chemotherapy be adjusted to the glomerular filtration rate in all individuals 65 and older, that myelopoietic growth factors be used upfront for moderately toxic chemotherapy, and that the patient hemoglobin be maintained at approximately 12 g/dL (10). In addition, less toxic agents should be used preferentially. In the management of NSCLC, these include pemetrexed, weekly taxanes, gemcitabine, and vinorelbine.

Treatment Goals

Improvement of survival and quality of life and symptom management are universal goals of medicine, including cancer treatment. In the manage-

Table 2. National Comprehensive Cancer Network guidelines for the management of older cancer patients

| All patients aged 70 and older should undergo some type of geriatric assessment. |
| The first dose of chemotherapy should be adjusted to the glomerular filtration rate. Subsequent doses may be escalated to avoid the risk of undertreatment. |
| Prophylactic filgrastim or pegfilgrastim should be used in patients aged 65 and older receiving moderately toxic chemotherapy (e.g., cyclophosphamide/doxorubicin/vincristine/prednisone [CHOP]). |
| Hemoglobin levels should be maintained at 12 g/dL during chemotherapy. |
| Drugs that should be preferentially used include capecitabine, pemetrexed, weekly taxanes, and pegylated liposomal doxorubicin. |

The Role of Chemotherapy

Do Older Individuals Benefit from Adjuvant Chemotherapy?

Adjuvant chemotherapy improves the cure rate of stage IIa-IIIa NSCLC by 5%–15% (14–18). It is legitimate to ask whether older individuals benefit from this therapy to the same extent as younger individuals, given that their life expectancy is reduced and their risk of complications increased.

Management of Non–Small-Cell Lung Cancer in the Older Patient

With this introduction on physiology of aging, the questions listed at the beginning of the chapter can now be addressed.
So far, only platinum-containing combinations of chemotherapy have been found to be effective in the Western world, and this treatment appears effective only in patients whose tumor demonstrates reduced DNA repair capacity (19). These are also the patients who would have a worse prognosis if left untreated.

Japanese investigators have demonstrated the effectiveness of an oral medication, a form of oral fluorouracil, whose catabolism is hampered by the concomitant administration of uracil (20). This medication, not available in the United States, may be particularly suitable for older individuals, given its limited toxicity.

Genomics and proteomics may direct the adjuvant treatment of lung cancer in the near future. It has been mentioned how decreased DNA repair ability, expressed by reduced concentration of DNA repair enzyme ERCC1, indicates tumors with high risk of recurrence and that are more susceptible to platinum-containing chemotherapy (19). In the near future, the tumor genomic profile might predict both the risk of recurrence and the sensitivity to chemotherapy (21).

As no elderly-specific trials have been conducted, one must rely on the age-related analysis of other trials to garner information related to older individuals.

The 1995 meta-analysis of all randomized adjuvant trials showed a benefit of platinum-based chemotherapy that was independent from age (22). The percentage of patients aged 70 and older in this study was very low, however. Furthermore, the meta-analysis involved trials performed in the 1980s, when the majority of lung cancer patients were current smokers or recent quitters. The situation today is quite different: The majority of lung cancers in the elderly affects long-term quitters, who may have a more indolent disease.

The investigators of the National Cancer Institute of Canada performed an age-related analysis of the result and concluded the following (16):

- Patients aged 65–75 received a 25% reduction in chemotherapy dose intensity.
- Patients aged 65–75 experienced the same reduction in recurrence rate and prolongation of survival of younger patients.
- The survival benefits disappeared for patients 75 and older; however, the number of patients in that age group was so small that definitive conclusions could not be drawn.

This study highlights two important points:

- Presumably, the reduction in dose intensity received by elderly individuals indicated increased risk of treatment complications. It would be desirable to establish whether a dose-intensity threshold
The Role of Chemotherapy

existed, below which chemotherapy was not effective in older patients. Such a threshold has been identified in other diseases, such as breast cancer (23). If that is the case, one should try to maintain the dose intensity by minimizing the risk of complications. In this study, myelopoietic growth factors were not routinely used in older individuals.

- Older patients are still largely excluded from clinical trials, despite the fact that they represent the majority of lung cancer patients. Seemingly, chronologic age is inadequate to assess the benefits of adjuvant chemotherapy in the older aged person. An estimate of physiologic age would be desirable so that patients with comparable life expectancy and treatment tolerance are included in the study.

Based on the information reviewed, adjuvant chemotherapy appears beneficial in individuals aged 65–74. Though a dose-intensity threshold has not been demonstrated for NSCLC, it appears prudent to use supportive care with growth factors to maintain the dose intensity in these patients, based on the experience of different diseases.

A number of questions remain open related to adjuvant chemotherapy in older patients:

1. Should there be randomized controlled trials for patients age 75 and older? Several answers to this question may be legitimate. In my view, patients 75 and older with a life expectancy of 5 years or longer and with a tumor poor in ERCC1 should receive adjuvant chemotherapy. Patients with tumors rich in ERCC1 should be included in randomized controlled studies of other agents. The enrollment in these trials should be based on physiologic rather than chronologic age and should require life expectancy of 5 years and longer and low risk of chemotherapy toxicity.

2. Could we obtain the same results with non-platinum-containing chemotherapy in older individuals? Certainly, the advent of new medications such as pemetrexed, gemcitabine, uracil-tegafur, and targeted agents allows more options. These options should be tested in clinical trials against the only form of treatment that has demonstrated to be beneficial—that is, platinum doublets. Genomics and proteomics may allow individualization of treatment in future clinical trials.

3. Clinical trials have demonstrated beyond doubt the efficacy of adjuvant chemotherapy of NSCLC in older individuals. Is this treatment also effective—that is, are the same benefits seen in clinical trials seen in patients managed in the community? The answer to this
important question may be provided only by analysis of a large number of patients. The Surveillance Epidemiology and End Results (SEER) initiative provides an appropriate venue for these studies (24,25). The SEER collects data on approximately 10% of the U.S. population with cancer. The sample studied is representative of the whole U.S. population in terms of sex, ethnic origin, income, and residence. When the SEER data are linked with Medicare records, one is able to relate the prognosis of patients 65 and older with treatment received and comorbidity. However, the SEER data are wanting in several respects, for older people. To allow meaningful evaluation of benefits and risk of treatment, they should include functional status, comorbidity grade, and level of social support.

Do Older Individuals with Locally Advanced Non–Small-Cell Lung Cancer Tolerate Combined-Modality Treatment?

The survival of patients with locally advanced NSCLC that is inoperable is improved by concomitant administration of radiation therapy and platinum-containing combination chemotherapy (26). The experience with this form of treatment in older individuals is limited and the results inconclusive.

In Japan, Atagi et al. conducted a trial of concomitant radiation therapy and daily carboplatin versus radiation therapy alone in patients older than age 70 (27). The trial was closed before conclusion due to four treatment-related deaths—one in the radiotherapy-only arm and three in the concomitant treatment arm. Only 46 patients had been enrolled at the time of closure, and at least two of the treatment-related deaths were ascribed to protocol violation that rendered the combined treatment more toxic. Furthermore, the use of single agent carboplatin in this context is unusual. Thus, one cannot draw firm conclusions from the results of this trial.

Several age-related analyses of phase II and III trials of combined chemo-radiation have been performed (Table 4). Whereas the older studies seemed to indicate a lack of benefit in patients ≥70 (28), the most recent studies showed that older individuals experience a prolongation of survival comparable to that of the younger individuals when receiving combined chemotherapy (29–31). The risk of toxicity was increased with age, however.

A number of limitations in these studies should be underlined:

- No attempt had been made to assess physiologic age.
- The percentage of older individuals enrolled in the clinical trials was small with respect to the incidence of NSCLC in this population—that is, the subjects were highly selected.
- Almost none of the patients were aged 80 and older.
Table 4. Age-related analyses of phase II and III trials of combined chemoradiation

<table>
<thead>
<tr>
<th>Author</th>
<th>Nature of the study</th>
<th>Efficacy</th>
<th>Toxicity</th>
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<tr>
<td>Movsas et al. 1999 (28)</td>
<td>Review of six phase II and III studies performed by the Radiation Therapy Oncology Group</td>
<td>Quality of life adjusted survival was improved by radiation therapy alone in patients 70 and older, and by the combination of chemoradiation in younger patients</td>
<td>Not reported</td>
</tr>
<tr>
<td>Langer et al. 2002 (29)</td>
<td>Retrospective analysis of a phase III trial comparing sequential and concomitant chemoradiation</td>
<td>Median survival was improved by concomitant chemoradiation in individuals aged $\geq 70$ (22 mos vs. 10 mos)</td>
<td>Neutropenia and esophagitis were more common in older individuals ($\geq 70$)</td>
</tr>
<tr>
<td>Rocha Lima et al. 2002 (30)</td>
<td>Comparison of sequential and concomitant radiation therapy in a phase III trial</td>
<td>2- and 5-yr survival were comparable for older and younger patients (39% and 18% vs. 36% and 13%)</td>
<td>Age associated with increased risk of neutropenia and pneumonitis</td>
</tr>
<tr>
<td>Schild et al. 2007 (31)</td>
<td>Review of two studies of the North Central Cancer Study group, one comparing concomitant chemoradiation with radiation qd or bid, the other comparing qd and bid concomitant chemoradiation</td>
<td>Concomitant treatment was associated with improved survival in patients aged $\geq 70$</td>
<td>Increased risk of neutropenia and renal toxicity with age</td>
</tr>
</tbody>
</table>
One may conclude then that age by itself is not a contraindication to combined-modality treatment, and selected patients aged 70–80 may benefit from it. One should be very careful, however, in applying these results to the whole aged population. Because this treatment is generally not curative, one should try to avoid life-threatening toxicity. It appears prudent to treat all individuals aged ≥80 with sequential chemoradiation outside of clinical trials. For individuals aged 70–80, it is reasonable to use concomitant treatment in subjects who are functionally independent and without serious comorbidity besides NSCLC.

The advent of new drugs and new radiation techniques may improve the tolerance of combined chemoradiation in older individuals. Findings of special interest include:

- The monoclonal antibody cetuximab, directed against the epidermal growth factor receptor, has improved the survival of patients with locally advanced cancer of the head and neck (32). This strategy, which is being studied in NSCLC, may be particularly advantageous for older individuals, as cetuximab appears better tolerated than cytotoxic chemotherapy.
- Intensity-modulated radiation therapy minimizes the toxicity of radiation to normal tissues and may be safer in combination with chemotherapy (33).
- Older individuals appear particularly vulnerable to mucositis, one of the main complications of combined chemoradiation (34). Ideally, these issues should be explored in randomized clinical trials in older individuals whose physiologic age has been assessed. Elderly-specific study is desirable in this area for the following reasons: (a) Chronologic age seems to be associated with increased risk of toxicity from concomitant chemoradiation; (b) a number of new treatment options may reduce the toxicity without compromising the efficacy of the treatment; (c) and elderly-specific trials in lung cancer have reduced the risk of toxicity without compromising the overall outcome (35).

Are Platinum-Based Doublets Superior to Single-Agent Chemotherapy in Older Individuals with Metastatic Non–Small-Cell Lung Cancer?

The seminal work of Gridelli et al. has demonstrated that treatment of older lung cancer patients with single-agent chemotherapy, vinorelbine or gemcitabine, leads to improved survival and quality of life of patients aged 70 and older with metastatic NSCLC (5, 6).
Later studies demonstrated that single-agent docetaxel is well tolerated and effective in individuals 70 and older with NSCLC and that single-agent docetaxel was more effective than single-agent vinorelbine in terms of response rate and progression-free survival (36–39).

A number of age-related retrospective analyses of randomized controlled trials of patients with metastatic disease showed that platinum-containing combination chemotherapy has comparable results in younger patients and those 70 and older (29,30,40). Older patients, however, experienced increased risk of chemotherapy-related myelosuppression.

No study of chemotherapy in advanced NSCLC has addressed the basic question of whether platinum-containing combination chemotherapy is superior in terms of time to progression to the sequential use of single agents. The answer to this question is particularly relevant to older individuals, as sequential use of single agent chemotherapy appears better tolerated than combination chemotherapy.

Based on available information, it is reasonable to use combination chemotherapy in patients aged 70 and older in whom a rapid response is desirable because metastases are life-threatening. In all other cases, single-agent chemotherapy in sequence is a reasonable, albeit not the only, option.

Germane to this discussion is the issue of second-line chemotherapy. Both docetaxel and pemetrexed have a response rate of approximately 15% when used second line (39). Age over 70 did not affect the effectiveness of treatment. Pemetrexed appeared preferable in the elderly, as it was associated with substantially lower myelosuppression.

Another important lesson learned from the management of metastatic NSCLC in older patients is the importance of the CGA in predicting the prognosis. Maione et al. determined that dependence in instrumental activities of daily living was an independent adverse prognostic factor for the 559 patients aged 70 and older enrolled in the MILES trial. One cannot overstate the importance of this finding, highlighting the need to complement the classic pretreatment evaluation with a CGA in older individuals (41).

What Is the Role of Targeted Therapy in the Management of Older Individuals?

Targeted therapy has assumed an increasingly important role in the management of NSCLC. Bevacizumab has increased the response rate and the survival of patients with metastatic disease treated with platinum doublets (42). The receptor-bound tyrosine kinase inhibitor erlotinib has improved survival (3). In addition, the initial experience with the epidermal growth factor receptor antibody cetuximab appears promising.
Targeted agents appear ideal for older individuals, thanks to sparing of normal tissues, but so far they do not seem to have lived up to their promises.

The addition of bevacizumab to carboplatin and paclitaxel resulted in increased risk of mortality, neutropenic infections, proteinuria, hemorrhage, and hypertension in individuals 70 and older (42). Erlotinib as a single agent was associated with increased risk and severity of skin rash in older individuals that mandated dose reduction or discontinuance of the drug (43). Even the complications of cetuximab may be more common and severe in individuals older than age 70 (44).

This is said so that caution is exercised with the use of these agents, whose efficacy appears well maintained in older individuals.

The main role of targeted agents in the management of NSCLC in the elderly includes potentiation of chemotherapy (bevacizumab and/or cetuximab in combination with platinum doublets); maintenance of chemotherapy-induced remission (erlotinib or cetuximab); and as a safer alternative to cytotoxic chemotherapy (erlotinib and cetuximab). In addition, the use of cetuximab in combination with radiation therapy in patients with locally advanced and inoperable NSCLC is being studied.

**Toward a Research Agenda**

This chapter demonstrates that some individuals aged 70–80 with NSCLC may benefit from the same forms of treatment that younger people receive, albeit with increased risk of complications. For chemotherapy, these include neutropenic infections and mucositis; for targeted therapy, these include enhancement of chemotherapy-related toxicity (bevacizumab), hypertension, hemorrhage and proteinuria (bevacizumab), severe skin rash, and fatigue (erlotinib and cetuximab). In addition, this chapter confirms the value of performing a CGA, as it may provide an estimate of life expectancy and treatment tolerance, and it may unearth medical and social conditions that hinder the administration of chemotherapy.

A number of questions still wanting an answer are outlined here:

- A general question of geriatric oncology is whether there is an age threshold beyond which the majority of individuals are physiologically old. In the case of NSCLC, one should notice that there is practically no information on the management of individuals ≥80. Thus, special caution is in order. This should include beginning chemotherapy for metastatic disease with reduced doses and consideration of single-agent chemotherapy in sequence.
Future studies of adjuvant chemotherapy should be based on the genomics and proteomics of the tumor as well as on assessment of physiologic age in patients 70 and older.

New and safer forms of combined-modality treatment of older individuals with locally advanced NSCLC should be explored.

The role of targeted treatment should be better defined. It is especially important to establish whether erlotinib or cetuximab may represent a valid alternative to cytotoxic chemotherapy. In the meantime, prevention of serious complications of this treatment in older patients is in order.

Given the diversity of the older population, one cannot automatically translate the results of clinical trials, obtained in selected patients, to the whole population. Thus, it is necessary to collect community-based data on the outcome of older patients with NSCLC. Although the SEER has done an excellent job for this purpose, more information is desirable, especially inclusion of function and comorbidity grade in all patients managed in the community.

Since the preparation of this chapter, a pooled analysis of five randomized controlled studies of adjuvant chemotherapy of lung cancer has appeared (45). This analysis could not demonstrate a definitive benefit in overall survival or disease-free survival for individuals aged 65 and older. However, the dose intensity of treatment was much lower in older than in younger patients. This pooled analysis does not contradict previous randomized controlled studies showing benefits of chemotherapy up to age 75. Rather, it reaffirms the importance of delivering an adequate dose of chemotherapy.

References


In North America, head and neck cancer (HNC) accounts for 3%–4% of all cancer diagnoses. Approximately 55,000 people in the United States will develop HNC in 2008, and almost 12,500 will die from it (1). The peak incidence of HNC is between the fifth and seventh decades of life. Figure 1 depicts the age distribution of HNC within the United States. Of note, 50% of HNC patients are older than age 60 (2). Given the high incidence of HNC in the older adult population, it is important for clinicians to understand and appreciate the unique challenges of treating this cohort of patients.

Historically, the most common risk factors for the development of HNC have been smoking and alcohol use. The combination of smoking and drinking is synergistic and results in a marked increased cancer risk (3). Data would indicate that older adults who present with HNC are less likely to have a history of smoking and drinking compared with younger adults (4). Because older adults with HNC may have a lower rate of exposure to these risk factors, the question arises as to whether the aging process itself may play a role in the development of HNC. More recently, there has been an increase in the incidence of oropharyngeal carcinomas associated with the human papilloma viruses (HPVs). These patients tend to be young and are less likely to have a history of smoking and drinking (5).
With the exception of HPV-associated oropharyngeal tumors, HNC cancers in the elderly present with similar histology and site and stage distribution when compared with younger patients, although some studies demonstrate an increase in larynx and oral cavity primaries among elderly patients (6). Data also suggest that HNC cancers in the older population are less likely to involve regional lymph nodes (7). However, these findings are not consistent across studies.
Factors Affecting Treatment Decisions and Outcome

The physiologic, psychological, and social stressors associated with HNC and its treatment are overwhelming, even for the most robust and healthy patients; thus, care must be taken when making decisions regarding aggressive and potentially morbid therapy. A number of factors must be considered, including the stage of the cancer, the patient's comorbid disease status, the patient's functional status, the availability of social support, and financial considerations. The potential risks and benefits from therapy may be dramatically altered in patients with significant biopsychosocial concerns at the time of diagnosis. Estimating the treatment benefits in patients where there are competing risks (e.g., moderate to severe underlying comorbid disease) is difficult at best (8). These issues become more complex in the elderly population (9). Understanding how these risk factors interact in the aging population is necessary to inform clinical judgment and to provide informed consent for patients and their families. A thorough pretreatment biopsychosocial assessment is critical in all HNC patients regardless of their age. However, older patients are more likely to have comorbid medical conditions and some degree of functional impairment; thus, a comprehensive assessment is of particular importance in this cohort of patients.

Functional Status

Functional decline and functional dependency are hallmarks of aging. Functional status among older adults varies tremendously and is not well reflected in chronologic age. Hamerman proposed a taxonomy of aging in which elderly patients were categorized as (a) functionally independent adults requiring minimal to no assistance in daily activities; (b) functionally independent adults with difficulty, often associated with functional decline; (c) frail older adults with failure to thrive, failure to cope, or disability; and (d) dependent elderly who may exhibit cachexia or confinement to bed most of the time or are dying (10). Frailty is an emerging concept in geriatrics that has garnered significant attention. Although there is considerable debate as to the definition of "frailty" and whether it is a separate process that is independent of aging, it is clear that the frail elderly population is growing rapidly (11). Central to the concept of frailty is increased vulnerability to stressors with increased risk for adverse outcomes (11).
HNC therapy is associated with significant morbidity. An understanding of the patient's physical and functional limitations is critical to make an appropriate treatment decision and to coordinate care. A number of tools are commonly used to assess functionality in the oncology population, including the Karnofsky performance status (PS) and the Activities of Daily Living Dependency. One of the critical acute effects of aggressive therapy is a decline in physical function with associated weakness and fatigue. Silver et al. conducted a prospective study in patients undergoing chemoradiation. Patients experience dramatic muscle mass loss (more than 6 kg) and a marked decrease in physical function post-treatment (12). Others have documented that fatigue is a common post-treatment complication in patients undergoing radiation-based treatment (13). Thus, radiation-based treatment regimens had a direct impact on physical function. Frail elderly HNC patients with impaired physical functioning at baseline may not have the functional reserve to tolerate aggressive treatment regimens.

In addition to the direct effects of treatment on functional status, the acute and late effects of therapy require aggressive supportive care. Dealing with feeding tubes, tracheostomy tubes, wound care, and oral hygiene is time-intensive and complicated and requires a degree of physical dexterity. The simple act of inserting the tip of a syringe into a feeding tube or threading a suction catheter into a tracheostomy tube may be difficult for patients whose eyesight is dwindling or whose hands are unsteady and afflicted by arthritis. Frail elderly patients who require assistance with activities of living at baseline are likely to need a marked increase in caregiver support and are likely to become totally dependent for a period of time.

Comorbidities

Increasing age is associated with increased incidence and severity of comorbid disease. Thus, assessment of comorbidities is critical to understanding the potential risks and benefits of therapy for a given patient or patient population. A number of tools have been developed to measure comorbid disease. These measurement tools have been well described in a review by Extermann (14). Two of the primary risk factors for HNC are tobacco use and alcohol consumption, which are also associated with increased risk for the development of a number of comorbid diseases, including chronic obstructive pulmonary disease, coronary artery disease, and cirrhosis. One would therefore expect a high rate of comorbidity in elderly HNC patients. The data would support this assertion.
In a sample of 330 HNC patients older than 70 years of age, Sanabria found that 75% had at least one comorbid medical condition. Piccirillo demonstrated that 21% of HNC patients had a moderate to severe level of comorbidity (15).

Comorbidity affects the overall survival of older patients with cancer. Numerous studies have demonstrated a correlation between comorbidity and overall survival in the general HNC population (16). Comorbidity has also been demonstrated to play an important role in the prognosis of older HNC patients. Reid et al. reported the results of a review of the National Cancer Institute's Surveillance, Epidemiology, and End Results database from 1985 through 1993. A total of 9,386 HNC patients older than age 65 were registered (17). A total of 1,125 patients had a Charlson Comorbidity index of 1 or greater. Comorbidity of 1 or greater was associated with a decrease in survival (hazard ratio = 1.5; 95% confidence interval 1.43–1.68). In addition, increasing comorbidity was associated with decreased survival (P <0.001). Others have demonstrated similar results.

Physiologic Factors

Aging is characterized by a progressive decline in the physiologic or functional reserve in multiple organ systems. Functional reserve may be defined as the ability to maintain function or increase function in response to increasing challenge. Physiologic changes associated with aging primarily occur at the cellular level. The rate of change is influenced by genetic and environmental factors (18). Over time, damage at the cellular level accumulates and results in the diminished functional reserve of organ systems. Decline in functional reserves may occur over a number of years without lowering functional capacity below threshold. An older person may function well under certain conditions but may be vulnerable to physiologically stressful situations (19). When functional systems reach a certain threshold of vulnerability, that is, the point at which reserves are so diminished that homeostasis cannot be maintained, organ dysfunction and systems failure may occur. The overall decrease in reserve capacity is an important consideration in cancer treatment decisions for the older adult. Diminished functional reserve of organs and body systems places the older cancer patient at increased risk for treatment-related toxicities and poor functional outcomes. A number of specific age-related physiologic changes and functional deficits may uniquely impact treatment in older patients with HNC. These issues are discussed in the following sections (Table 1).
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Age-related factors</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired swallowing</td>
<td>Decreased facial and masticatory muscle strength</td>
<td>Pretreatment swallowing evaluation</td>
</tr>
<tr>
<td></td>
<td>Impaired swallowing initiation</td>
<td>Swallowing exercises</td>
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<tr>
<td></td>
<td>Insufficient lubrication</td>
<td>Diet modification</td>
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<td></td>
<td>Reduced lingual pressure</td>
<td>Promote oral hydration</td>
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<tr>
<td></td>
<td>Delayed pharyngeal swallowing</td>
<td>Post-treatment evaluation and rehabilitation</td>
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<td>Mucositis</td>
<td>Thinning of oral mucosa</td>
<td>Ongoing assessment of oral mucosa during and after treatment</td>
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<td></td>
<td>Loss of elasticity and atrophy of mucosa</td>
<td>Aggressive oral care regimen</td>
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<td></td>
<td>Altered immune response</td>
<td>Promote oral hydration</td>
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<tr>
<td></td>
<td>Diminished cell proliferation and migration</td>
<td>Prevent and treat oral infections</td>
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<td></td>
<td></td>
<td>Adequate pain management</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Decreased glomerular filtration area and permeability</td>
<td>Eliminate or dose reduce renal toxic drugs</td>
</tr>
<tr>
<td></td>
<td>Decreased glomerular filtration rate</td>
<td>Provide adequate hydration with renal toxic agents</td>
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<tr>
<td></td>
<td>Decreased renal tubular function</td>
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<tr>
<td>Nutritional impairment</td>
<td>Baseline malnutrition Poor dentition Altered swallowing Changes in body composition</td>
<td>Baseline nutritional assessment</td>
</tr>
<tr>
<td></td>
<td>Altered taste and smell</td>
<td>Weight loss history</td>
</tr>
<tr>
<td></td>
<td>Financial/social issues</td>
<td>Monitor weight closely</td>
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<tr>
<td></td>
<td></td>
<td>Dietary evaluation by registered dietician</td>
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<td></td>
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<td>Dietary counseling</td>
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<tr>
<td></td>
<td></td>
<td>Nutritional supplements (continued)</td>
</tr>
</tbody>
</table>
Early consideration for percutaneous endoscopic gastrostomy if swallowing impaired

| Xerostomia       | Decreased salivary gland function
|                  | Comorbid diseases
|                  | Medication effects
|                  | Aggressive oral care regimen
|                  | Ongoing dental evaluation
|                  | Long-term fluoride treatment
|                  | Promote oral hydration
|                  | Salivary substitutes and oral moisturizers
|                  | Pharmacologic salivary stimulants
|                  | Minimize medications associated with xerostomia

| Dermatitis       | Thinning of epidermis
|                  | Flattening of dermal-epidermal junction
|                  | Decrease in cell turnover
|                  | Dermal vascular changes
|                  | Decreased fibroblasts, mast cells, and macrophages
|                  | Ongoing assessment and monitoring for early skin reactions
|                  | Wash with warm water and mild, nonperfumed soap
|                  | Dry with soft, clean towel
|                  | Avoid skin irritants such as perfumes
|                  | Use only approved ointments and lubricants
|                  | Wear loose-fitting cotton clothing
|                  | Avoid direct sun exposure

| Dehydration      | Decrease in total body water
|                  | Altered ability to concentrate urine
|                  | Decreased thirst
|                  | Enhanced propensity for dehydration
|                  | Prevent and aggressively treat nausea, vomiting, and diarrhea
|                  | Consider insensible fluid loss with radiation dermatitis
|                  | Promote adequate hydration
|                  | Administer intravenous fluids if needed

(continued)
### Table 1. Key age-related physiologic impairments for consideration in head and neck cancer patients (Continued from page 69)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Age-related factors</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Deterioration of myelin</td>
<td>Determine presence of neuropathy before starting treatment</td>
</tr>
<tr>
<td></td>
<td>Preexisting neuropathy</td>
<td>Identify risk factors (diabetes)</td>
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<tr>
<td></td>
<td></td>
<td>Ongoing assessment and monitoring during treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue neurotoxic drugs if indicated</td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>Diminished cerebral blood flow</td>
<td>Establish baseline neurocognitive functioning</td>
</tr>
<tr>
<td></td>
<td>Increased neuronal loss</td>
<td>Ongoing assessment and monitoring for change</td>
</tr>
<tr>
<td></td>
<td>Altered levels of neurotransmitters</td>
<td>Minimize polypharmacy, particularly anticholinergics and benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Changes in memory</td>
<td>Titrate opioids slowly; consider switching opioids</td>
</tr>
<tr>
<td></td>
<td>Slowed cognitive processing speed</td>
<td>Prevent and aggressively treat dehydration</td>
</tr>
<tr>
<td></td>
<td>Increased reaction time</td>
<td>Correct electrolyte abnormalities</td>
</tr>
<tr>
<td>Poor dentition</td>
<td>Loss of dentition, demineralization, and decay</td>
<td>Dental evaluation</td>
</tr>
<tr>
<td></td>
<td>Poorly fitting dentures</td>
<td>Aggressive oral care</td>
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<tr>
<td></td>
<td></td>
<td>Oral examination on routine basis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assess dentures and other dental prosthetics for fit</td>
</tr>
<tr>
<td>Voice alterations</td>
<td>Altered structure and function of laryngeal cartilages,</td>
<td>Referral to speech-language pathologist</td>
</tr>
<tr>
<td></td>
<td>joints, and vocal folds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Altered fine neuromuscular control of larynx</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Swallowing Function

One of the critical acute and late effects of HNC treatment is dysphagia (20). Surgical excision of the tumor may result in loss of structures critical for deglutition. Radiation-based therapy causes inflammation of the mucosa and soft tissues of the oral cavity and pharynx. After radiation therapy is completed, damaged tissues may develop scarring and fibrosis. Scar tissue formation, coupled with chronic lymphedema, may result in permanent swallowing dysfunction. The sequelae of dysphagia include (a) decreased oral intake and decreased caloric intake with resulting weight loss, (b) dietary adaptations resulting in nutrient deficiencies, and (c) chronic aspiration that may result in aspiration pneumonia or pneumonitis.

Patients with pretreatment swallowing dysfunction are at greater risk for nutritional impairment and other related complications before, during, and after treatment. Aging is associated with alterations in swallowing function. Older patients with HNC are likely to have preexisting swallowing deficits due to neural, muscular, and structural changes associated with aging. Common age-related swallowing changes include decreased facial muscle and masticatory strength, impaired swallowing initiation, diminished lingual pressure, altered bolus control, and delayed pharyngeal swallowing due to changes in pharyngeal peristalsis (21).

All elderly HNC patients should be referred for evaluation by a speech-language pathologist. The speech-language pathologist will conduct a clinical evaluation of swallowing, which will include the following: (a) assessment of the adequacy of swallow function, (b) recommendations for further testing, (c) development of a treatment plan including patient education and swallow therapy, (d) consultation with a nutritionist to

Table 1. Key age-related physiologic impairments for consideration in head and neck cancer patients (Continued)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Age-related factors</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerodynamic changes resulting in loss of breath support for phonation</td>
<td>Referral to audiologist for evaluation Hearing aids Evaluate and treat middle ear effusions</td>
<td></td>
</tr>
</tbody>
</table>
ensure adequate and safe diet, and (e) evaluation to rule out significant aspiration. Patients with significant baseline dysfunction or those with considerable weight loss at diagnosis may require feeding tube placement before treatment.

**Mucosal Changes**

Some degree of mucositis occurs in all patients receiving standard-dose radiation for head and neck malignancies. For patients receiving concurrent chemoradiation, 60%–90% develop grade 3–4 mucositis (22). The sequela of mucositis are significant and include pain, dysphagia, altered voice, airway compromise, increased rates of infection, and increased health care costs (23). Elderly patients have alterations in mucosal protective mechanisms that may contribute to increased and more prolonged mucositis. That being said, to date, there are no compelling data to indicate that elderly patients experience more intense or prolonged mucositis when compared with younger patients. There are, however, significant methodologic concerns regarding the assessment, documenting, and reporting of toxicities in large randomized trials (24). Clinical experience would support the contention that elderly patients have less reserve and are more likely to experience adverse events related to the complications of mucositis.

**Nutrition**

Malnutrition is common in the elderly. This may be due to a number of issues, including poor diet quality, poor dentition, impaired swallowing, homebound status, and financial limitations. A number of age-related physiologic changes negatively affect nutritional status (25). Malnutrition may be present in patients with a normal or increased body weight. HNC patients are frequently from lower socioeconomic status; thus, cost issues may be exacerbated. Baseline assessment of diet quality and nutritional status is important in all older adults regardless of weight or swallow function.

Weight loss during and immediately after treatment is also common in HNC patients (26). One of the major factors contributing to weight loss is decreased caloric intake due to tumor- or treatment-related symptoms, including dysphagia, odynophagia, poor dentition, xerostomia, thickened secretions, mucosal sensitivity, and altered sensation. Socioeconomic factors, such as financial issues, lack of caregiver support, and substance abuse, may also play an important role. In addition to decreased caloric intake, HNC patients experience metabolic alterations secondary to their tumor or its treatment.
Because malnutrition is often a preexisting problem in the elderly population, particular care must be taken to ensure that these patients are seen by a certified dietitian, who can conduct a thorough nutritional assessment at baseline and periodically during treatment and follow-up. Integral to the nutritional assessment is a determination as to whether the patient is able to function sufficiently to carry out the recommended diet plan. This becomes particularly important in patients who require a feeding tube. Management of a feeding tube is complicated and requires a considerable degree of dexterity. Elderly patients may require significant caregiver support. Those patients who do not have adequate caregiver support may need to be transferred to an assisted-living accommodation or a nursing facility. Although this may be a sensitive issue for patients and their families, it is important to set realistic expectations at the outset of treatment so that appropriate supportive measures can be ensured.

Decreased Thirst
Radiation therapy results in breakdown of the mucosal and dermal barrier. This results in increased insensible loss of fluids in a similar manner to patients with burns. When this coincides with decreased oral intake due to dysphagia and odynophagia, patients are at risk for dehydration. Older adults may experience a decreased perception of thirst when dehydrated (27). Thus, elderly patients undergoing chemoradiation must be educated regarding the need to maintain fluid intake and should be monitored carefully for evidence of dehydration.

Voice
Voice, speech, and hearing are necessary for effective and satisfying communication. Problems in any of these functions negatively affect quality of life (QOL), psychological well-being, and social function. Changes in these functions commonly occur with aging and can be further impaired by treatment in older patients with HNC. Age-related changes in the structure and function of the larynx can alter voice. Common changes include vocal fold atrophy and bowing with prominence of vocal processes, vocal fold edema, and connective tissue loss and muscle atrophy with resulting vocal fold approximation deficits. Age-related changes in pulmonary function also result in decreased breath support for phonation (28,29).

In addition to age-related changes, tumor and treatment may affect vocal functions including speech, resonance, and voice (30). Treatment of HNC may require resection of structures needed for normal speech, resonance, and voice. In general, the more extensive the surgical resection, the more significantly the vocal function is compromised. Surgery
may also result in damage to nerves that innervate structures involved in vocalization. Acutely, radiation therapy may result in alterations of voice due to pain and edema from mucositis and thickened mucus. In the post-treatment period, xerostomia, scarring, fibrosis, and chronic lymphedema may contribute to decreased vocal function.

Hearing Loss
HNC patients may experience hearing loss after treatment with radiation and/or chemotherapy. Because sensorineural hearing loss is common in older adults, older HNC patients may be at greater risk for hearing loss after treatment. Ho et al. found that older HNC patients (older than 50 years of age) and those with baseline hearing deficits were more likely to exhibit measurable sensorineural hearing loss after treatment (31). In another study, age, radiation dose to the cochlea, and concurrent chemotherapy were predictive for post-treatment sensorineural hearing loss (32). HNC patients with sensorineural hearing loss should be referred to an audiologist for audiometric testing and hearing aid evaluation. Middle ear effusions commonly cause nonsensorineural hearing impairment after treatment for HNC. Thus, the workup for hearing loss after treatment should include an evaluation for and appropriate treatment of middle ear effusions.

Xerostomia
Xerostomia due to radiation therapy results in significant symptom burden, including oral discomfort, difficulty with speaking, difficulty forming a food bolus, and increased oral infections (33). Most important, xerostomia results in dental problems, including demineralization, decay, and dental loss. Radiation-induced xerostomia may be amplified by baseline alterations in salivary function commonly found in older adults. Age-related changes in structure and function of salivary glands include decreased protein synthesis, decreased amylase secretion, decreased salivary flow rates, and insufficient lubrication. Xerostomia in older adults also may be related to prescription and nonprescription medications and comorbid medical conditions such as Sjögren's syndrome and other rheumatologic disorders, diabetes, liver disease, and dehydration (34,35).

Dental Issues
In the past, elderly patients expected loss of dentition as a natural part of aging. Diseased teeth were extracted, and many old elderly (older than age 85 years) were edentulous. More recent generations of elderly have practiced good oral hygiene throughout their lives and expect to retain their teeth. There has been a general decline in tooth loss associated with
aging. Within the United States, the rate of edentulism has dropped from 20.3% in 1972 to 13.9% in 2001 (36). Nonetheless, there are tremendous challenges to oral care in the elderly. Barriers to oral health in the elderly include lack of education, cost of dental care, transportation, and access to dental health care professionals. Furthermore, patients may have physical impairments that limit their ability to perform oral hygiene measures. This is particularly problematic in nursing home patients who rely on busy staff to aid in oral care.

Oral care in the HNC population is a critical issue. Radiation therapy-induced xerostomia results in numerous oral complications, the most critical of which is dental decay with secondary dental loss. Furthermore, radiation therapy results in an arterial endarteritis in the maxilla and mandible. Thus, post-radiation extraction of decaying teeth may predispose to the development of osteoradionecrosis. Aggressive dental hygiene, fluoride prophylaxis, and routine care with a skilled dentist can minimize acute and late oral care issues. Providing the needed level of oral care for elderly patients can be a challenge. Before initiation of radiation therapy, patients should undergo a thorough dental evaluation. Teeth that are decayed and cannot be salvaged should be extracted 10–14 days before the initiation of radiation therapy. Radiographs should be obtained to rule out preexisting dental infections. Patients and caregivers should be educated about the importance of aggressive oral hygiene and provided with an oral care regimen. The oral care regimen should include routine follow-up with a dentist or dental hygienist.

Skin Frailty
Age-related clinical changes in skin include atrophy, drying, roughness, altered pigmentation, sagging, and wrinkling. Other age-related factors that affect wound healing include decreased levels of growth factors, diminished cell proliferation and migration, and diminished extracellular matrix secretion (37). One of the common complications of radiation therapy is dermatitis. Dermatitis may range from mild erythema to severe, confluent moist desquamation. Aggressive chemoradiation regimens are more likely to result in severe desquamation; thus, they may not be appropriate for elderly patients with frail skin. During treatment, skin must be carefully monitored for evidence of ulceration and weeping. Gentle skin care regimens should be used, and tape or bandages that tear or excoriate skin should be avoided.

Metabolic Changes
Older adults experience changes in body composition, including decreased plasma volume, less total body water, lower plasma albumin levels, and
a decreased ratio of lean body mass to the percentage of body fat (27). These changes result in altered pharmacokinetics of chemotherapeutic agents and in problems maintaining water balance—increased susceptibility to dehydration. Age-related changes in renal function include a decreased glomerular filtration rate, impaired concentrating ability, and altered excretion of water and other electrolytes. These changes in renal function may significantly affect the ability to deliver potentially renal toxic agents such as cisplatin. Treatment regimens with carboplatin may be preferable in older adults because it causes less renal toxicity. Agents that are renally excreted and those that are renally toxic may require dose reduction.

Neurologic Issues
Multiple neuroanatomic and neurophysiologic changes occur with aging. Overall brain tissue volume decreases, and the cerebral ventricles and sulci become enlarged. Changes in myelin and neuronal atrophy result in a reduction in white matter and an increase in white matter hyperintensities. Neuroimaging studies also have shown evidence of a reduction in cerebral blood flow and a reduction in glucose and oxygen metabolism, as well as changes in the level and functioning of neurotransmitters (38). These age-related changes in the central nervous system are associated with deficits in multiple cognitive processes, including working memory, attention, processing speed, and executive function (39). At one cancer center, 18% of older patients exhibited cognitive impairment based on screening with the Mini-Mental State Examination (40). Older cancer patients with baseline neurocognitive deficits may have difficulty learning new information and understanding the scope of their disease and treatment. They also may be at greater risk for delirium during treatment and for long-term neurocognitive impairment after treatment. Thus, baseline neurocognitive impairment may adversely affect treatment tolerance, compliance, follow-up, rehabilitation, and recovery.

The need to treat cognitively impaired older patients with cancer is increasingly common. Patients with mild to moderate dementia at baseline may be able to safely undergo HNC therapy with curative intent as long as strategies are identified to ensure that patients follow medication and supportive care measures. This requires the presence and active involvement of caregivers in activities of daily living. Treatment of patients with severe dementia presents significant medical and ethical issues. Because toxicity associated with HNC treatment is often severe and protracted in nature, curative treatment regimens may not be feasible or advisable for patients with severe dementia. A thorough discus-
sion of the risks and benefits of therapy with the caregiver is needed before such treatment is undertaken.

Platinum compounds and taxanes, commonly used agents in HNC treatment, are known to cause sensory or sensorimotor neuropathies. Age-related changes in the peripheral nervous system, including a decrease in peripheral nerve myelin and comorbid disease, may place older patients at increased risk for chemotherapy-induced peripheral neuropathy. The extent of neuronal damage from chemotherapy depends not only on the drug and the total cumulative dosage given, but also on preexisting nerve damage caused by diabetic neuropathy, alcohol neuropathy, or inherited neuropathy (41).

Treatment Outcomes for Elderly with Head and Neck Cancer

As with many cancers, clinicians have historically treated elderly HNC patients less aggressively than their younger counterparts. In a study reported by Derks et al., 89% of patients aged 45–60 received standard treatment as compared with 62% of patients who were 70 years of age or older (42). Nonstandard therapy was associated with marital status, tumor stage, and comorbidity. Similarly, Vaccher et al. reported that 31% of patients aged 70 years or older received “nonradical” therapy versus 21% of patients younger than 70 years of age ($P = .001$) (43). Elderly HNC patients are also less likely to be treated with combined modality therapy for locally advanced disease. In a report by Sarini et al., chemotherapy was used infrequently in combination with radiation in the elderly patients and was largely reserved for palliation (6).

The arguments for using less aggressive therapy in the elderly include decreased efficacy and increased toxicity. Early retrospective trials pointed toward a decrease in survival in elderly patients. More recently, it has been recognized that “fit” elderly patients appear to tolerate treatment without undue toxicity. Sarini et al. and Vaccher et al. demonstrated a decrease in overall survival for elderly patients when compared with younger cohorts; however, the disease-specific survival was identical (6,43). The difference in survival may be attributed to increased rates of death due to intercurrent illness. Other investigators have demonstrated clinically equivalent overall survival for elderly patients (44,45). Even though many questions remain to be answered, the preponderance of available data would suggest that fit elderly patients enjoy the benefits of curative therapy.
Clinical Trial Participation

Although there has been considerable attention paid to the inclusion of minorities and women in clinical trials for over two decades, there has been little attention paid to the recruitment of elderly patients until quite recently. The Southwest Oncology Group conducted a retrospective review of enrollment to 164 clinical trials representing 15 tumor types and 16,396 patients (46). Overall, elderly patients composed 63% of the cancer patients within the United States, but only 25% of patients enrolled in Southwest Oncology Group clinical trials were elderly. The proportion of elderly patients in clinical trials compared with the overall proportion of elderly HNC patients was 24% versus 49%. Because of the low accrual rates to clinical trials, data regarding treatment outcomes are limited.

Elderly HNC patients do not enroll in clinical trials for several reasons. First, HNC therapy is associated with significant morbidity. Clinicians and patients are fearful that aggressive therapy will be associated with undue toxicity, even in the “fit” elderly population. Second, elderly patients may lack the social supports to avail themselves of clinical trials. Most important, clinical trials usually exclude patients with a poor PS. A significant percentage of elderly patients fail to meet entry criteria for clinical trials; thus, data to aid clinicians in the management of this cohort of patients are entirely lacking. Because of the lack of participation in clinical trials, much of the literature pertaining to treatment of the elderly HNC population is composed of retrospective studies. Although these studies provide important clinical insights, there are clear methodologic limitations.

Surgery in the Elderly Head and Neck Cancer Patient

Surgical mortality rises with increasing age (47). Concern has also been expressed that elderly patients are more likely to develop surgical and medical complications. For this reason, some would argue that caution should be used in undertaking aggressive surgical procedures in elderly HNC patients. Bhattacharyya reported on 3,942 patients from the National Hospital Data Survey database who underwent head and neck procedures between 1995 and 1997 (45). Medical morbidity and mortality rates were 5.6% and 2.98%, respectively. Older patients were more likely to develop medical complications ($P < 0.001$) and had a higher risk of fatality ($P < 0.001$). The author did not report on the rates of local complications.
Others argue that a major contributing factor to the increased morbidity and mortality is the increased rates of comorbid disease in the elderly population and that fit elderly patients should not be denied potentially curative therapy. Boruk et al. conducted a chart review on 157 patients undergoing major HNC surgery of which 31 patients were 70 years of age or older (48). There was no correlation between age and complications or hospital length of stay. Clayman et al. reported on 43 HNC patients 80 years of age or older who underwent surgical resection. They were compared with a control group of patients 60 years of age and younger (N = 79). Major complications were noted in 23.2% of octogenarians versus 20.2% in the control group (P = nonsignificant) (49). Coskunfirat et al. assessed the safety and efficacy of microvascular free tissue transfer in the elderly population. One hundred two surgical procedures were conducted in 94 patients 70 years of age or older. The overall success rate was 96%, with 30% of patients experiencing at least one medical complication. In this study, neither the patient’s age nor the operative time predicted for complications (50).

In general, studies in the head and neck population would indicate that surgery in appropriately selected patients is well tolerated and does not significantly impact survival. That being said, appropriate preoperative assessment and counseling about postoperative complications is critical. Preventive measures to decrease the risk of pulmonary embolism, pneumonia, and acute renal failure should be a standard part of postoperative care.

Radiation-Based Therapy for Locally Advanced Disease

There are a number of major questions regarding the treatment of elderly HNC patients with radiation therapy (51,52). First, can elderly patients receive the full planned dose of therapy? If so, do elderly patients garner the same benefit from radiation therapy in terms of disease-specific and overall survival? Is radiation therapy associated with increased toxicity in elderly patients? What is the role of altered fractionation schemas in the elderly? Finally, what is the role of combined chemotherapy and radiation in elderly patients? Although participation in randomized clinical trials has been limited, data pertaining to these issues are beginning to answer some of these questions.

Pignon and Scalliet (53) conducted a retrospective analysis of 1,589 HNC patients in five European Organization for Research and Treatment of Cancer (EORTC) trials to determine (a) whether elderly patients undergoing radiation therapy experience increased frequency or
severity of treatment related toxicity, (b) whether elderly patients had a decrease in locoregional control, and (c) whether elderly patients had a decrease in overall survival. Patients older than age 70 years accounted for 12% of study patients. Three specific acute toxicities were reported: objective mucosal reaction, functional mucosal reaction, and weight loss. There was no significant difference in observed mucositis frequency or grade based on age. There was a significant difference in functional mucosal reaction, with elderly patients experiencing an increase in the incidence and severity of function loss due to mucositis. The incidence of grade 4 functional mucosal reaction increased from 7.7% for patients younger than age 50 to 31.3% for patients older than age 70. There was a trend toward an increase in severe weight loss in patients older than age 60. Elderly patients were more likely to have a higher PS on study entry. This difference was lost post-treatment. The occurrence of late toxicities, locoregional control, and overall survival was not significantly different in the elderly population. Results from small retrospective studies confirm these findings (54). Of note, Chin et al. reported an increase in the duration of hospitalization for patients 70 years of age and older when compared with patients younger than 70 (54).

Accelerated or altered radiation fractionation schedules have been investigated for their potential to improve locoregional control and survival. The Meta-Analysis of Radiotherapy demonstrated an improvement in overall survival for patients treated with altered fractionation schedules with a pooled hazard ratio of 0.92 (0.86–0.97, P = 0.003) (55). However, the survival benefit is lost in patients older than age 70, thus creating questions about the benefit of this strategy in the elderly population. The loss of benefit was postulated to be due to increased rates of death from intercurrent illness. Data on comorbidities and functional status were not reported, so it is not possible to account for these confounding factors. Allal et al. reported on the tolerability of accelerated radiation therapy for elderly HNC patients (56). Thirty-nine patients 70 years of age or older were compared with 81 patients younger than 70 years of age. All patients were treated with a planned total dose of 69.9 Gy to be delivered in 41 fractions over 38 days. The planned radiation therapy was completed in all patients. Three (7%) elderly patients had an unplanned treatment interruption due to toxicity or lack of compliance. No significant difference in acute or late toxicities was noted. Locoregional control and 3-year survival were similar between the two groups.

Data would fail to support a clinically significant decrease in tolerability or efficacy of radiation in the fit elderly population. However, some have argued that the "old" elderly patients are the most likely subset of patients to experience undue treatment toxicity without benefit.
To address the issue of toxicity in this select patient population, Schofield et al. conducted a retrospective analysis of 98 HNC patients who were 80 years of age or older (57). Patients were treated with primary radiation therapy; 96 patients received the planned radiation dose. One patient died during therapy, one patient refused therapy after his first dose of radiation, and six patients died within 6 months of completing therapy. Late toxicities (as defined by an event requiring surgical intervention) occurred in six patients (3.1%). Disease-specific 5-year survival was 59%, and overall 5-year survival was 28%.

The data regarding combined chemoradiation in the elderly head and neck population remain scant. In the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), data from 50 studies representing 9,471 patients were reviewed (58). Only 692 patients were older than age 70. Overall, the analysis demonstrated an improvement in overall survival for the use of concurrent chemotherapy plus radiation versus radiation alone. However, the survival benefit decreased with increasing age and was lost in patients over the age of 70. Phase I and II clinical trials in using concurrent chemoradiation in the fit elderly have demonstrated feasibility and acceptable levels of toxicity in the elderly (59,60).

Treatment: Metastatic Disease

There are no reports of clinical trials in the head and neck population that target treatment for metastatic disease in the elderly. Argiris et al. conducted a secondary analysis of two Eastern Cooperative Oncology Group (ECOG) trials that compared cisplatin doublets in patients with recurrent or metastatic HNC (E1393 and E1395) (61). Of 428 patients enrolled in these two trials, 109 (30%) were 65 years or older, and 53 (13%) were 70 years or older. The analysis compared patients who were younger than 70 versus 70 years of age or older. Elderly patients met standard entry criteria, including ECOG PS of 0 or 1 and normal organ system function. Elderly patients received the same number of treatment cycles as younger patients. Response rate was 28% for patients 70 or older compared with 33% for patients younger than 70. There was a decrease in survival for elderly patients (5.3 vs. 8 months); however, the difference was not statistically significant. This was due to an increase in treatment-related deaths early in therapy. The 1- and 2-year survival rates were similar for both groups. Elderly patients were more likely to experience severe thrombocytopenia ($P = .0003$), diarrhea ($P < .0001$), and renal insufficiency ($P = .002$).
Novel Targeted Agents

Targeted agents have been approved for use in a number of malignancies. Cetuximab is currently the only agent within this category that has been approved for use in the treatment of squamous carcinoma of the head and neck. Cetuximab has been approved for concurrent use with radiation therapy as part of primary treatment or in the metastatic setting (62). There are no data specifically describing the tolerability of cetuximab in the elderly population. That being said, in general, cetuximab toxicities are relatively modest, with a pustular rash and hypomagnesemia being the most common adverse effects. There are no studies comparing concurrent cetuximab plus radiation to chemotherapy plus radiation; thus, it is difficult to clearly delineate the relative risks and benefits of these two approaches. Currently available data would support the fact that cetuximab with radiation is associated with lesser degrees of acute toxicity than concurrent chemoradiation (62). Thus, it is reasonable to use cetuximab as a radiation sensitizer in patients who may not be able to tolerate concurrent chemoradiation (e.g., elderly, those with a poor PS, patients with a decrease in renal function, and those with baseline hearing impairment).

Quality of Life

QOL is a global construct that captures a patient's overall sense of well-being. In general, health-related quality-of-life tools assess several functional domains, including physical, functional, social, and emotional well-being. Treatment for HNC is associated with a marked decrement in QOL immediately post-treatment (63). In general, QOL returns toward baseline 12 months post-treatment. Using the EORTC Core Quality of Life Questionnaire (QLQ 30) and the Head and Neck Cancer Quality of Life Questionnaire (HN 35), Derks et al. compared the QOL at 1 year after diagnosis of 78 patients 70 years of age or older versus 105 patients who were 45-60 years of age (64). Elderly patients were more likely to be female, have oral cavity tumors, and have moderate to severe comorbidities. Elderly patients were less likely to get standard of care (65% vs. 98%; P < .001). In addition, elderly patients were less likely to receive chemoradiation therapy or surgery followed by radiation therapy. At 1 year post-treatment, there was no difference in disease-free survival or number of deaths. At baseline, 3 months, and 6 months post-treatment, elderly patients had lower scores on the physical functioning scale. The difference
was nonsignificant at 12 months. Other than physical functioning, there were no other differences in QOL between the young and elderly cohort.

**Conclusion**

Aggressive multimodality regimens are being used with increased frequency for the treatment of locally advanced HNC. These treatment regimens are associated with a marked increase in acute and late toxicities. At this point, the maximum tolerability in the healthy population has been reached. Although data would support feasibility and tolerability of aggressive curative surgery or single-modality radiation in the fit elderly population, there are little data to guide clinicians regarding more aggressive multimodality treatment regimens. Part of the problem is the low rate of accrual of elderly patients to head and neck clinical trials and the lack of studies designed to address treatment paradigms in the elderly. In the absence of adequate data, health care providers must exercise clinical judgment in treatment decision making. A number of issues should be assessed before making a treatment plan in an elderly HNC patient. First, elderly patients are more likely to experience comorbid disease, which can affect survival. Second, it is clear that elderly patients experience physiologic alterations that may predispose to adverse events. Finally, social and functional status at the outset of treatment may affect the patient's ability to comply with complex, time-consuming supportive care measures. Careful and comprehensive assessment of the elderly patient's health status must be coupled with ongoing, frequent assessments during and after treatment to identify problems in a timely manner. Using a holistic approach, appropriate treatment decisions can be rendered and adequate support provided to elderly, thus maximizing the benefit and minimizing the risk of treatment.

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**References**

Unlike patients with some other common epithelial cancers, the older prostate cancer patient referred for evaluation and management is in fact the rule not the exception, given that 70 is the average age of newly diagnosed patients in the United States. Historically, urologists applied the “10-year rule” to men when considering making a prostate cancer diagnosis and by extension to consideration of curative intent local therapy (surgery/radiation therapy). Men with relatively limited life expectancies are not typically considered candidates for radical prostatectomy; however, with the aging of our population, an increase in numbers of healthy older patients, and their increased sophistication, continues to generate an enlarging number of patients diagnosed with prostate cancer, some of whom ultimately developed advanced disease. Androgen-deprivation therapy (ADT) for metastatic disease and docetaxel-based chemotherapy for patients with castrate-progressive metastatic prostate cancer are standards of care; however, numerous questions remain regarding the “early” use of ADT and both timing and duration of chemotherapy. As there is no current evidence demonstrating a benefit of adjuvant systemic therapy for prostate cancer (with the exception of ADT when used in conjunction with external beam radiation therapy), this chapter focuses on the role of ADT and chemotherapy in the older patient with metastatic prostate cancer as primary therapy.
Androgen-Deprivation Therapy

ADT, administered by means of either surgical or medical castration, has been the standard initial management of patients with metastatic prostate cancer for more than six decades. The introduction of prostate-specific antigen (PSA) testing into clinical practice in the late 1980s was the major driver of a striking stage migration over the past two decades. One obvious consequence has been the significant decline in the number of patients who now present to physicians with evidence of unsuspected metastatic prostate cancer. Although the use of ADT (in the United States) has significantly increased over the past 15 years, the bulk of patients treated are those with nonmetastatic disease—that is, patients with PSA-only evidence of disease (1).

Although the side effects of ADT, including loss of libido and hot flashes, have been well described (Table 1), emerging data provide disturbing evidence of increasing risks of osteoporosis, fracture, incident diabetes, cardiovascular morbidity, and mortality (2,3).

Over the past 2-3 years, there appears to be a heightened awareness in the urologic oncology community to the evolving database of ADT-related morbidity. This recognition may lead to a decrease in the use of

<table>
<thead>
<tr>
<th>Symptom</th>
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<tr>
<td>Decreased libido</td>
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<tr>
<td>Erectile dysfunction</td>
<td>Common</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Common</td>
</tr>
<tr>
<td>Muscle mass loss</td>
<td>Common</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Occasional</td>
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<td>Weight gain</td>
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<td>Diabetes</td>
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<td>Cardiovascular disease</td>
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this therapy in nonmetastatic settings in which there are limited data regarding disease outcomes.

Intermittent androgen deprivation has been proposed as a potential important therapeutic modification that could potentially delay time to the development of “androgen-independence” and decrease therapy-related morbidity and expense. Although several small phase II and III trials have been reported and provide some evidence of feasibility and early evidence that this approach does not appear to negatively affect patient outcome, definitive phase III trials are ongoing (4). With respect to the impact of intermittent therapy on decreasing morbidity associated with ADT, an important consideration is not frequently considered—the time interval from therapy discontinuation to recovery of testicular androgen production. Several small studies have evaluated the time to testosterone recovery (to normal range of testosterone) after cessation of luteinizing hormone-releasing hormone (LHRH) agonist therapy. Although most studies report recovery times in the range of 4–7 months, some small experiences note that patients treated for prolonged periods (4 years) have protracted recovery periods of greater than 2 years (5–7). Advancing age has been widely believed to be associated with an increased time to testosterone recovery, and although this generalization appears grounded in physiologic principles, two prospectively conducted studies report that increasing age was not associated with delayed testosterone recovery (5,6).

Managing Hot Flashes

Hot flashes occur in 50%–80% of men receiving testosterone-suppressive therapy. Although the majority of men when questioned note that they experience hot flashes, a subset of men, perhaps as many as 25%–35%, are distressed by hot flashes to the extent that they note a significant negative impact on their quality of life.

The pathophysiology of hot flashes is incompletely understood, and although likely to be multifactorial in origin, the underlying mechanism is believed to be related to an alteration in the hypothalamic hormonal feedback mechanism. A hot flash is experienced as a sudden feeling of heat that lasts for several minutes, followed by sweating and shivering, with or without a sudden reddening of the skin on the neck, chest, and head. Hot flash triggers include changes in body position, ambient temperature changes, and ingestion of warm or cold liquids.

Various agents have been studied, typically in very small trials. A significant confounder is the recognition that studies of agents in the man-
Management of hot flashes are impacted by a relatively large and well-recognized placebo response effect. Management options can be broadly divided into hormonal and nonhormonal approaches. Estrogen administration either in the form of diethylstilbestrol or in transdermal preparations has a relatively high response rate, although dose-dependent side effects may include thromboembolic and cardiovascular adverse events. Breast and nipple swelling/tenderness is also seen in a small number of patients. Megestrol acetate, a synthetic derivative of progesterone, also appears to have modest activity, at the cost of weight gain and fluid retention. Nonhormonal interventions include dietary interventions including soy (or other products rich in phytoestrogens) and vitamin E. Data regarding the usefulness of these approaches are scarce and relatively unconvincing, although these agents are without significant side effects. Agents such as clonidine have been tested prospectively and have no demonstrated value. Newer agents such as the venlafaxine and paroxetine have demonstrated efficacy in several small experiences.

Given the relative dearth of prospective studies, the management of men with symptomatic hot flashes undergoing androgen deprivation remains far more of an art form than a science. A proposed management algorithm is as follows:

1. Soy, 25–100 mg/day × 4 weeks; re-evaluate
2. Venlafaxine, 37.5 mg/day × 2–3 weeks; re-evaluate
3. Megestrol acetate, 20–40 mg/day × 2–3 weeks; re-evaluate
4. Diethylstilbestrol, 0.25–0.5 mg/day × 2–3 weeks; re-evaluate

Decreased Libido/Erectile Dysfunction

In many older patients with prostate cancer, multiple coexisting factors typically affect both libido and erectile dysfunction. In addition to age-related issues, libido may be affected by disease-related stress and anxiety as well as by concomitant medications (e.g., antidepressants). Similarly, erectile dysfunction may be in part related to comorbid conditions including diabetes, vascular disease, and hypertension. A relatively large percentage of men who ultimately receive ADT had initial management of their prostate cancer with either radical prostatectomy and/or radiation therapy (brachytherapy and/or external beam). These local therapies have a well-characterized impact on erectile dysfunction that is typically manifested to a greater degree in older patients.

The addition of ADT to patients with already compromised libido and/or erectile dysfunction adds to the management dilemma. Although
there are limited prospective data, some data suggest that a subset of patients respond to phosphodiesterase-5 inhibitors and intracorporal injection therapy (8).

Osteoporosis

From a historical context, ADT-associated osteoporosis was not widely recognized or considered a clinically meaningful problem when patients with metastatic prostate cancer had median survivals in the 2- to 4-year range. Over the past decade, there has been randomized trial evidence of a decrease in skeletal-related events associated with use of zoledronic acid in patients with castrate-progressive metastatic disease, in a sense masking the osteoporosis issue. With prolonged use of ADT in the nonmetastatic setting, there has been renewed interest in the potential morbidity associated with ADT-related osteoporosis.

ADT decreases circulating levels of both estrogen and testosterone, which maintain bone mass through suppression of bone resorption and promotion of bone formation. There is evidence that ADT accelerates bone loss beyond that seen with aging and that a relatively high percentage of men with prostate cancer have low bone mineral density (BMD) before receiving ADT (9). Long-term ADT is associated with significant and progressive decrease in BMD, with several prospective studies demonstrating that BMD is decreased by 0.6%–4.6% yearly in patients with nonmetastatic prostate cancer receiving ADT, a rate that exceeds the age-related bone loss of 0.5%–1.0% yearly observed in healthy men. Studies suggest that the most significant loss of BMD occurs within year 1 of ADT, and most fractures occur in healthy men without osteoporosis (10).

Although there is no definitive agreement regarding assessment and management of ADT-related osteoporosis for the patient with nonmetastatic prostate cancer, the following are reasonable considerations:

Baseline Assessment and Prevention

- Consider baseline measure of BMD
- Calcium, 1,200–1,500 mg/day
- Vitamin D, 400–600 IU/day

Ongoing Assessment and Management

- For patients with normal baseline BMD measurement, repeat evaluation every 1–1½ years.
• For patients with baseline osteopenia or osteoporosis, repeat evaluation every 6–12 months.
• For patients with T scores of less than –2.5 or those who have experienced fractures, administer bisphosphonate therapy: 70 mg of alendronate orally once weekly or 4 mg of zoledronic acid intravenously once or every 3 months for up to 1 year (10).

Metabolic Effects

Over the last several years, there is emerging evidence that use of ADT increases the risk of incident diabetes and cardiovascular disease. Various studies have demonstrated that use of LHRH agonists are associated with changes consistent with the metabolic syndrome, including increased fat mass, increased fasting plasma insulin levels, decreased insulin sensitivity, and increased serum triglycerides. In addition, there is evidence that LHRH agonist use leads to increases in both high-density lipoprotein and low-density lipoprotein cholesterol that are distinct from the classic metabolic syndrome (11). In a cross-sectional analysis of men with prostate cancer undergoing at least 12 months of ADT, more than 50% demonstrated the presence of the metabolic syndrome (12). Although no specific guidelines have yet been promulgated, for men at potentially high risk secondary to comorbid conditions, the use of ADT in settings in which definitive data of benefit do not exist should be carefully considered.

Cognitive Dysfunction and Depression

Among the side effect profiles of ADT potentially unmasked by extended exposure in the nonmetastatic setting is the impact on cognitive function and depression. There is a dearth of prospective investigation in this area; however, there is some suggestion from both population studies and small randomized studies that testosterone levels in the castrate range may be associated with impaired memory, decreased reaction time, decline in visuomotor skills, and depression (13). However, given the background of an aging population with multiple comorbidities, the actual contribution of ADT may be modest (14).

In clinical practice, this issue is relatively infrequently raised as an issue by patients and family, and there are no interventions known to be of value. The potential of intermittent androgen deprivation to mitigate the impact on global function remains unknown.
Weight Gain and Muscle Mass Loss

For patients started on ADT, one of the most immediate and distressing side effects is weight gain. Evidence suggests that the average patient will gain between 2.3 and 6 kg after initiation of medical castration (15). Therapy with LHRH agonists frequently leads to both an increase in weight and percent fat body mass and decrease in percentage of both lean body mass and muscle size in men with nonmetastatic prostate cancer. The increase in fat body mass results primarily from accumulation of subcutaneous rather than intraabdominal adipose tissue (16).

Although studies of resistance exercise have failed to demonstrate objective changes in weight or body composition, it does provide improvement in muscular fitness and overall quality of life (17). Increase in appetite and subsequent weight gain tends to occur relatively rapidly after initiation of therapy in most men. From a practical standpoint, it is important to "aggressively" educate patients on this issue, attempting to define a prospective need for a regular exercise program and efforts (or renewed efforts) to restrict caloric intake to attempt to mitigate this issue.

Chemotherapy

For physicians of a certain age, there is a historical picture of a patient with hormone-refractory metastatic (now termed castrate-progressive metastatic) prostate cancer as one of an elderly gentleman with extensive bone metastases in moderate to severe pain with a declining performance status and cancer cachexia. This patient might have received "palliative"-intent chemotherapy with doxorubicin or cyclophosphamide, tolerated it poorly, and then succumbed to his disease. Partly as a consequence of a significant increase in use of ADT, the population of patients with castrate levels of testosterone and asymptomatic low-volume metastatic disease has been enriched (1,18). Today, the prototypical picture of a patient with castrate-progressive metastatic disease is an asymptomatic patient (ADT started for biochemical progression) with a rising PSA and low-volume nodal or bone metastases looking for therapeutic options.

The "modern" era of prostate cancer chemotherapy began with the seminal phase III studies that led to the U.S. Food and Drug Administration approval of mitoxantrone in combination with prednisone. These studies demonstrated the palliative impact of mitoxantrone, albeit with no evidence of a survival benefit (19,20).

Docetaxel administered intravenously every 3 weeks along with daily oral prednisone was approved for use in the management of patients with
advanced prostate cancer after the report of a three-arm randomized trial (TAX 327) demonstrating a modest, but real survival benefit for patients treated with this regimen, in contrast to weekly docetaxel or mitoxantrone and prednisone (21). A recent update of this trial confirmed the benefit of every-3-week docetaxel on survival, with more patients surviving 3 years in the docetaxel every-3-week arm (18.6%) compared with the mitoxantrone plus prednisone arm (13.5%). There is reasonable evidence that the efficacy of docetaxel is not influenced by age. In TAX 327, the median age at enrollment was 68 years, with 20% of the patients aged 75 years or older. Subgroup analyses demonstrated that the survival benefit with docetaxel administered every 3 weeks was consistent in patients younger than 65 years of age, 65 years of age or older, or 75 years of age or older (22).

There are striking little data in the medical literature that speak to toxicity/efficacy differences of docetaxel in the elderly patient. Ten Tije et al. conducted a prospective evaluation of the pharmacokinetics and toxicity of docetaxel (75 mg/m² administered every 3 weeks) in cancer patients younger/older than 65. They demonstrated that docetaxel plasma pharmacokinetics were unaltered in older patients, with a trend (not statistically significant) for increased neutropenia and febrile neutropenia (23). Beer and colleagues evaluated patient data from two pooled phase II clinical trials of weekly docetaxel (36 mg/m² for 6 of every 8 weeks) in men with castrate-progressive metastatic prostate cancer. Baseline characteristics and outcome measures of men age 70 years or older (N = 52) were compared with patients younger than 70 years of age (N = 34). Overall disease response and time to disease progression were similar, and there was also no difference in overall hematologic and nonhematologic toxicities (24).

One of the major clinical dilemmas faced by clinicians managing patients with advanced prostate cancer is determining the optimal time to initiate docetaxel-based therapy. A recent updated analysis of TAX 327 noted that although survival for patients with minimal disease burdens was better than for those with significant pain, this survival benefit was seen in all three arms of the study. However, the chances of prolonging survival with docetaxel plus prednisone administered every 3 weeks were similar among patients with lower and higher tumor burdens, and therefore, the issue of when to treat to achieve maximal benefit remains unresolved (22).

Myelosuppression

In TAX 327, the weekly docetaxel arm was included, as it was anticipated that this schedule would be better tolerated by older patients; however, in a recent analysis of the updated results of this study, the
authors note the following: "[E]xcept for reduced myelosuppression which rarely was clinically important [chapter author’s italics], weekly docetaxel was less effective than the 3-weekly schedule and more likely to reduce quality of life. This schedule should be used only in exceptional circumstances, for example, in men with compromised bone marrow reserve who are at high risk of septic neutropenia" (25).

Management Options

- For the frail or compromised patient, initiate therapy at 60 mg/m² every 3 weeks and adjust upward if well tolerated to a standard dose of 75 mg/m².
- For the patient manifesting a neutropenic fever, modify to 60 mg/m² with or without growth factor support.
- For patients with significant risk of myelosuppression—for example, previously treated for other neoplasms or known bone marrow compromise, consider mitoxantrone, 10–12 mg/m².

Fatigue/Asthenia

Development of therapy-related side effects obviously varies from patient to patient; however, there are typically “class” differences between patients who initiate therapy with or without disease-related symptoms. Therapy-related fatigue in the asymptomatic patient typically manifests by cycle 4 of therapy. Although the median number of cycles of therapy in TAX 327 was approximately 10, asymptomatic patients typically received 6–8 cycles of therapy, primarily as a consequence of progressive asthenia (21). Somewhat in contrast, the symptomatic patient, who typically has pain and other disease-related symptoms—such as, fatigue, weakness, and mild to moderate cachexia—typically manifests therapy-related fatigue later, especially those patients who manifest significant responses to therapy. In this setting, patients typically receive more therapy, and therapy-related fatigue may manifest beyond cycle 4.

There are no specific interventions, other than the consideration of a drug holiday. In the asymptomatic patient who receives six cycles of therapy, re-treatment on disease progression remains a viable option if there was evidence of a disease response (PSA and/or radiographic) and a reasonable off-therapy interval (4–6 months). More heavily treated patients may also manifest a response to therapy, assuming a reasonable drug-free interval; however, therapy-related toxicity in addition to disease burden may limit the amount of additional docetaxel that will be tolerated.
Fluid Retention

In TAX 327, approximately 20% of patients treated with docetaxel every 3 weeks manifested grade 3 and 4 peripheral edema (21). In clinical practice, fluid retention most commonly leads to complaints of dyspnea on exertion, typically by cycle 4 of therapy. Patients with mild to moderate congestive heart failure or chronic obstructive pulmonary disease may manifest symptoms earlier.

Management Options

- Have the patient weigh and record daily, starting with cycle 1.
- Consider instituting or modifying the diuretic dosage with weight gain of more than 5 lb.
- Consider a drug holiday if the patient is unresponsive to the above or manifests a decline of performance status.

Sensory Neuropathy

Thirty percent of patients treated with docetaxel every 3 weeks manifested grade 3 or 4 neuropathy in TAX 327 (21). The development of sensory neuropathy is typically more insidious than seen with paclitaxel and may be clinically evident if carefully assessed in patients without preexisting sensory deficits as early as cycle 3. For the majority of patients without preexisting neuropathy, this toxicity is rarely a cause of either dose modification or therapy discontinuation.

References


CME Post-Test

1. The________ includes assessments of functional status, comorbidity, nutritional status, cognitive and psychosocial function, and polypharmacy to assess an elderly patient's suitability for chemotherapy and decide whether interventions are needed before therapy begins.
   a) Functional Assessment of Cancer Therapy-General
   b) Comprehensive geriatric assessment scale
   c) Standard medical evaluation
   d) Rolland-Morris Disability Questionnaire

2. Which of the following statements is true?
   a) An overview of colorectal cancer trials involving 5-fluorouracil with either leucovorin or levamisole (Ergamisol) showed numerous significant interactions between age and outcomes.
   b) The most important factor when choosing chemotherapy for an elderly patient is body mass index.
   c) Resection of hepatic metastases should be considered in well selected, fit, older colorectal cancer patients evaluated at specialized centers with significant experience.
   d) It is recommended that reduced irinotecan (Camptosar) doses be used in patients over the age of 60 years, those who underwent prior pelvic irradiation, or patients with poor performance status.

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3. In a breast cancer patient 75 years of age who has an estrogen receptor–negative tumor, stage II disease, and comorbidities, the best available adjuvant chemotherapy that causes manageable toxicity will change the outcome in _____ of cases.
   a) 3%
   b) 13%
   c) 23%
   d) 33%

4. Suggested risk factors for adverse drug events in elderly patients include:
   a) Use of 3 or more drugs.
   b) Female gender.
   c) High body weight.
   d) Age $\geq$ 75 years.

5. In treating elderly cancer patients, the National Comprehensive Cancer Network guidelines recommend that:
   a) The initial chemotherapy dose be adjusted to the glomerular filtration rate in all individuals at least 65 years of age.
   b) Myelopoietic growth factors be used upfront for moderately toxic chemotherapy.
   c) Patient hemoglobin level be maintained around 12 g/dL.
   d) All of the above.

6. Several studies using chemotherapy in elderly patients with advanced non–small-cell lung cancer concluded that use of platinum-containing combination regimens results in a superior time to progression when compared with sequential use of single agents.
   a) True
   b) False

7. Data suggest that when compared with younger patients, older head and neck cancer patients:
   a) Are more likely to be infected with human papillomavirus.
   b) Are more likely to have a history of smoking and alcohol use.

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c) Are less likely to have a history of smoking and alcohol use.
d) Are more likely to have malignancies that involve regional lymph nodes.

8. Sarini reported that in elderly patients with head and neck cancer, combined use of chemotherapy with radiation was infrequent and largely reserved for palliation.
   a) True
   b) False

9. In treating men with prostate cancer, there is evidence that use of luteinizing hormone-releasing hormone agonists is associated with changes including:
   a) Decreased fat mass.
   b) Increased insulin sensitivity.
   c) Increased serum triglyceride levels.
   d) All of the above.

10. Updated analyses of the TAX 327 study of men with castrate-progressive prostate cancer given either weekly docetaxel (Taxotere) plus prednisone given every 3 weeks or weekly docetaxel or mitoxantrone plus prednisone found:
    a) Men ≥70 years of age and those <70 years of age showed no difference in overall hematologic and nonhematologic toxicities.
    b) Survival for patients with minimal disease burdens was better than for those with significant pain in all three study arms.
    c) Weekly docetaxel was less effective than the drug given on a 3-weekly schedule and was more likely to reduce quality of life.
    d) All of the above.

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