



Dear Colleague:

*I am pleased to present this monograph, summarizing current data and important concepts regarding a rapidly growing patient population—elderly people with cancer. Until recently, our practices as physicians had been hampered by the paucity of specific information on optimal treatment in this population. Fortunately, a number of well-designed studies have increased our understanding of the ways in which aging affects the risk of cancer and the prospects for treatment and cure.*

*Developments in two areas are particularly germane to the management of cancer in the elderly. First, with a greater understanding of aging as a multidimensional process, we now have practical tools to assess older patients and match them to treatment approaches from which they are most likely to benefit. Second, we have effective means of preventing or minimizing chemotherapy-induced myelosuppression—to which the elderly may be particularly susceptible—and other toxic effects.*

*In light of these advances, it is critical to recognize the growing clinical evidence suggesting that age itself is not the chief determinant of outcome, and that elderly but otherwise-healthy patients can attain the same benefits from standard cytotoxic chemotherapy as younger patients. With these principles reflected in improved strategies for managing cancer in the elderly, it is an exciting time for us as oncologists and geriatricians.*

*This monograph presents a practical clinical approach to the treatment of the older patient with cancer. It is our hope that this information will contribute to clearer clinical decision making for you and better outcomes for your patients.*

Sincerely,



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## Introduction

Elderly patients with cancer are a growing portion of the overall patient population in the United States, and they will account for a greater portion of the nation's total medical expenditures in the coming years. This increase in the numbers of elderly patients alters the demographics of cancer and highlights the need to develop more age-appropriate treatment protocols.

To maximize clinical benefits and cost-effectiveness, treatment should be targeted as specifically as possible to the patient. Unfortunately, a paucity of data on cancer in the elderly has made it difficult to define treatment strategies specific to these patients. Indeed, the elderly have been routinely and systematically excluded from or underrepresented in most cancer studies.

Recent research in this patient population, however, has begun to reveal some important principles. For example, certain precautions are appropriate in dealing with elderly patients with cancer, such as the need for a comprehensive geriatric assessment as the basis for planning treatment. On the other hand, some concerns are unfounded, such as the assumption that all or even most elderly patients are too frail to tolerate standard chemotherapy.

Many issues remain to be resolved, starting with the criteria used in defining this population. In different studies, the age-stratification boundary is 60, 65, or 70 years, with the boundary age itself sometimes included in the younger group and sometimes in the older group. Such differences in study design make it difficult to compare and combine data from different clinical trials. Another issue that limits the usefulness of many published reports is that the elderly patients in those studies are not necessarily representative of the general population of elderly patients with cancer. The inclusion and exclusion criteria of many trials tend to select for patients who are more fit and functional than average, and this bias may skew the data and limit the applicability of the conclusions based on those data.

Nonetheless, that very selection bias has brought to light what is probably the single most important principle to have emerged from research to date, which is that age itself is far less important as a predictor of clinical outcome than is the older patient's physical, mental, emotional, and functional status. It now appears that, when given the same standard therapy, otherwise-healthy older patients can gain benefits comparable to those gained by younger patients.

This monograph provides a practical review of cancer in the elderly population, with emphasis on epidemiology,

age-related physiologic and pathologic changes that affect the risk of cancer and the effectiveness and tolerability of treatment, the clinical approach to elderly patients, and strategies for minimizing neutropenia and other treatment-related toxic effects in this population.

## Cancer and the aging population

Ongoing epidemiologic research over the past several decades has consistently confirmed a continuing trend toward an aging population. The over-65 age group is growing faster than other age groups, and therefore accounts for an increasing percentage of the total population. The portion of the population older than 65 rose from approximately 8% (12 of 150 million) in 1950 to 13% (34 of 260 million) in 1990. By the year 2030, fully 20% of the population (70 of 350 million) will be older than 65 (Figure 1).<sup>1</sup>

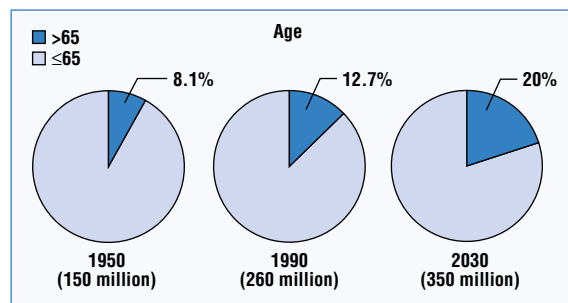


Figure 1. The US population is aging. Persons older than 65 were approximately 8% of the population (12 of 150 million) in 1950 and 13% (34 of 260 million) in 1990. This age group is expected to account for 20% of the population (70 of 350 million) in the year 2030. Adapted from Yancik.<sup>1</sup>

As the populace ages, the incidence and prevalence of cancer and many other age-related diseases will rise. The overall risk of cancer—that is, the combined incidence for all sites and types of malignancy—increases rapidly after age 60 (Figure 2). This age-related increase in cancer affects men more than

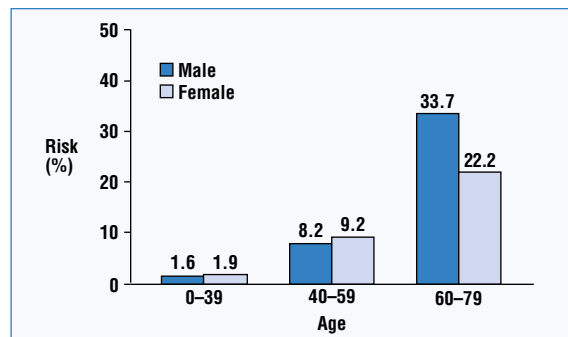


Figure 2. The risk of cancer increases with age. The combined incidence for all sites and types of cancer increases rapidly after age 60, especially in men. The overall lifetime cancer risks are 43.6% in men and 38.1% in women. Adapted from American Cancer Society.<sup>2</sup>

women. Men's lifetime incidence of prostate cancer is slightly higher than women's lifetime incidence of breast cancer (15.9% and 12.6%, respectively), and the lifetime incidence of lung cancer is also higher in men than in women (8.1% vs 5.7%). Overall, the lifetime cancer risks in men and women are 43.6% and 38.1%, respectively.<sup>2</sup>

With several of the types of cancer that are relatively common in the elderly population both the incidence and the mortality rate are higher in older patients than in younger patients (Figure 3).<sup>1</sup> The proportions of cases of breast cancer and ovarian cancer are slightly higher in women younger than 65, but the proportions of cases of non-Hodgkin's lymphoma (NHL) and cancers of the lung, prostate, and colon are all higher in persons older than 65. Similarly, the proportions of deaths due to all of these cancers are higher in patients older than 65 than in younger patients.

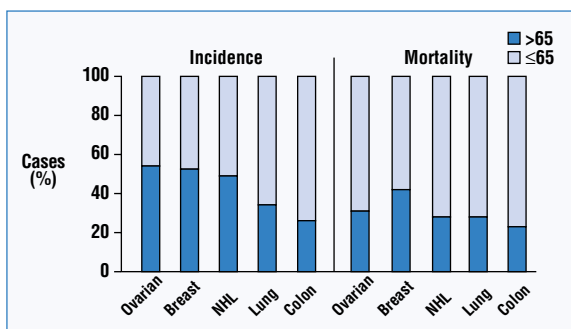


Figure 3. Cancer is a common disease and a common cause of death in the elderly. Both the incidence and the mortality rate in most of the cancers commonly seen in elderly patients are higher in patients older than 65 than in younger patients. Adapted from Yancik.<sup>1</sup>

The disproportionate impact of cancer in the older population is shown dramatically by the fact that the overall incidence of cancer in the years 1950 through 1990 rose more in patients older than 65 than in younger patients (26% vs 10%) and that overall cancer mortality in that period rose by 15% in patients older than 65 and fell by 5% in younger patients (Figure 4).<sup>3</sup> In all, approximately two thirds of cancer-related deaths occur in the over-65 population.

### Biologic changes associated with aging

Just as aging in the general population alters the demographics of cancer, aging in the individual patient alters the biology of cancer. These biologic changes affect the risk of cancer, tumor activity, and the response to treatment.

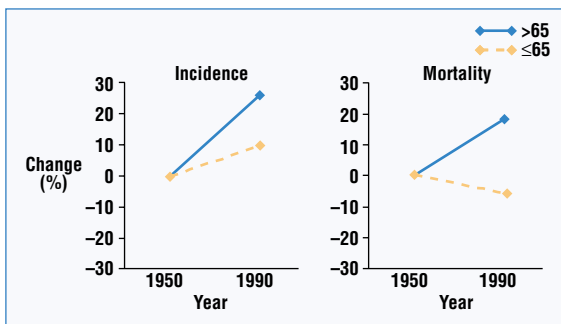


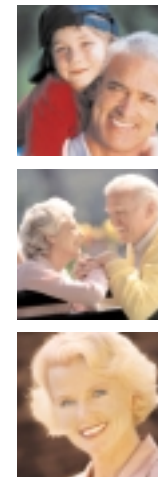
Figure 4. The changes in cancer incidence and mortality have been worse in the elderly than in younger patients. From 1950 to 1990 the incidence of cancer (all sites and types combined) increased by 26% in patients older than 65 but by only 10% in younger patients. The overall cancer mortality in that period increased by 15% in older patients and decreased by 5% in younger patients. Adapted from Lyman.<sup>3</sup>

### Changes in tumorigenesis and host defenses

The increase in the risk of cancer in the aging population may be attributed mainly to two processes. Aging is associated with slowly accruing damage to DNA and with a progressive decline in host defenses against tumor growth. Damage to DNA occurs as a result of cumulative exposure to carcinogenic chemicals, radiation, and viruses. Another source of damage is the cumulative effects of endogenous processes that lead to the formation of reactive oxygen species, which are highly damaging to cellular structures. In summary, carcinogenesis is a time-consuming process. Hence, the incidence for many types of cancer increases with age. The older the patient, the greater the potential for DNA damage to have accrued. The greater the cumulative damage to DNA, the greater the potential for malignancy.

Damage to DNA may take the form of abnormal linkages within and between nucleic acid strands, breaks in nucleic acid strands, or altered sequence of bases. General damage typically leads to cellular senescence (loss of mitotic ability) and apoptosis (programmed cell death). However, damage that involves certain specific genes may lead to cancer. The activation of oncogenes stimulates tumor growth, while the deactivation of tumor suppressor genes allows cellular growth to continue uncontrolled.

In younger persons, various mechanisms protect against DNA damage. Enzymes such as superoxide dismutase, catalase, and peroxidase deactivate reactive oxygen species; glutathione maintains a chemical environment that limits oxidative damage; and scavenger molecules such as vitamin C, vitamin E, and vitamin A remove reactive oxygen species. Other protective mechanisms are endogenous hormones that maximize



cellular repair activity, and mitochondria-mediated apoptosis of DNA-damaged cells.

Aging is associated with decreases in the production and activity of protective enzymes and hormones, in the capacity to repair or bypass damaged DNA, and in immune defenses against viruses and tumor growth. In addition, damage to mitochondrial DNA interferes with apoptosis, thus allowing DNA-damaged cells with malignant potential to persist.

#### *Changes in pharmacokinetics*

A number of specific age-related pharmacokinetic changes may result in an increase in the toxicity of chemotherapy in older patients. The volume of distribution ( $V_d$ ) shrinks because of a decrease in total body water. For drugs that bind to erythrocytes (such as anthracyclines and epipodophyllotoxins), the  $V_d$  will also be affected by anemia, which is common in older patients with chronic disease. Similarly, hypoproteinemia (in most cases secondary to inadequate synthesis or excessive renal loss) can alter the  $V_d$  for numerous drugs that have significant binding to albumin and other serum proteins.

While changes in total body water, erythrocyte mass, and serum protein levels can affect the  $V_d$  of chemotherapeutic drugs, a decrease in the glomerular filtration rate (GFR) can cause decreased clearance of drugs. The decrease in the GFR is due to a gradual loss of nephrons. A lower GFR is of particular concern in the case of drugs and drug metabolites whose clearance depends heavily on renal excretion (including such drugs as methotrexate, bleomycin, and carboplatin and the daunorubicin metabolite daunorubicinol).

A decreased GFR does not necessarily mean, however, that drug clearance decreases by a precise mathematical factor. In fact, clearance and area under the plasma concentration curve (AUC) may be highly variable with chemotherapeutic agents, and the relation between renal function and drug clearance is less straightforward than might be suspected. Because active tubular secretion of creatinine increases as the GFR falls, the accuracy of creatinine clearance as a measure of the GFR becomes progressively poorer as the true GFR becomes critically low.<sup>4,5</sup> Note that this inaccuracy occurs whether creatinine clearance is measured precisely:

$$\text{Creatinine Clearance (mL/min)} = \frac{\text{Urine Creatinine (mg/mL)} \times \text{Urine Volume (mL/d)} \times 100 \text{ mL/dL}}{\text{Serum Creatinine (mg/dL)} \times 1440 \text{ min/d}}$$

or estimated by using the Cockcroft-Gault formula<sup>6</sup>:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 0.85 \text{ in Women}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

In addition, renal excretion as a percentage of total excretion varies with each chemotherapeutic drug, and a decrease in renal excretion may be offset to some degree by an increase in hepatic excretion. On the other hand, hepatic metabolism also tends to decrease in older patients owing to reductions in hepatic blood flow and cytochrome P-450 enzyme system activity.

To summarize, age-related pharmacokinetic changes can increase the toxicity of chemotherapeutic drugs, but the effects tend to be highly variable.

#### *Changes in pharmacodynamics*

Age-related changes can also affect pharmacodynamics, often resulting in increased resistance to the anti-tumor activity of chemotherapeutic drugs.<sup>7</sup>

Older people are more likely to express the multidrug resistance (MDR) gene, which causes tumor cells to extrude natural drugs such as antibiotics and plant derivatives, and this mechanism may account for the drug resistance that is often seen in older patients with acute myeloid leukemia (AML).<sup>8</sup> In addition, chemotherapeutic drugs that depend on inducing apoptosis are less effective if a significant proportion of the tumor cells have lost this capacity.

Finally, the tumoricidal effects of chemotherapy and radiotherapy are greatest in well-oxygenated cells that are rapidly proliferating. Therefore, treatment in older patients may be less effective, because the tumors in this age group are often relatively anoxic (owing to impaired circulation) and indolent (owing to a natural-selection process, as more-aggressive tumors typically cause death at an earlier age).<sup>7</sup>

#### *Changes in cancer activity*

Aging often involves a decline in tumor aggressiveness and a corresponding decline in chemotherapy effectiveness. As stated above, tumor indolence in elderly patients may arise from a natural-selection process (as patients with more-aggressive tumors usually die at a younger age) and from compromised circulation (as poor oxygenation limits cell proliferation).

Aside from these general age-related changes, certain disease-specific changes related to aging may also affect tumor activity and the response to therapy. For example, it has been suggested that increased levels of

interleukin 6 (a lymphopoietic growth-stimulating factor) in older patients may account for the shorter durations of chemotherapy-induced remission in NHL in them than in younger patients.<sup>9</sup>

### *Tolerability and toxicity with chemotherapy*

It is widely believed that the incidence and severity of toxic effects from chemotherapy are greater in older patients than in younger patients, and clinical experience often reinforces this belief. For example, an age-related decline in hematopoiesis increases the patient's susceptibility to chemotherapy-induced myelosuppression. Older patients are also more likely to be in poorer general health, and chemotherapy-induced toxicity is more likely to occur in organ systems affected by chronic pathology. However, because aging is often associated with progressive comorbidity, disability, and loss of independence, it is difficult to gauge the effects of aging itself, considered independently of the presence of any age-related disease or dysfunction.

While the response to chemotherapy (percentage of patients with complete or partial remission) and clinical outcome (duration of disease-free and overall survival) are certainly poorer in elderly patients with chronic comorbidity than in younger and healthier patients, the evidence to date suggests that the benefits and toxic effects of chemotherapy in otherwise-healthy older patients are comparable to those in younger patients. That is, age by itself is not predictive of treatment failure and chemotherapy is not necessarily less effective or less tolerable in older patients.

The pharmacokinetic and pharmacodynamic changes associated with aging should therefore be regarded as mechanisms by which the tolerability and effectiveness of chemotherapy may become diminished in older patients. Still, it is vital to distinguish between the physiologic changes associated with aging and the pathologic changes associated with chronic disease and disability. The latter are the main determinants of the clinical outcome.

Chemotherapy-induced toxic effects may take several forms. Some degree of myelosuppression is to be expected, because chemotherapeutic drugs target proliferating cells, which include hematopoietic cells as well as tumor cells. Rapid cell turnover is also characteristic of mucous membranes, and another common form of chemotherapy-induced toxicity is mucositis (manifesting as oral ulceration). Cardiotoxic and neurotoxic effects are more likely to occur in the presence

of underlying disease, such as cardiomyopathy secondary to chronic hypertension or ischemia. In addition, chemotherapy or chemotherapy-induced anemia can cause fatigue, and severe fatigue can contribute to deterioration in functional status and loss of independence, which are linked to a poorer overall prognosis.<sup>7</sup>

### *Chemotherapy-induced myelosuppression*

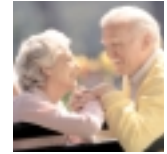
The manifestations of chemotherapy-induced myelosuppression include anemia, which causes fatigue; thrombocytopenia, which causes increased bleeding (especially in the presence of age-related vessel fragility); and neutropenia, which increases the risk of potentially fatal infections, with the degree of that risk related directly to the severity and duration of the neutropenia.

Myelosuppression is often managed with a delay and/or a dose reduction in the next scheduled cycle of chemotherapy, to allow hematopoietic activity to recover. However, such modifications to the chemotherapy regimen result in a lower relative dose intensity (the ratio of delivered dose intensity to planned dose intensity). Numerous studies, particularly in breast cancer and NHL, have established that long-term survival may be compromised if the total dose or relative dose intensity falls below a threshold value.<sup>10-14</sup>

A superior alternative to dose modification may be the prophylactic use of granulocyte colony-stimulating factor (G-CSF), which has been shown to reduce the severity and duration of chemotherapy-induced neutropenia,<sup>15,16</sup> thereby minimizing the need for dose modifications<sup>16-18</sup> and the risk of a compromised outcome due to suboptimal delivery of the chemotherapy. This strategy may be particularly beneficial in elderly patients, who generally have increased susceptibility to, and poorer recovery from, myelotoxic effects.<sup>19-21</sup>

Prolonged or severe myelotoxic effects may reflect a diminished hematopoietic reserve, which may occur with aging or age-related comorbidity.<sup>22,23</sup> This decrease in hematopoietic reserve does not typically affect the basal-state granulocyte counts. Rather, it limits the response to stress or to stimuli that would normally trigger rapid hematopoiesis.

For example, the normal neutrophil response to bacterial infection may be blunted in elderly patients, leaving them highly vulnerable to potentially life-threatening infectious complications. In a study of patients with aggressive NHL, the risk of grade 4 neutropenia (defined as an absolute neutrophil count [ANC] of less than  $500 \times 10^6/L$ ) was three times



greater in patients aged 70 or older than in patients aged 61 to 69, a highly significant difference ( $P = 0.00001$ ).<sup>24</sup> Correspondingly, elderly patients are at a higher risk of death from infection secondary to neutropenia.<sup>7</sup>

Even when the chemotherapy regimen is relatively benign and myelotoxicity is limited, elderly patients tend to be more vulnerable than younger patients. In one study, postmenopausal women with breast cancer were treated with the following regimen administered in 4-week cycles: oral cyclophosphamide 100 mg/m<sup>2</sup> on days 1 through 14 and intravenous methotrexate 40 mg/m<sup>2</sup> and 5-fluorouracil 600 mg/m<sup>2</sup> on days 1 and 8.

This triple-drug combination (CMF) is considered relatively nontoxic, especially with a 4-week dosing interval instead of the 3-week interval that is often used. Consequently, no grade 4 toxic effects were reported in any of the 299 women who completed at least one cycle of treatment. Grade 3 hematologic toxic effects, however, were twice as common in the older women as in the younger women, occurring in 9.2% of 76 women aged 65 or older and in 4.5% of 223 women younger than 65 (Figure 5). This differ-

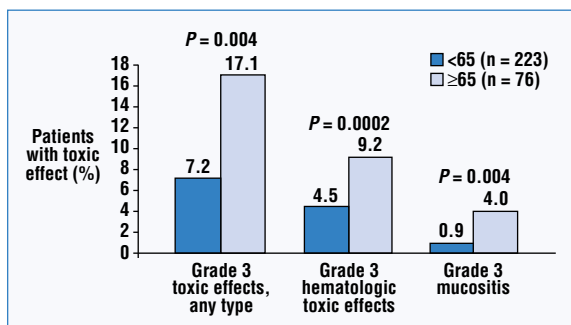


Figure 5. The incidence of toxic effects from chemotherapy increases with age. In a study in 299 postmenopausal women with breast cancer treated with CMF grade 3 neutropenia ( $ANC 500 \times 10^6/L$  to  $1000 \times 10^6/L$ ) was twice as common in women aged 65 or older as in younger women. Significant age-related differences were also seen in the rates of grade 3 mucositis and overall grade 3 toxic effects. Adapted from Crivellari et al.<sup>19</sup>

ence is highly significant ( $P = 0.0002$ ).<sup>19</sup> Because neutropenia was more frequent in the older patients, so too were chemotherapy delays and dose reductions, resulting in delivery of less than 85% of planned dose in 51.9% of the women aged 65 or older but in only 35.4% of those younger than 65 (Figure 6). Again, this age-related difference was highly significant ( $P = 0.0008$ ).

Similar conclusions were drawn in a study in 44 women with breast cancer, comprising 33 patients aged

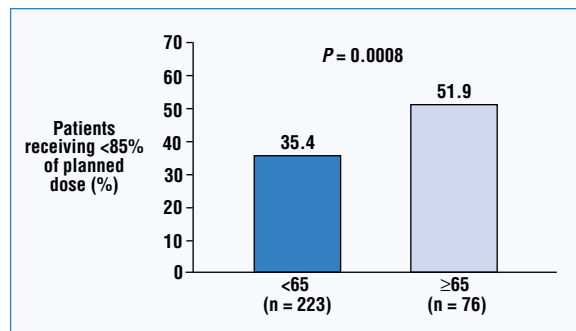


Figure 6. The likelihood of receiving the planned dose of chemotherapy decreases with age. In the same study cited in Figure 5, the proportion of the older patients receiving less than 85% of planned dose was significantly greater than that of the younger patients. Adapted from Crivellari et al.<sup>19</sup>

35 to 64 and 11 aged 65 or older. The women were treated with four cycles of intravenous doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup> at 3-week intervals (standard AC). There were no significant age-related differences in cardiac function, pharmacokinetic measures, or quality-of-life measures, but the difference in chemotherapy-induced myelosuppression between the younger and the older women was striking.<sup>20</sup>

The ANC nadir deepened progressively with increasing age (Figure 7). Over the course of the trial, the mean decline in the ANC nadir was approximately  $10 \times 10^6/L$  for each additional year of age, and this

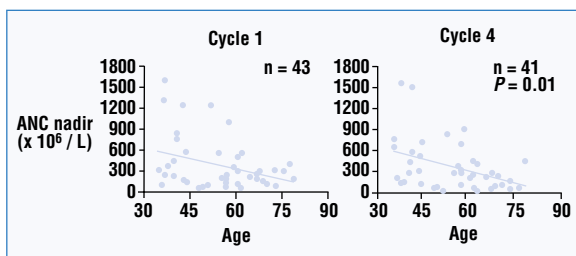


Figure 7. The chemotherapy-induced ANC nadir deepens with increasing age. In a study in 44 women with breast cancer treated with standard AC, the mean ANC nadir declined by approximately  $10 \times 10^6/L$  for each additional year of age. The inverse correlation between age and ANC nadir was significant in cycle 4 ( $P = 0.01$ ). Adapted from Dees et al.<sup>20</sup>

correlation achieved statistical significance ( $P = 0.02$ ). The inverse correlation between age and ANC nadir did not quite reach statistical significance in cycle 1 ( $P = 0.06$ ), but it was significant in cycle 4 ( $P = 0.01$ ), suggesting that repeated cycles of chemotherapy can have a cumulative effect on the myeloproliferative capacity in older patients. This interpretation is consistent with the concept of a limited hematopoietic reserve in the elderly, as was mentioned earlier.

With age considered as a categorical (<65 vs ≥65 years) rather than a continuous variable, the cumulative impact of repeated cycles of chemotherapy in the elderly was unmistakable. The mean ANC nadir remained essentially unchanged from cycle 1 to cycle 4 in the younger women, but decreased by 47% (from  $179 \times 10^6/L$  to  $94 \times 10^6/L$ ) in the older women (Figure 8). As a result, the age-related difference in the mean ANC nadir went from nonsignificant in cycle 1 to significant in cycle 4 ( $P < 0.01$ ).

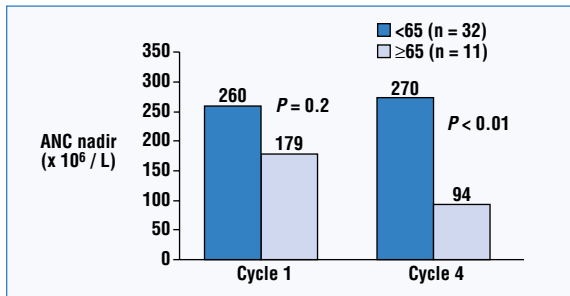


Figure 8. The hematopoietic reserve declines with age. In the same study cited in Figure 7, the mean ANC nadir remained unchanged in the younger women from cycle 1 to cycle 4 but declined by 47% in the older women, so that the age-related difference in the mean ANC nadir went from nonsignificant in cycle 1 to significant in cycle 4 ( $P < 0.01$ ). Adapted from Dees et al.<sup>20</sup>

The same study also found a clear age-related difference in the frequency of severe neutropenia. In both the first and the last cycles of chemotherapy grade 4 neutropenia ( $ANC < 500 \times 10^6/L$ ) occurred in 66% of the women younger than 65 and in all of those 65 or older (Figure 9). The difference was statistically significant ( $P = 0.02$  in both cycles). It was also

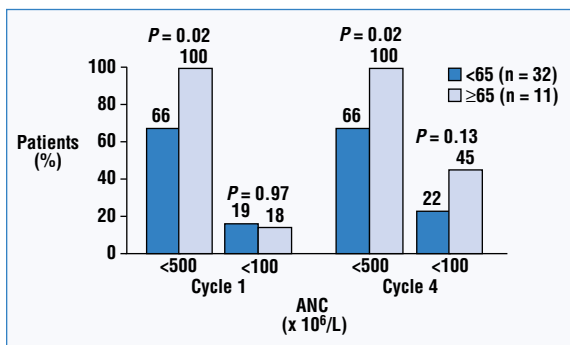


Figure 9. Severe chemotherapy-induced neutropenia is more common in elderly patients. In the same study cited in Figure 7, grade 4 neutropenia ( $ANC < 500 \times 10^6/L$ ) occurred in 66% of the women younger than 65 and in all of those 65 or older in both the first and the last cycle of chemotherapy ( $P = 0.02$  in both cycles). Extreme neutropenia ( $ANC < 100 \times 10^6/L$ ) was twice as common in the older women as in the younger women in cycle 4. Adapted from Dees et al.<sup>20</sup>

observed that extreme neutropenia ( $ANC < 100 \times 10^6/L$ ) occurred in similarly small numbers of younger and older women in cycle 1 but was twice as common in the older women as in the younger women in cycle 4. The numbers of patients were too small for this difference to reach statistical significance, but the pattern is consistent with the previously mentioned finding that the mean ANC nadir dropped sharply from cycle 1 to cycle 4 in the older women.

The likelihood and severity of neutropenia during chemotherapy varies not only with age but also with the regimen used. Data from 16,580 patients treated with any of 290 different chemotherapy regimens were compiled from 95 separate Eastern Cooperative Oncology Group trials over a 14-year period (1971–1984). In this analysis, six agents—dactinomycin, vinblastine, methotrexate, etoposide, methyl-CCNU, and doxorubicin—were associated with a clear age-related increase in the risk of serious neutropenia ( $ANC < 1000 \times 10^6/L$ ).<sup>21</sup> The patients were stratified by age into three groups: younger than 60, 60 to 69, and 70 or older. For each of the six drugs identified, the risk of grade 3 or grade 4 neutropenia in each of the two older groups was compared with the risk in the younger group and was reported as a percent increase. Among these six drugs, the most dramatic age-related differences were seen with dactinomycin, with which the risks of serious neutropenia in the patients aged 60 to 69 and 70 or older were, respectively, 94% higher and 319% higher than the risk in the patients younger than 60. The smallest age-related differences were seen with doxorubicin, with which the risks were, respectively, 12% and 42% higher in the patients aged 60 to 69 and 70 or older than in the younger patients (Table 1).

Table 1. Increase in Risk of ≥Grade 3 Hematologic Toxic Effects With Chemotherapeutic Drugs, by Patient Age

Chemotherapeutic drug	Increase in risk (%)*	
	Age 60–69	Age ≥70
Dactinomycin	94	319
Etoposide	91	155
Vinblastine	44	149
Methotrexate	25	119
Methyl-CCNU	27	52
Doxorubicin	12	42

\*Increase in risk is calculated from the risk in patients younger than 60. Data are from 16,580 patients treated with 290 different regimens in 95 Eastern Cooperative Oncology Group trials. Adapted from Begg et al.<sup>21</sup>



While the risk of serious neutropenia with each of these drugs was substantially higher in patients older than 60 than in patients younger than 60, it is difficult to draw reliable conclusions from this data analysis, for at least two reasons. First, these age-related increases in risk were based on each of the six drugs used alone, and chemotherapeutic drugs are almost always used in combination. Second, because of the wide diversity of trials surveyed, it is difficult to exclude all factors that might confound the analysis (for example, differences in dose, scheduling, and dose intensity; renal, hepatic, and cardiac function; and the effects of any previous treatment).

These studies all suggest that elderly patients have a more limited hematopoietic reserve than younger patients, and are therefore more susceptible to chemotherapy-induced myelosuppression. However, this does not imply that standard (full-dose) treatment should be withheld in older patients. On the contrary, standard chemotherapy is warranted in older patients because there is evidence that they can obtain benefits comparable to those seen in younger patients and because there are effective ways to cope with neutropenia and other treatment-related toxic effects.

### *Treatment of common cancers in the elderly*

The following section reviews published reports on the treatment of common, age-related hematologic and nonhematologic cancers in which chemotherapy plays a significant role. In general, the data indicate that the clinical outcome in each type of malignancy is predicted not by age itself but by the degree of comorbidity and functional decline that may be present. Elderly patients who are otherwise healthy can obtain the same benefits from chemotherapy as younger patients. Furthermore, older patients are as able as younger patients to tolerate chemotherapy, but their management may require more attention to supportive care.

The risk of myelosuppression clearly increases with age. Too often, the management of myelosuppression consists of below-standard planned chemotherapy dose at the outset and treatment delays and dose reductions during chemotherapy delivery. When such modifications in the regimen are used to avoid or allow recovery from chemotherapy-induced myelosuppression, dose intensity is compromised, with negative implications for treatment success. Furthermore, because myelosuppression tends to be more severe in elderly patients, their treatment modifications during chemotherapy delivery tend to be more extensive, and are therefore more likely to lower the dose intensity

to below the threshold of optimal therapeutic effectiveness. Instead of reliance on treatment modification, the prophylactic use of hematopoietic growth factors to minimize the severity and duration of chemotherapy-induced myelosuppression may be particularly beneficial in the elderly.

### *Non-Hodgkin's lymphoma*

Non-Hodgkin's lymphoma is the most common and most extensively studied of the age-related hematologic malignancies. Early evidence that older and younger patients with NHL have comparable responses to chemotherapy came about somewhat unexpectedly. In a classic study from the Southwest Oncology Group, 307 patients with advanced diffuse histiocytic lymphoma were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), with or without adjunctive bleomycin and/or immunotherapy.<sup>25</sup>

The study population included 81 older patients (aged 65 or older), in whom the protocol required an automatic 50% reduction in the chemotherapy doses. In accordance with the protocol, 58 of the 81 older patients were given half-dose therapy. However, in violation of the protocol, the other 23 older patients were given the same full-dose treatment as the 226 younger patients in the study.

In the entire study population of 307 patients, the rate of complete response showed a statistically significant age-related decline (Figure 10). The rate was 65% in patients younger than 40, 60% in patients aged 40 to 54, 55% in patients aged 55 to 64, and 37% in patients

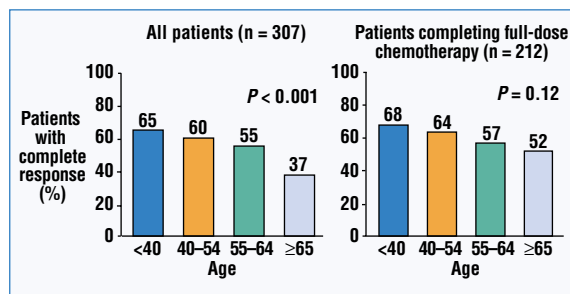


Figure 10. Standard (full-dose) CHOP produces comparable benefits in younger and older patients with diffuse histiocytic lymphoma. In a Southwest Oncology Group study, 307 patients were treated with CHOP, with or without adjunctive bleomycin and/or immunotherapy. The protocol required a 50% dose reduction in patients 65 or older, but 23 of these 81 patients were given full-dose treatment. The rate of complete response in the entire study population showed a statistically significant age-related decline. However, among the patients (regardless of age) who completed full-dose therapy, there were no significant age-related differences in the complete response rate, the duration of remission, or the frequency of treatment-related complications. Adapted from Dixon et al.<sup>25</sup>

aged 65 or older ( $P < 0.001$ ). However, analysis of the data from all patients (including older patients) who completed the full-dose therapy showed no significant age-related differences in the complete response rate, the duration of remission, or the frequency of treatment-related complications.

The clear implication is that the lower response rate and the higher rates of relapse and mortality in the older patients were most likely due not to their age but to the fact that the half-dose regimen they were given was inadequate treatment. These findings were supported by later research that showed that older patients with aggressive NHL derive benefit from treatment comparable to that derived by younger patients<sup>26</sup> and that older patients should be treated similarly to younger patients, with the intent to cure.<sup>27</sup>

Additional support for the concept that otherwise-healthy elderly patients with NHL can and should be given treatment the same as that given to younger patients came from a study in 350 patients aged 60 or older.<sup>28</sup> The treatment regimen in this trial was etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone, and bleomycin (VNCOP-B). As primary prophylaxis against chemotherapy-induced neutropenia, 71% of the patients were also given G-CSF. The overall response rate was 83%, with 58% of patients having a complete response and 25% having a partial response (Figure 11). (The effectiveness of G-CSF in minimizing the severity and duration of neutropenia will be discussed below.)

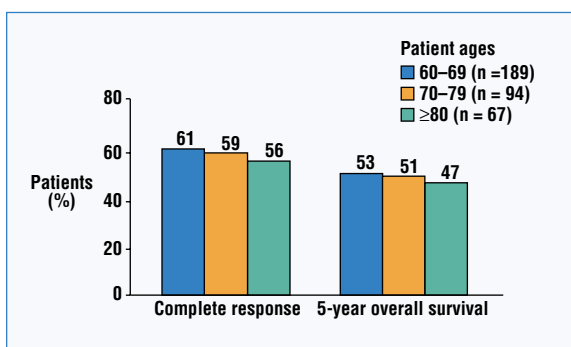


Figure 11. Full-dose chemotherapy with the use of G-CSF achieves good results in older patients with NHL. In this trial, 350 patients aged 60 or older were treated with VNCOP-B, and 71% of them were given G-CSF as primary prophylaxis against chemotherapy-induced neutropenia. The overall response rate was 83% (58% complete response and 25% partial response). There were no statistically significant age-related differences in the response rates and 5-year survival rates between the oldest patients (aged 80 or older) and the youngest (aged 60–69), indicating that age itself is not predictive of treatment effectiveness. Adapted from Zinzani et al.<sup>28</sup>

Aside from the fact that high response rates were achieved in an elderly patient population, the most significant finding in this study was that there were no significant age-related differences in the response rates and 5-year disease-free and overall survival rates when the patients were stratified into three age groups: 60 to 69 ( $n = 189$ ), 70 to 79 ( $n = 94$ ), and 80 or older ( $n = 67$ ). That is, the response to chemotherapy and the rates of overall survival were similar in the oldest patients (aged 80 or older) and in the youngest (aged 60–69). Thus, age by itself was not predictive of outcome. Two other factors did show highly significant correlations with longer survival: localized disease and good performance status ( $P = 0.001$  and  $0.0002$ , respectively).

The collective evidence from these studies in aggressive NHL consistently points to the conclusion that otherwise-healthy elderly patients can obtain the same benefits from standard chemotherapy as can younger patients.

With respect to tolerability and toxicity, treatment-related mortality is most often due to infection, and fatal infection is most often due to chemotherapy-induced neutropenia. This pattern was vividly seen in a retrospective study that reviewed data from 267 older patients (aged 60–94) with aggressive NHL who were seen consecutively over the period 1982 to 1991. The chemotherapy regimen was CHOP, and a total of 35 deaths (13% of 267 patients) were attributed to toxic effects of this treatment. Of particular interest, 83% (29 of 35) were attributed to infection and 63% (22 of 35) occurred in the first cycle of chemotherapy. Of the deaths due to infection, 66% (19 of 29) occurred in patients with severe chemotherapy-induced neutropenia (Figure 12).<sup>29</sup>

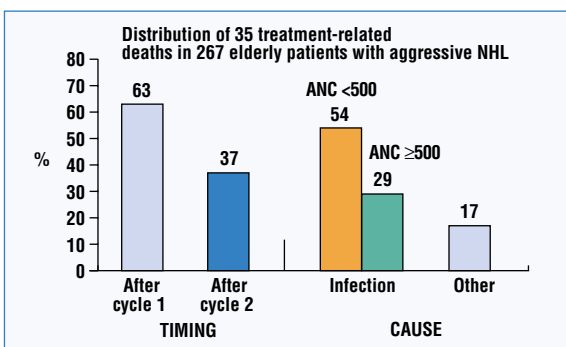


Figure 12. Most treatment-related deaths are due to infection and occur early in older patients with aggressive NHL. Treatment with CHOP was associated with 35 deaths in 267 patients aged 60 to 94. Of these deaths, 83% (29 of 35) were attributed to infection and 63% (22 of 35) occurred in the first cycle of chemotherapy. Of the deaths due to infection, 66% (19 of 29) occurred in patients with grade 4 neutropenia. Multivariate analysis showed that poor performance status—not age or dose intensity—was the only independent predictor of treatment-related mortality. Adapted from Gómez et al.<sup>29</sup>



Multivariate analysis was performed to identify risk factors that showed statistically significant correlations to treatment-related mortality. The analysis considered age itself (60–69 vs 70–79 vs ≥80), tumor size and histology, staging and extranodal involvement, performance status, B symptoms, International Prognostic Index score, relative dose intensity of doxorubicin, and serum lactate dehydrogenase level. Notably, neither age nor dose intensity was an independent predictor of treatment-related mortality, indicating that older patients could tolerate standard chemotherapy. In fact, the only variable shown to be an independent predictor of treatment-related death was poor performance status.

If the main cause of treatment-related death in elderly patients with NHL is infection secondary to chemotherapy-induced neutropenia, then reducing the incidence, severity, and duration of neutropenia should also reduce treatment-related mortality. Primary prophylaxis with G-CSF has been shown to be an effective approach in minimizing the incidence, severity, and duration of neutropenia in this population.<sup>30</sup>

Two studies have shown the usefulness of G-CSF in this role. In the Nordic Lymphoma Study Group trial, 458 patients older than 60 years with high-grade NHL were randomized to treatment with CHOP or CNOP (CNOP is the same regimen as CHOP except that mitoxantrone replaces doxorubicin), with or without adjunctive G-CSF. The value of prophylaxis with G-CSF was clearly seen. In patients who received a complete regimen the incidence of grade 4 neutropenia (ANC <500 × 10<sup>6</sup>/L) was significantly lower in those who were given G-CSF than in those who were not (62% vs 91%;  $P < 0.001$ ). Similarly, the need for hospitalization for infection was lower in the patients who were given G-CSF than in those who were not (32% vs 47%;  $P < 0.001$ ).<sup>31</sup>

The other study is the previously mentioned trial in 350 patients aged 60 or older with NHL who were treated with VNCOP-B, 71% of whom were also given G-CSF as primary prophylaxis against chemotherapy-induced neutropenia.<sup>28</sup> The high overall response rate (83%) may be at least partially attributable to the fact that the use of G-CSF minimized the need for chemotherapy delays and dose reductions. The incidence of neutropenia was significantly lower in the patients who were given G-CSF than in those who were not (23% vs 56%;  $P = 0.00005$ ), as was the incidence of infection (5% vs 21%;  $P = 0.004$ ) (Figure 13).

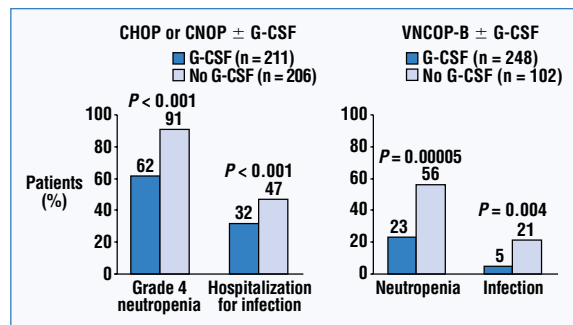


Figure 13. The use of G-CSF reduces neutropenia and infection in elderly patients with NHL. Left: The incidence of grade 4 neutropenia and the need for hospitalization because of infection in 417 patients aged 60 or older who were treated with CHOP or CNOP were both significantly lower in the patients who were given adjunctive G-CSF than in those who were not. Right: The incidences of neutropenia and infection in 350 patients aged 60 or older who were treated with VNCOP-B were both significantly lower in the patients who were given G-CSF as primary prophylaxis than in those who were not. Adapted from Bjorkholm et al<sup>31</sup> and Zinzani et al.<sup>28</sup>

The prophylactic use of G-CSF reduces the incidence, severity, and duration of chemotherapy-induced neutropenia, thereby helping maintain adequate dose intensity, whereas reliance on chemotherapy delays and dose reductions to manage the occurrences of neutropenia compromises the dose intensity.

A clinically effective method should also be cost-effective. The cost-effectiveness of using G-CSF as prophylaxis against neutropenia in patients with aggressive NHL was studied in 23 patients aged 60 to 70 who were treated with induction chemotherapy (CHVmp/VB) with or without adjunctive G-CSF. The aggregate costs of treating infection secondary to chemotherapy-induced neutropenia (hospitalization, antibiotic prophylaxis and treatment, diagnostic procedures, supportive care) in 11 patients who were not given prophylaxis were compared with those same costs plus the cost of the G-CSF in 12 patients who were given prophylaxis.<sup>32</sup> The prophylaxis group showed statistically significant advantages over the no-prophylaxis group in several measures: incidence of grade 3 or grade 4 neutropenia (4.8% vs 27.7%;  $P < 0.001$ ), incidence of chemotherapy dose delays because of neutropenia (19% vs 32%;  $P = 0.05$ ), mean duration of chemotherapy dose delays (10.1 days vs 25.9 days;  $P = 0.05$ ), incidence of severe infection (4.8% vs 15.6%;  $P = 0.01$ ), and mean hospital stay per course of chemotherapy (0.2 day vs 1.1 day;  $P = 0.05$ ) (Figure 14). The G-CSF was well tolerated, and the lower rate of infection and its associated costs of treatment in the prophylaxis group justified the cost of G-CSF prophylaxis. That is, the aggregate costs were lower with G-CSF than without it, because the

cost of providing prophylaxis with G-CSF was less than the additional costs of treating infections in the patients who were not given G-CSF.

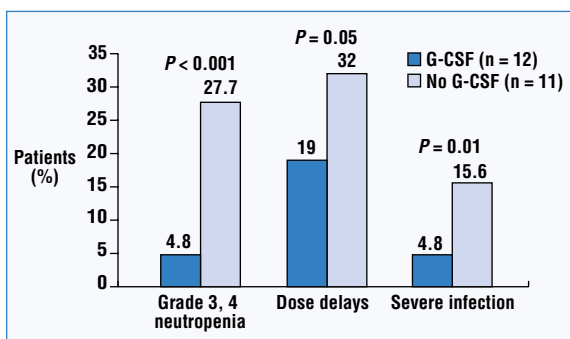


Figure 14. The use of G-CSF as prophylaxis against neutropenia is cost-effective in patients with aggressive NHL. In 23 patients aged 60 to 70 treated with CHVP/VB with or without G-CSF prophylaxis, the prophylaxis group had a lower incidence of grade 3 or grade 4 neutropenia (4.8% vs 27.7%;  $P < 0.001$ ), a lower rate of chemotherapy dose delays because of neutropenia (19% vs 32%;  $P = 0.05$ ), and a lower incidence of severe infection (4.8% vs 15.6%;  $P = 0.01$ ). The mean duration of chemotherapy dose delays and hospital stays per course of chemotherapy were also shorter in the prophylaxis group. Because of the lower rate of infection and its associated costs of treatment in the prophylaxis group, overall costs were lower with the use of G-CSF than without it. Adapted from Zagonel et al.<sup>32</sup>

The studies cited above indicate that otherwise-healthy elderly patients with aggressive NHL benefit from standard chemotherapy, but they are more susceptible to chemotherapy-induced myelosuppression than younger patients. The use of G-CSF as primary prophylaxis against neutropenia in these elderly patients is both clinically effective and cost-effective.

#### Acute myeloid leukemia

Another common age-related hematologic malignancy is AML. All major population subgroups—males and females, whites and blacks—show the same, rapidly increasing incidence with age (Figure 15). The disproportionate impact of AML on the elderly is evident in

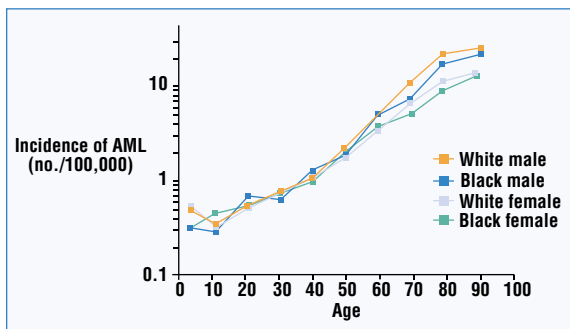


Figure 15. Acute myeloid leukemia is a disease of the elderly. All major population subgroups—males and females, whites and blacks—show the same, steadily increasing incidence with age. Adapted from Lancet et al.<sup>8</sup>

comparing the incidences in the entire US population and in people older than 75: 2.6 vs 16 per 100,000.<sup>8</sup> The greater incidence in the elderly may be due to greater cumulative exposure to carcinogens and to the effects of radiation and chemotherapy for other malignancies, and also to improved screening and surveillance.

A number of published reports all point to the conclusion that elderly patients with AML benefit from full-dose induction chemotherapy initiated immediately at the time of diagnosis (Figure 16). For example, the regimen of mitoxantrone and cytarabine produced a 58% complete remission rate in a population of 104 elderly patients.<sup>33</sup> The most commonly used regimen for AML, however, is daunorubicin and cytarabine, which has produced complete remission rates of 52%<sup>34</sup> and 53%.<sup>35</sup> Of particular interest, this same regimen was studied with and without the adjunctive use of G-CSF in a controlled trial in 173 patients. In the group that was not given G-CSF prophylaxis against chemotherapy-induced neutropenia, the rate of complete remission was 47%, which is consistent with the rates in the other trials that evaluated the daunorubicin-cytarabine regimen. The rate of complete remission was considerably higher, however—70%—in the group that was given G-CSF, and this between-group difference was statistically significant ( $P = 0.002$ ).<sup>36</sup> This study also found no evidence to support the theoretical concern that the use of a hematopoietic growth factor might stimulate malignant proliferation. Subsequent research has confirmed the value of G-CSF prophylaxis in reducing chemotherapy-induced neutropenia in elderly patients with AML.<sup>37,38</sup>

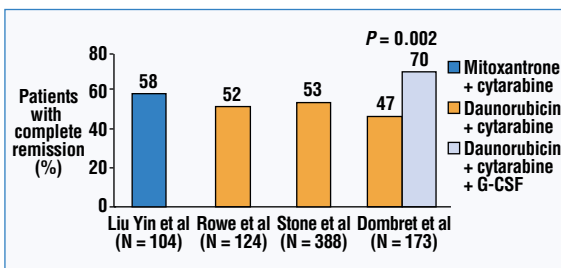
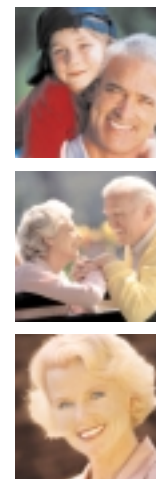


Figure 16. Elderly patients with AML benefit from standard induction chemotherapy. Treatment with mitoxantrone and cytarabine or with daunorubicin and cytarabine has produced complete remission rates of approximately 50% in several studies. In the study by Dombret et al, the complete response rate in the chemotherapy plus G-CSF arm was 70%, significantly higher than the 47% rate in the chemotherapy-alone arm. Adapted from Liu Yin et al,<sup>33</sup> Rowe et al,<sup>34</sup> Stone et al,<sup>35</sup> and Dombret et al.<sup>36</sup>



In AML, as in other cancers that occur with greater frequency in the elderly, age itself is not the chief determinant of treatment outcome. The poorer outcome in older patients than in younger patients may be attributable to poorer performance status, which is predictive of poor outcome in many types of cancer, and also to a higher incidence of cytogenetic abnormalities and multidrug resistance, which has been linked specifically to AML.<sup>8</sup>

The practical lesson to be gained from these study findings is that older patients with AML who are otherwise healthy should be given full-dose induction chemotherapy and that the adjunctive use of G-CSF as primary prophylaxis against chemotherapy-induced neutropenia may enhance the benefits achieved.

### Breast cancer

Among the nonhematologic cancers associated with aging, breast cancer is the most common type of malignancy (other than skin cancers) in women,<sup>39</sup> with a lifetime prevalence of approximately 1 in 8.<sup>2</sup> It is also the leading cause of cancer-related death in women older than 65, and the second leading cause of cancer-related death (after lung cancer secondary to smoking) in women of all ages.<sup>2</sup>

The incidence of breast cancer rises with age, peaking at about age 75 and then declining slightly (Figure 17).<sup>40</sup> Over the past 25 years the overall incidence has risen, mainly in women older than 50.

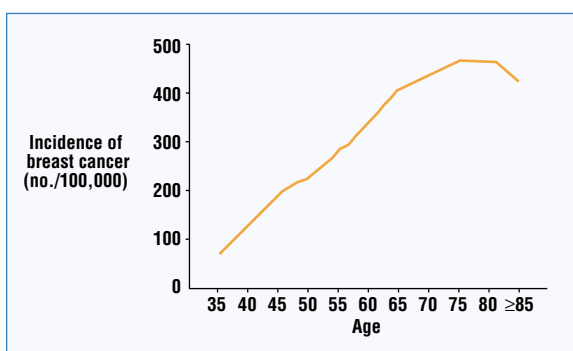


Figure 17. The overall incidence of breast cancer rises with age. In the United States the incidence peaks at about age 75 and then declines slightly. Adapted from Yancik and Ries.<sup>40</sup>

Mortality from breast cancer is higher in women aged 65 or older than in younger women,<sup>1</sup> but aging has complex effects on the aggressiveness of breast cancer and its responsiveness to treatment.<sup>41</sup> A higher proportion of the tumors in elderly women are of a more indolent type, such as papillary carcinoma, possibly because of the previously mentioned selection phenomenon (more-aggressive tumors cause death at a younger age). A less aggressive tumor implies a

lower proliferative rate, but cytotoxic chemotherapy is less effective against tumors in which a lower fraction of the cells are in the S phase of mitosis at any given time. Finally, a higher proportion of the breast tumors in elderly women are positive for estrogen receptors, which means that they are amenable to treatment with hormonal blockade.

The net impact of these age-related variables is that disease-free and overall survival in patients with breast cancer tend to be longer as the age at onset rises. While age-related changes in tumor aggressiveness and response to treatment can certainly affect survival in older women with breast cancer, the main determinant of outcome, as with other cancers, is the extent of comorbidity and functional loss.

Another determinant is the type of treatment given. A meta-analysis of 47 trials in approximately 18,000 women of all ages showed that the use of adjuvant chemotherapy after surgery provided significant advantages over surgery alone in women aged 50 to 69 (Figure 18).<sup>42</sup> Adjuvant chemotherapy reduced the risk of recurrence by 22% in women aged 50 to 59

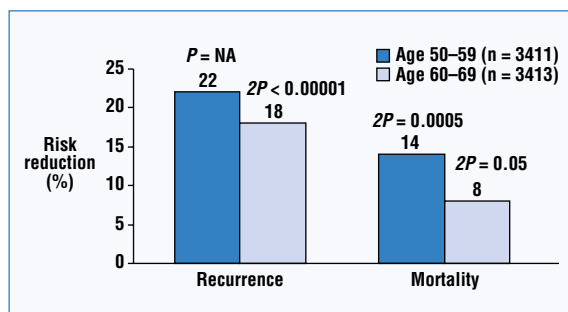


Figure 18. Adjuvant chemotherapy reduces the recurrence of breast cancer and reduces mortality in older women. A meta-analysis of 47 trials in approximately 18,000 women of all ages showed that the use of adjuvant chemotherapy following surgery reduced the risk of recurrence by 23.8% ( $2P < 0.00001$ ). Similarly, cancer-related mortality was reduced by 15.2% ( $2P = 0.00001$ ). Adapted from Early Breast Cancer Trialists' Collaborative Group.<sup>42</sup>

( $n = 3411$ ) and by 18% in women aged 60 to 69 ( $n = 3413$ ). The overall reduction in all age groups combined was 23.8%, a highly significant effect ( $2P < 0.00001$ ). (The  $2P$  designation indicates a statistical measure with just one degree of freedom—in this case, with vs without adjuvant chemotherapy.) Similarly, cancer-related mortality was reduced by 14% and 8% in the 50-to-59 and 60-to-69 age groups. The overall reduction in mortality for women of all ages was 15.2% ( $2P < 0.00001$ ). The number of women aged 70 or older was insufficient to determine the significance of the benefits of adjuvant chemotherapy.<sup>42</sup> The efficacy of adjuvant chemotherapy in older

women with breast cancer is a complex issue. The ability of adjuvant chemotherapy to reduce disease-related mortality declines with increasing age and infirmity.<sup>43</sup> However, in certain subsets of patients (including patients with hormone receptor-negative tumors and those with hormone receptor-positive tumors and increased expression of HER2/*neu*), adjuvant chemotherapy may reduce the recurrence rate to the same extent in older women as in younger women.

The most commonly used adjuvant chemotherapy regimen in older women with breast cancer is CMF. This is regarded as a relatively mild and tolerable regimen, with a low rate of treatment-related mortality (overall, 0.43% in trials dated 1978–1985, falling to 0.1% in trials dated 1986–1998).<sup>44</sup>

Because metastatic disease carries an entirely different prognosis, the treatment goal is also different—palliation rather than cure. Cytotoxic chemotherapy is reserved for patients in whom primary endocrine therapy has failed.<sup>39</sup>

The importance of dose intensity in chemotherapy for breast cancer was established in the landmark study of Bonadonna et al, a 20-year follow-up of 386 patients who had been treated with surgery with or without adjuvant chemotherapy consisting of 12 cycles of CMF.<sup>10</sup> The main findings are that survival was significantly increased in the patients who were given adjuvant chemotherapy but the benefit in older women who were given chemotherapy was less because they were given lower doses. The threshold for therapeutic effectiveness was the delivery of at least 85% of the planned chemotherapy dose. Subsequent research emphasizes the importance of not only total dose delivered but also dose intensity as a key determinant of outcome in breast cancer.<sup>11</sup>

As previously discussed, the main obstacle to delivering an adequate total dose and maintaining adequate dose intensity is chemotherapy-induced myelosuppression and the reliance on treatment delays and/or dosage modifications to allow hematopoietic recovery. The use of G-CSF prophylaxis to accelerate the production and release of neutrophils was shown to be beneficial in terms of minimizing the likelihood that patients with breast cancer treated with adjuvant CMF would be treated with less than 85% relative dose intensity (Figure 19). In a controlled study in 72 women with breast cancer and at least one prior episode of chemotherapy-induced neutropenia, G-CSF was given as secondary prophylaxis (prophylaxis after a documented episode of neutropenia) to

50 women; the other 22 women were given placebo. The percentage of women in each group in whom the relative dose intensity was less than 85% was calculated, and a failure to maintain at least 85% relative dose intensity was seen in only 26% of the women who were given G-CSF but in 55% of those who were given placebo ( $P < 0.05$ ).<sup>17</sup> This study was not specifically designed to compare the benefits in older and younger women, but an earlier study had already shown that older and younger patients derive comparable benefits from G-CSF prophylaxis against chemotherapy-induced neutropenia.<sup>45</sup>

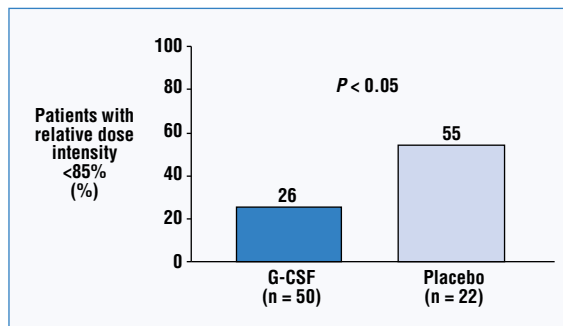
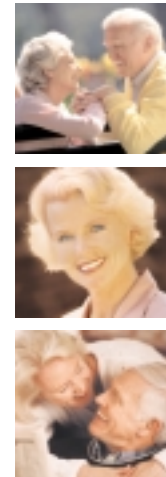


Figure 19. Granulocyte colony-stimulating factor helps in maintaining an adequate chemotherapy relative dose intensity in women with breast cancer. Women with breast cancer and at least one prior episode of chemotherapy-induced neutropenia were given G-CSF as secondary prophylaxis ( $n = 50$ ) or placebo ( $n = 22$ ). A relative dose intensity of less than 85% was seen in only 26% of the G-CSF group but in 55% of the placebo group ( $P < 0.05$ ). Adapted from de Graaf et al.<sup>17</sup>

The conclusions on breast cancer in older women are similar to those on other forms of cancer in the elderly. The main determinants of outcome and survival are tumor characteristics and comorbidities, not age itself. Furthermore, otherwise-healthy older women can and should be treated with the same standard adjuvant chemotherapy as younger women, and G-CSF prophylaxis against chemotherapy-induced neutropenia helps in maintaining the total dose and relative dose intensity above the critical threshold for therapeutic effectiveness.

#### Colorectal cancer

Colorectal cancer shows a steadily rising incidence with increasing age in both men and women (Figure 20).<sup>40</sup> The incidence rises continuously from adulthood through the ninth decade of life, so that 90% of all cases occur in people older than 50. Colorectal cancer accounts for 13% of all cancers in the United States, with an age-adjusted incidence of 60.8 per 100,000 in men and 42.3 per 100,000 in women (1985–1989).<sup>46</sup>

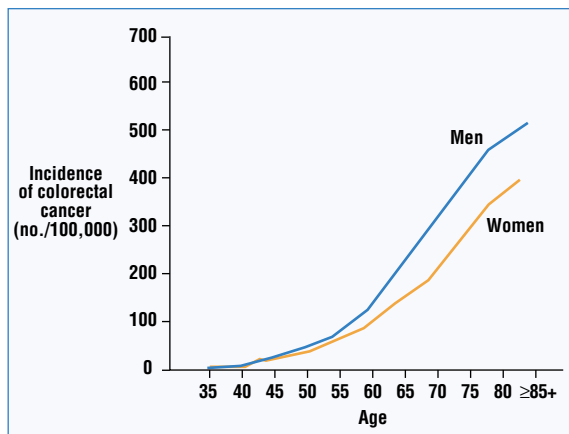


Figure 20. Colorectal cancer shows a steady age-related rise in incidence throughout life, with no peak or drop-off. Ninety percent of all cases occur after age 50. Adapted from Yancik and Ries.<sup>40</sup>

As in breast cancer, adjuvant chemotherapy increases survival in colorectal cancer. A meta-analysis of seven trials in 3351 patients who were treated with either surgery alone or surgery plus chemotherapy (5-fluorouracil plus either leucovorin or levamisole) found greater survival in all age groups (Figure 21). Patients were stratified into four age groups: younger than 50, 50 to 60, 60 to 70, and older than 70. In patients treated with adjuvant chemotherapy, both disease-free survival and overall survival were increased, measured as relative risk versus surgery alone. The increases in disease-free survival and overall survival with adjuvant chemotherapy in all ages combined were shown, respectively, to be 0.71 and 0.76 relative risk versus surgery alone ( $P < 0.0001$  in both measures).<sup>47</sup>

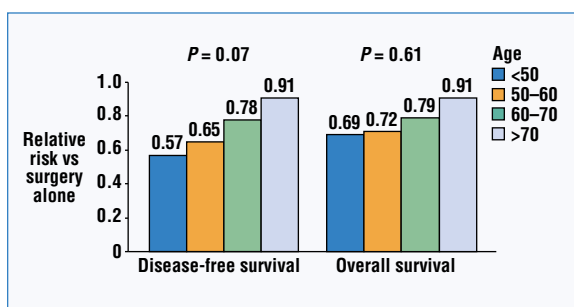


Figure 21. Adjuvant chemotherapy for colorectal cancer increases survival in all age groups. A meta-analysis of seven trials in 3351 patients treated with either surgery alone or surgery plus chemotherapy (5-fluorouracil plus either leucovorin or levamisole) found that adjuvant chemotherapy increased both disease-free survival and overall survival, measured as relative risk vs surgery alone. The increases in disease-free survival and overall survival in all ages combined were statistically significant. The increase was greatest in the youngest patients and least in the oldest patients, but the trend was not statistically significant. Adapted from Sargent et al.<sup>47</sup>

As might be expected, when the results were compared between the age groups, the relative risks were lowest in the youngest patients and highest in the oldest patients (that is, the reduction in risk was greatest in the youngest patients and least in the oldest patients). However, this age-related trend was not statistically significant. Another finding from this meta-analysis is that treatment-related toxic effects (nausea and vomiting, diarrhea, stomatitis, and leukopenia) were similar in all age groups. Six of the seven studies showed no statistically significant differences in toxic effects between the age groups, and one showed a higher incidence of leukopenia in elderly patients.

The conclusion is that elderly patients with colorectal cancer obtain benefits from adjuvant chemotherapy comparable to those seen in younger patients, and with no increase in toxic effects except perhaps myelosuppression. As with other cancers, these findings are in otherwise-healthy older patients; survival could be significantly lower in elderly patients with comorbidities and impaired functional status.

#### Lung cancer

Among the common age-related cancers in which chemotherapy is part of primary management, lung cancer remains the least amenable to treatment. (Most research has focused on non-small-cell lung cancer.)

The great majority of cases of lung cancer can be linked to smoking. Because risk accrues slowly with cumulative exposure to tobacco smoke, the incidence rises with age, peaking at about age 70 to 75 in both men and women (Figure 22).<sup>40</sup> The fact that smoking typically begins in adolescence or early adulthood and that the incidence of lung cancer peaks decades later indicates that carcinogenesis and the onset of symptoms occur slowly. The decline in incidence beyond age 75 to 80 reflects the fact that many smokers die before that age, not only of lung cancer but also of cardiovascular disease and chronic obstructive pulmonary disease. With a dwindling percentage of smokers left in the oldest age groups, the incidence of lung cancer falls.

In the past, smoking rates were substantially higher in men than in women. Consequently, the lifetime incidence of lung cancer and the incidence at any given age have been higher in men than in women. With the increase in smoking among women over the past generation, however, lung cancer incidence and mortality have risen to the extent that lung cancer is now the leading cause of cancer-related death in women in the United States, having surpassed mortality from breast cancer in the late

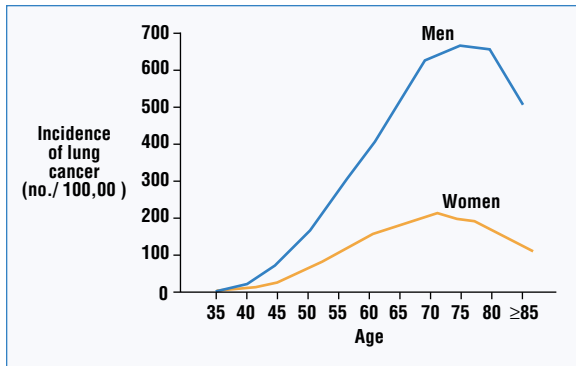


Figure 22. The incidence of lung cancer increases with age. The rates are higher in men than in women because smoking rates have traditionally been higher in men. The incidence peaks at about age 70 to 75 and then declines, because high mortality in smokers leaves a diminishing percentage of smokers in the oldest age groups. Adapted from Yancik and Ries.<sup>40</sup>

1980s. In fact, lung cancer mortality in American men may be leveling off because of a decrease in smoking over recent years, even while it is increasing in women.<sup>2</sup>

Lung cancer is not a uniquely American problem. Worldwide, rising smoking rates have been accompanied by an increase in the incidence of lung cancer. Moreover, because treatment offers only limited benefit and the prognosis remains poor, lung cancer mortality rates have been rising worldwide.<sup>2</sup>

The limited effectiveness of treatment is reflected in the fact that lung cancer, by no means the most common type of malignancy, is the leading cause of cancer-related death in the United States. The poor prognosis is also seen in the 5-year survival rate of 14%,<sup>2</sup> a discouraging value that has not shown much improvement in the past two decades.<sup>48</sup>

Nevertheless, chemotherapy does offer some benefit, even if the increase in survival is modest. Several regimens have been tried, and the mainstay of chemotherapy is platinum-based drugs. Cisplatin has traditionally been considered the most active single agent, but it is also highly toxic.

Two studies of platinum-based chemotherapy indicate that elderly patients with lung cancer who are otherwise fit can obtain benefits comparable to those obtained by younger patients (Figure 23). In one study, 574 patients were treated with cisplatin plus either etoposide or paclitaxel. Regardless of the regimen, median survival was almost identical in 488 patients younger than 70 and in 86 patients aged 70 or older (36 weeks and 34 weeks, respectively; the difference was nonsignificant).<sup>49</sup> A smaller trial was conducted in a total of 110 patients aged 34 to 84,

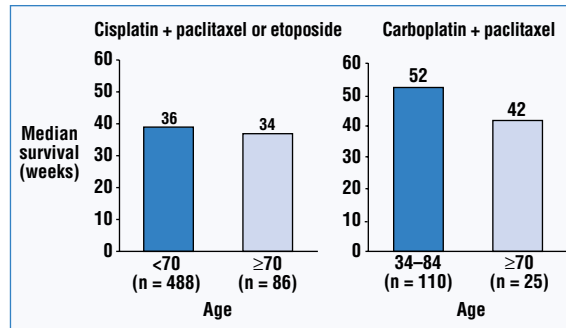


Figure 23. Chemotherapy produces comparable outcomes in younger and older patients with lung cancer. In two studies, there were no significant age-related differences in median survival time with various platinum-based chemotherapy regimens. Adapted from Langer et al<sup>49</sup> and Rosvold et al.<sup>50</sup>

including 25 patients aged 70 or older. The chemotherapy regimen was carboplatin and paclitaxel. There were no differences between the entire study population and the subgroup of older patients in median survival time (52 weeks and 42 weeks, respectively) or toxic effects.<sup>50</sup> Both carboplatin and paclitaxel are likely to produce neutropenia that could interfere with maintaining the total dose and relative dose intensity above the threshold for therapeutic effectiveness, and G-CSF prophylaxis might be especially useful as an adjunct to this regimen.<sup>48</sup>

Vinorelbine, a newer vinca alkaloid, has been tested alone and in combination with other chemotherapeutic agents. In one trial, the median survival in patients aged 70 or older was 28 weeks with vinorelbine monotherapy and 21 weeks with supportive care but no chemotherapy. Similarly, 1-year survival was 32% with vinorelbine and 14% with supportive care only. These findings indicate that elderly patients with lung cancer can benefit from this single-agent regimen.<sup>51</sup> In a study that compared the regimen of vinorelbine and cisplatin with the regimens of cisplatin alone and cisplatin plus other vinca alkaloids, survival was longest with the vinorelbine-cisplatin combination.<sup>52</sup> Another study found that this combination is useful in elderly patients even if the cisplatin is used at reduced doses.<sup>53</sup>

Despite the generally poor prognosis associated with lung cancer, chemotherapy produces some small but meaningful increases in survival. The results of these studies indicate that elderly patients who are otherwise healthy can benefit just as younger patients can, and with no greater toxic effects except myelosuppression, to which the elderly are generally more susceptible.



### *The role of G-CSF in elderly patients treated with cytotoxic chemotherapy*

The overriding conclusion from these reports of treatment outcomes in common cancers in the elderly is that age itself is not a contraindication to full-dose adjuvant or induction chemotherapy. The main limiting factors are comorbidity and poor functional status. Standard chemotherapy has the same benefits in older patients who are otherwise healthy and fit as in younger patients. Giving the chemotherapy at a reduced total dose and reduced relative dose intensity on the basis of age alone compromises the outcome. The poorer outcome that is often seen in elderly patients also reflects the greater prevalence of comorbidities and poor performance status in this age group. Finally, while susceptibility to myelosuppression increases with age, the use of G-CSF to accelerate the production and release of neutrophils reduces the incidence, severity, and duration of chemotherapy-induced neutropenia. As a result, there is a lower risk of infection and less need for hospitalization and intravenous antibiotics for febrile neutropenia. In addition, there is less need for treatment delays and chemotherapy dose reductions to allow for recovery from chemotherapy-induced neutropenia.

The optimal use of G-CSF is as prophylaxis against, rather than treatment for, chemotherapy-induced neutropenia. Primary prophylaxis refers to use of the growth factor before there has been any occurrence of neutropenia. Secondary prophylaxis refers to its use in subsequent chemotherapy cycles after the occurrence of neutropenia in at least one previous cycle. Primary or secondary prophylaxis with G-CSF (with the dose based on the patient's weight) is given daily in each cycle of chemotherapy, starting 24 hours after the chemotherapy administration has been completed and continuing, if possible, until the ANC has risen to at least  $10,000 \times 10^6/L$ .

The current guidelines of the American Society of Clinical Oncology recommend the use of a hematopoietic growth factor after an episode of chemotherapy-induced neutropenia, to prevent infection without having to resort to chemotherapy delays and dose reductions—that is, the recommendation is to use the growth factor as secondary prophylaxis.<sup>54</sup> However, as was mentioned above, at least one study has found that death due to neutropenic infection in patients aged 60 or older frequently occurs in the first cycle of chemotherapy.<sup>29</sup> Therefore, primary prophylaxis, started 24 hours after the completion of the first cycle of treatment, should be considered in elderly patients who are treated with myelosuppressive chemotherapy.<sup>55</sup>

Just as it has been shown that standard chemotherapy is equally effective in otherwise healthy elderly patients with cancer and in younger patients in terms of inducing remission and increasing survival, it has also been shown that G-CSF is equally effective in older patients and younger patients in terms of minimizing chemotherapy-induced neutropenia. A dose-response study showed that G-CSF produces similar dose-related increases in the peak neutrophil count in healthy volunteers regardless of their age. The trial assessed peak neutrophil counts following the administration of 30- $\mu\text{g}$  and 300- $\mu\text{g}$  doses of G-CSF in 19 volunteers aged 20 to 30 and 19 volunteers aged 70 to 80. In both age groups the mean peak neutrophil count was about  $10,000 \times 10^6/L$  after the 30- $\mu\text{g}$  dose and  $13,000 \times 10^6/L$  after the 300- $\mu\text{g}$  dose (Figure 24).<sup>56</sup> These findings in healthy volunteers are consistent with other research that has shown that the effectiveness of G-CSF in raising neutrophil counts is comparable in elderly patients and younger patients who are treated with chemotherapy for a variety of malignancies.<sup>45</sup>

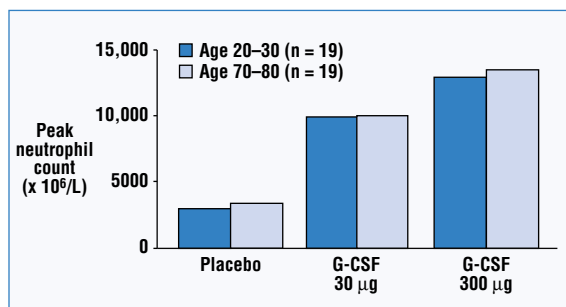


Figure 24. The response to G-CSF is similar in younger and older volunteers. In this dose-response study in 19 volunteers aged 20 to 30 and 19 volunteers aged 70 to 80, the mean peak neutrophil counts in both age groups were about  $10,000 \times 10^6/L$  and  $13,000 \times 10^6/L$  after the administration of G-CSF in 30- $\mu\text{g}$  and 300- $\mu\text{g}$  doses, respectively. Adapted from Chatta et al.<sup>56</sup>

Apart from chemotherapy-induced myelosuppression, the risk of cardiotoxicity secondary to full-dose anthracycline therapy in older patients has also been of concern. In a phase II multicenter trial involving 20 elderly patients (median age 71) with intermediate-grade lymphoma (IGL), standard CHOP was given every 21 days for six cycles. With G-CSF prophylaxis started on day 3 and continuing until the ANC rose above  $10,000 \times 10^6/L$ , the relative dose intensity was 99.4% for doxorubicin and similarly high for the other agents in the regimen. Yet even with full-dose anthracycline therapy, there was no evidence of treatment-related cardiotoxicity, and the researchers concluded that full-dose CHOP with G-CSF support is a safe regimen in elderly patients with IGL.<sup>57</sup>

In summary, G-CSF provides an effective means of averting or minimizing chemotherapy-induced neutropenia. It is as effective in older patients as in younger patients, acting to accelerate the production and release of neutrophils. Used as prophylaxis, G-CSF reduces the incidence, severity, and duration of neutropenia without recourse to chemotherapy delays and dose reductions, which would adversely affect the total chemotherapy dose and relative dose intensity and thus compromise outcome and survival.

While it is clear that standard chemotherapy is warranted in otherwise-healthy elderly patients with cancer, it is also clear that many elderly patients are not otherwise healthy but are, in fact, burdened with various degrees of comorbidity and functional impairment. Furthermore, because these factors (rather than age itself) are the main impediments to therapeutic success in elderly patients, it is essential that each patient be thoroughly examined and assessed before treatment is begun.

### *The Comprehensive Geriatric Assessment*

As an adjunct to the general and cancer-specific clinical and diagnostic examinations, the Comprehensive Geriatric Assessment (CGA) is an integral tool. It is a systematic examination of every aspect of a patient's life that might have an impact on the course of the disease and the outcome of treatment.<sup>7</sup> The CGA is a screening tool, with more-specific instruments used for further delineating any risk factors that are identified in the screening. The main areas of focus are the patient's functional, physical, mental, emotional, pharmacotherapeutic, and socioeconomic status.

#### *Functional status*

Functional status is a measure of the patient's degree of independence, and it is one of the key determinants of treatment success or failure. Screening during the CGA typically involves asking the patient such direct questions as

- Can you go to the store and shop by yourself?
- Can you prepare food and feed yourself?
- Can you get dressed by yourself?
- Do you need any help in using the toilet, or in showering or bathing?

If the answers to these or similar screening questions indicate any significant loss of independence, follow-up with a more detailed functional rating tool is warranted.

The Katz Activities of Daily Living (ADL) rates basic functions—the ability to perform such routine activities as bathing, dressing, using the toilet (and freedom from incontinence), getting into or out of bed, chairs, or vehicles, and feeding oneself, all with little or no assistance.<sup>58</sup> The Lawton Instrumental Activities of Daily Living (IADL) rates more-sophisticated functions—the ability to use the telephone, to shop for and prepare food, to attend to cleaning, laundry, and other routine household tasks, to travel by car or other means, to be responsible for taking one's medication, and to handle finances, all with little or no assistance.<sup>59</sup>

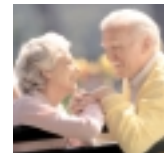
The Katz and Lawton scales are designed for use in elderly patients, but not specifically patients with cancer. In contrast, the Eastern Cooperative Oncology Group Performance Status rating tool<sup>60</sup> and the Karnofsky scale<sup>61</sup> are designed for use in patients with cancer, but not specifically elderly patients. The ADL and IADL may be better indicators of the issues that are of greatest concern to the patient, and the Performance Status and Karnofsky scales focus more on issues that are of concern to the physician. The geriatric-patient scales and the oncology-patient scales show only limited correlation.<sup>62</sup>

There is no clear consensus that one rating tool is better than the others. What is important then is that some tool be used at the outset of treatment and that any improvement or deterioration in the patient's functional status be periodically assessed by using the same tool.

#### *Comorbidity*

Comorbidities are serious medical conditions that are not directly related to the cancer itself but involve the cardiovascular system, the respiratory system, the renal or hepatic system, or any other major organ system. These conditions are usually chronic rather than self-limiting or acute and easily treated.

During the CGA in an elderly patient with cancer, the number and severity of comorbid conditions can be assessed with such tools as the Charlson Comorbidity scale<sup>63</sup> and the Cumulative Illness Rating Scale—Geriatric (CIRS-G).<sup>64</sup> The Charlson scale is a list of 19 conditions whose presence is associated with at least a 20% increased risk of death. On the basis of these relative risks, each condition is weighted from 1 to 6. The CIRS-G offers a more far-reaching assessment. Conditions that affect any organ system are rated on a scale of 0, indicating no problems, to 4, indicating a severe or life-threatening condition.



It is important to note that comorbidity, like impaired functional status, is a key negative prognostic factor in elderly patients with cancer and that comorbidity can also adversely affect the patient's functional status. Yet there is surprisingly little direct correlation between these assessments.<sup>62</sup> That is, comorbidity and functional status are independently significant and must therefore be assessed independently.

#### *Socioeconomic factors*

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Adequate housing, the presence of a reliable caregiver, having medical insurance, and being able to pay for treatment and for the necessities of life are factors that should be assessed, not assumed, in elderly patients. Problems in any of these areas can adversely affect the patient's ability to obtain and comply with treatment, and may therefore compromise the treatment outcome. Social workers are usually best equipped to help patients in these areas.

#### *Cognition*

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Cognition refers to the patient's mental status with respect to memory, orientation, comprehension, and logical thinking. Patients must have intact cognition to participate fully in the treatment. Conversely, cognitive impairment is a potentially serious impediment to compliance with treatment, and may necessitate a reliable caregiver to ensure that the patient attends all scheduled medical visits and complies with all prescribed medications and medical instructions.

Cognitive impairment may be an irreversible comorbid condition, such as that in patients with Alzheimer's disease, or it may be a potentially reversible condition brought on by stress, fatigue, acute illness, or depression. Depression and cognitive impairment can, in fact, mimic each other, and it is important to distinguish between the two so as to provide appropriate help.

Standard screening starts with such simple tests as orientation as to person, place and time, counting up or down by ones or sevens, and recalling three objects that were shown 5 minutes earlier. A more detailed screening tool is the Folstein Mini Mental Status Examination.<sup>65</sup> Serious cognitive impairment, whether a primary problem or a condition secondary to another problem such as depression, requires more-intensive workup and, in some cases, referral to a specialist.

#### *Emotional condition*

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The main concern with respect to emotional condition is depression, which is common in both geriatric and oncology populations, and is therefore especially common in elderly patients with cancer. As was men-

tioned above, depression and cognitive disorders can be mistaken for each other, and either type of condition could adversely affect the patient's functional status and the outcome of cancer treatment.

Depression is a classic example of an underdiagnosed disorder. Clinicians frequently do not detect and recognize depression, especially when there are no obvious manifestations of emotional distress, which is not an uncommon presentation. Because of the high prevalence of depression in elderly patients with cancer, a high index of suspicion is warranted. During the CGA it is marginally adequate to ask, "Do you often feel sad or hopeless?" The preferred approach is to use a specific rating tool, such as the Geriatric Depression Scale<sup>66</sup> or the classic Beck Depression Inventory.<sup>67</sup>

While depression in elderly patients is hardly unexpected, it is no less a clinical problem than major depression in a patient with no obvious source for stress or grief. Depression itself is the problem. It can be a crippling condition regardless of whether there is any obvious cause. Resolving depression through an appropriate regimen of counseling and pharmacotherapy can produce significant improvements in the patient's willingness to cooperate with cancer treatment and, especially, in the patient's quality of life. The necessary first step is detection and diagnosis, and for this reason a methodologic screen for depression is an important component of the CGA.

#### *Nutrition*

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Nutrition is often deficient in elderly patients, for such diverse reasons as depression, poor dentition, functional impairment, cognitive impairment, lack of appetite due to chronic comorbid disease, and lack of a caregiver. Elderly patients with cancer may also face additional problems brought on by chemotherapy, such as nausea, vomiting, diarrhea, and painful oral ulcerations.

Malnutrition can have serious effects on a patient's immune function and ability to tolerate chemotherapy. While weight loss may indicate a problem with nutrition, it is important to distinguish between correctable malnutrition and the irreversible wasting that may accompany terminal malignancy.

Screening for possible nutritional problems during the CGA can be done with questions that elucidate the types and amounts of food the patient eats on an average day and by establishing whether there is any correctable problem that is interfering with nutrition. Correcting such problems and establishing a suitable dietary plan are simple measures that can substantially improve the patient's clinical outcome and quality of life.

## Pharmacotherapy

Many elderly patients, both with and without cancer, take a variety of medications on a long-term basis. Some may be essential for managing comorbid disorders, and others may have been ordered for conditions that are no longer present or relevant. A thorough review of all medications taken, prescription drugs and over-the-counter drugs alike, may find unnecessary drugs that can be discontinued and can also alert the physician to potential drug interactions that could arise when chemotherapy is initiated. (The risk of interactions increases rapidly with each agent taken.) Patients themselves may not know why they are taking certain drugs.

The classic method of pharmacy assessment is as applicable in geriatric patients as in any other patients. The patient should be instructed to collect and bring in every medicine container that he or she is currently using. The physician should establish, by questioning the patient and by chart review, whether the medication is necessary, and then, one at a time, cautiously withdraw any medication for which no valid clinical purpose can be found.

## Geriatric syndromes

Aging is associated with conditions that present a serious threat to survival. Classic geriatric syndromes are dementia, delirium, severe depression, frequent falls (especially falls that result in hip fracture or other characteristic injury), neglect and/or abuse, and spontaneous fractures.

The clinical assessment and CGA should detect such problems. Some problems defy solution, but others may be eliminated or at least minimized. For example, depression is usually treatable, falls may be averted through such simple measures as better lighting and the use of devices to aid in stability, and neglect or abuse may be stopped through the intervention of social service agencies.

Identification of and, when possible, intervention in geriatric syndromes is an essential part of comprehensive patient care. A successful outcome with chemotherapy is irrelevant if the patient dies of an unrelated geriatric problem that might have been corrected had it been recognized and addressed.

## The frail elderly

Frailty is, to some degree, a subjective impression, but the term *frail elderly* is used to describe a distinct and growing patient population. There are no formal criteria for defining frailty, but several criteria have been adopted by consensus. These criteria include loss of

independence in activities of daily living, the presence of three or more comorbid conditions that involve major organ systems, and the presence of any geriatric syndrome.

Age itself—typically, 85 or older is suggested—is a more controversial criterion of frailty. Most patients at this age would probably qualify as frail by the aforementioned criteria of functional loss and severe comorbidity, but it is probably more accurate to regard extreme age as a reason to suspect frailty rather than as a defining criterion.

There are at least 6 million frail elderly patients in the US population, accounting for a fifth of the over-65 population.<sup>68</sup> An estimated 400,000 frail elderly patients have cancer, and two thirds of them require some form of treatment. Death in frail elderly patients with cancer usually occurs as a result of extreme age-related declines in physiologic reserves rather than as a direct result of the cancer itself. As discussed in the following sections, this fact has profound implications for treatment decisions.

## The stages of aging

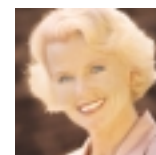
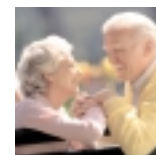
Analysis of CGA data from a large number of patients shows the extent of the problems commonly seen in elderly patients and makes it possible to create a system for classifying older patients with cancer and making appropriate management decisions.<sup>7</sup>

The CGAs performed in 200 patients aged 70 or older who were seen consecutively at the H. Lee Moffitt Cancer Center and Research Institute show a high prevalence of such conditions as dependence in ADL and/or IADL, serious comorbidity, memory impairment, malnutrition, and polypharmacy (Table 2). Because of these findings, it was determined that a CGA is warranted in all patients aged 70 or older.<sup>7</sup>

Table 2. Common Problems in the Elderly, by Comprehensive Geriatric Assessment\*

Measure	% of patients
Dependence	
ADL	18
IADL	72
Serious comorbidity	
Charlson scale	36
CIRS-G scale	94
Memory impairment	22
Poor nutrition	19
Polypharmacy	41

\*Findings are from 200 patients aged 70 or older seen consecutively at the H. Lee Moffitt Cancer Center and Research Institute. Adapted from Balducci and Extermann.<sup>7</sup>



The stages of aging have been classified in a detailed theoretical model.<sup>69</sup> The following classification system, however, which is based on CGA data, may be more useful in the clinical setting:

- Group 1 comprises otherwise-healthy older patients who are functionally independent and have no serious comorbidities. This description implies intact cognition, adequate nutrition, absence of geriatric syndromes, and absence of polypharmacy. Patients in this category are candidates for any form of standard cancer treatment aimed at cure, as would be used in younger patients.
- Group 2 comprises patients who are partially dependent and have no more than two comorbid conditions. These patients may benefit from modified cancer treatment, such as chemotherapy with the dose initially reduced and then titrated up as tolerated.
- Group 3 comprises the frail elderly, as previously defined. Their characteristics include functional dependence, three or more comorbid conditions, or the presence of any geriatric syndrome. These patients are candidates for palliative treatment only.

Not surprisingly, aging itself affects the distribution of patients in this grouping system (Figure 25). A theoretical model indicates that at age 70 approximately three fourths of patients would be in group 1, most of the others in group 2, and relatively few in group 3. By age 80, the percentage of patients still in group 1 has decreased considerably, most patients are in group 2, and the percentage in group 3 has increased. By age 90, the greatest number of patients would be in group 3, most others would be in group 2, and very few patients would still be in group 1. In other words, aging is associated with a progressive move from group 1 into groups 2 and 3.<sup>7</sup>

### Management decisions in elderly patients with cancer

The CGA and the general and cancer-specific diagnostic evaluations all contribute to the information base on which clinical decisions are made. The decision to treat cancer in an elderly patient is based not only on the type and stage of the disease, but also on the patient's physical and mental ability to tolerate treatment. Just as age itself is not an automatic contraindication to standard cancer treatment, a diagnosis of cancer by itself is not an automatic indication for treatment. Factors that relate to both the disease and

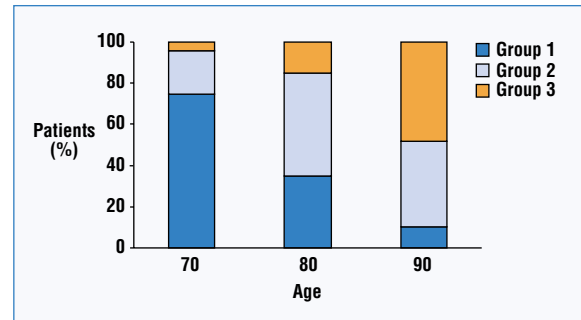


Figure 25. Health and independence progressively decline with age. In this theoretical model, group 1 is older patients who are otherwise healthy and fit, group 2 is patients with some degree of dependence in routine activities and no more than two comorbidities, and group 3 is frail patients who are dependent, with three or more comorbidities or at least one geriatric syndrome. With aging and increasing infirmity, the distribution of patients in this schema shifts as patients move from a lower- to a higher-number group. Adapted from Balducci and Extermann.<sup>7</sup>

the patient must be considered in deciding whether and how to treat the cancer. For example, chemotherapy in intermediate-grade lymphoma is beneficial in virtually every circumstance, but the benefit of adjuvant chemotherapy in breast cancer varies with the likelihood that the patient will die of the disease. Statistically, chemotherapy becomes beneficial only when the risk of cancer-related death exceeds a certain threshold, and that threshold is lower in a 70-year-old woman than in an 80-year-old woman.<sup>43</sup>

### Disease factors

The diagnosis and staging of cancer follow standard criteria, but the patient's age may affect these assessments. The tumor cell type indicates its proliferative rate and invasiveness, but these measures may vary in older patients, as in the previously cited example of breast cancer, which may be less aggressive but also less responsive to chemotherapy in older women.

Aging can also affect the prospects for treatment in terms of the stage at which the disease is diagnosed. Cancer in older patients is often diagnosed at a more advanced and therefore less treatable stage than in younger patients. A delayed diagnosis may be due in part to a clinical bias against aggressive diagnosis in the geriatric population, and in part to older patients' reluctance to seek treatment.

### Patient factors

The clinical workup and CGA should document potential risk factors that could affect the outcome of treatment. Age-related declines in major physiologic functions (especially cardiovascular function, renal and hepatic function, and hematopoietic reserve) may

lessen the patient's ability to withstand surgery, radiation, and cytotoxic chemotherapy.

Comorbid diseases and functional impairment are clearly associated with a poorer prognosis. Similarly, problems with mental, emotional, or nutritional status, polypharmacy, and lack of family or social support can interfere with the effectiveness and tolerability of treatment, with negative implications for outcome and survival.

Patient assessment is more subjective than tumor assessment, but no less important. The clinician must rely on estimates of the patient's life expectancy with and without cancer treatment, the probable impact of the disease and its treatment on the patient's quality of life, and all information obtained during the CGA.

### The management algorithm

The data from the tumor assessment, the clinical workup, and the CGA can be used to make management decisions that are rational and objective. For this purpose, a simple algorithm may be used (Figure 26).<sup>7</sup>

The first step is classifying the patient into one of the three groups (group 1, otherwise healthy and fit; group 2, partially dependent and with no more than two comorbidities; group 3, frail, dependent, with three or more comorbidities or a geriatric syndrome). That this classification is the first step in the decision algorithm illustrates the supreme importance of functional status and comorbidities as predictors of treatment outcome.

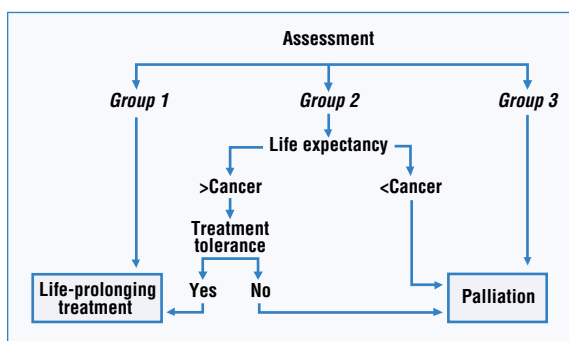


Figure 26. The management strategy in elderly patients with cancer is based on the full workup, including the CGA, and their classification as group 1 (otherwise healthy and fit), group 2 (partially dependent and with no more than two comorbidities), or group 3 (frail, dependent, with three or more comorbidities or a geriatric syndrome). Patients in group 1 can receive standard treatment aimed at cure, and those in group 3 should receive palliative treatment only. The decision in patients in group 2 is based on whether their life expectancy without cancer would be greater or less than it would be with the cancer left untreated and whether they could tolerate cancer treatment. Adapted from Balducci and Extermann.<sup>7</sup>

For patients in group 1 or group 3, the appropriate course is relatively simple. Those in group 1, like younger patients, are candidates for standard life-prolonging treatment. Those in group 3 cannot tolerate aggressive chemotherapy and are likely to die of unrelated conditions. They should therefore receive palliative treatment only.

The decision is more complex for patients in group 2, and is based on which is likely to cause death to occur sooner—untreated cancer or other health problems. If the patient will probably die of other causes before death from cancer would occur, there are no benefits to be gained from standard anticancer treatment and the appropriate action would be to provide palliative therapy. Conversely, if the cancer is likely to be the cause of death, it would be appropriate to provide life-prolonging anticancer treatment according to what the patient can tolerate. Some patients in this situation are close to group 1 status and could tolerate standard treatment with intent to cure. Others would require modified treatment (for example, less toxic alternative regimens or lower initial chemotherapy doses with dose escalation as tolerated). Finally, some of these patients are close to group 3 status and should be given palliative treatment only.

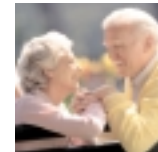
In summary, treatment with intent to cure is appropriate in nonfrail elderly patients whose life would probably be cut short if the cancer were left untreated and in whom aggressive anticancer treatment is tolerable. Palliative treatment is appropriate in frail elderly patients who would probably die of conditions unrelated to cancer and in patients in whom aggressive anticancer treatment is intolerable.

### Minimizing toxic effects

A proactive approach to minimizing the toxic effects of chemotherapy is warranted in all patients, and is especially important in elderly patients. Comorbidity and physiologic decline may leave older patients more susceptible to treatment-related toxic effects, and even those older patients who are otherwise healthy and fit are more likely than younger patients to be susceptible to chemotherapy-induced myelosuppression.

### General measures

The CGA may find correctable conditions that could adversely affect the patient's ability to tolerate chemotherapy. For example, correcting poorly fitting dentures that have been causing oral irritation can reduce the severity of chemotherapy-induced mucositis. Correcting dehydration and malnutrition can



reduce the systemic toxic effects of chemotherapeutic agents. Eliminating, as far as possible, polypharmacy can reduce the risk of adverse drug interactions.

Treatment for common toxic effects can be arranged in advance (for example, fluids and oral rinses for relieving mucositis and medications for relieving nausea and vomiting). Teaching patients about preventive hygiene can reduce the risk of infection secondary to chemotherapy-induced neutropenia. Antibiotic prophylaxis may be deemed necessary in certain circumstances, according to the oncologist's clinical judgment.

#### Minimizing myelotoxic effects

As was discussed earlier, primary prophylaxis with G-CSF reduces the incidence, severity, and duration of chemotherapy-induced neutropenia. As a result, the risk of infection is reduced without having to resort to chemotherapy dose delays and reductions. This strategy is especially beneficial in elderly patients, who are at increased risk of myelosuppression.

Guidelines have been developed that recommend the use of hematopoietic growth factors such as G-CSF in all patients older than 70 (Table 3) who are treated with combination chemotherapy at a dose intensity equivalent to that of a standard CHOP regimen.<sup>70</sup>

Table 3. Recommended Guidelines for Minimizing the Toxic Effects of Chemotherapy in Elderly Patients

- Use hematopoietic growth factors (eg, G-CSF) in patients >70 treated with combination chemotherapy with a dose intensity equivalent to that of CHOP
- Use erythropoietin to maintain hemoglobin concentration at  $\geq 12$  g/dL
- Consider dose adjustments of renally excreted drugs according to patient's GFR

Adapted from Balducci and Yates.<sup>70</sup>

#### Dose adjustment based on renal function

The toxic effects of chemotherapy may be minimized by modifying the dosage to adjust for age-related declines in renal function, without compromising the therapy's effectiveness.<sup>71</sup> Standard dose adjustments based on set values for the GFR have been suggested for several commonly used chemotherapy drugs, but precise modifications could be based on the patient's GFR and the percentage of drug excretion that is renal. The Kintzel-Dorr formula<sup>72</sup> is used to compute the adjustment factor for the standard dose:

$$\text{Adjustment Factor} = 1 - (\text{Renal Excretion Fraction} \times \frac{120 - \text{GFR}}{120})$$

For example, if the standard dose of a drug is 50 mg/m<sup>2</sup> and the renal excretion fraction at that dose is 0.35, then the adjustment for a patient with a body surface area of 1.7 m<sup>2</sup> and a GFR of 40 mL/min would be computed as follows:

$$\text{Standard Dose} = 50 \text{ mg/m}^2 \times 1.7 \text{ m}^2 = 85 \text{ mg}$$

$$\begin{aligned} \text{Adjustment Factor} &= 1 - (0.35 \times \frac{120 - 40}{120}) \\ &\approx 1 - 0.23 \\ &= 0.77 \end{aligned}$$

$$\begin{aligned} \text{Adjusted Dose} &= \text{Standard Dose} \times \text{Adjustment Factor} \\ &= 85 \text{ mg} \times 0.77 \\ &\approx 65 \text{ mg} \end{aligned}$$

Pharmacokinetic parameters are highly variable for chemotherapy agents, however, especially in elderly patients. As was previously discussed, elderly patients often have a diminished volume of distribution and diminished renal function. When the true GFR is very low, the estimate of renal function by creatinine clearance or the Cockcroft-Gault formula may be inaccurate. In addition, hepatic metabolism and excretion may also be altered, affecting the renal excretion fraction.

As a result of these variations and uncertainties, the same doses of a chemotherapy drug can have dramatically different AUC values in different patients even if their body surface areas are similar.<sup>73</sup> Consequently, another method of adjusting the chemotherapy dose is to make the adjustments on the basis of keeping the AUC within defined limits; to date, this method has been used mainly with carboplatin.

The goal of adjusting doses on the basis of the patient's physiologic profile is worthwhile. At present, however, adjustments cannot be made with absolute precision, and must therefore be guided as much by the oncologist's experience as by mathematical formulas.

#### Clinical biases and misconceptions

The treatment of cancer in the elderly has been hampered by a number of misconceptions whose sum effect is to encourage undertreatment. A common error is overgeneralization—for example, the assumptions that not just some but all cancers in the elderly

are relatively indolent and that not just some but all elderly patients are frail. The first false assumption implies that elderly patients do not need standard treatment, and the second implies that they cannot tolerate it.

There is also widespread factual misinformation. For example, some clinicians believe that frailty implies imminent death, when in fact frail patients may live for years. Others mistakenly believe that life expectancy at any age equals life expectancy at birth minus current age, when in fact people who have reached old age can be expected to continue living past the age that was their life expectancy at birth.

The result of these misconceptions is often undertreatment, which compromises long-term outcomes, contributing to higher cancer-related death rates in elderly patients than in younger patients. This self-fulfilling pattern then reinforces the belief that standard chemotherapy is inappropriate in elderly patients. Because chemotherapy is less effective and less tolerable in elderly patients who have comorbidities and functional impairment, the key is to tailor the treatment to the individual patient's status as determined by the clinical workup, tumor assessment, and CGA.

Unfortunately, the ability to individualize treatment is limited by the paucity of data on cancer in elderly patients. Elderly patients have been routinely excluded from or underrepresented in the study populations of clinical trials in a variety of common cancers (Figure 27).<sup>74</sup> A review of 164 trials in 16,396 patients by the Southwest Oncology Group found that the percentages of elderly patients in the study populations were much lower than their percentages in the entire

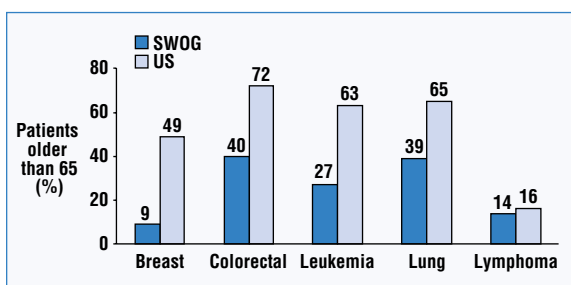


Figure 27. Clinical trials in cancer routinely exclude elderly patients. A review of 164 trials in 16,396 patients by the Southwest Oncology Group found that the percentages of patients older than 65 in the study populations were much lower than the percentages in the entire US populations with those types of cancer. This disparity was seen in all types of cancer except lymphoma. The greatest underrepresentation was in breast cancer—women older than 65 account for 49% of all patients with breast cancer nationwide but only 9% of the subjects in those trials ( $P < 0.001$ ). Adapted from Hutchins et al.<sup>74</sup>

US populations with those types of cancer. Overall, patients older than 65 account for 63% of all patients with cancer in the United States but only 25% of the patients in those trials ( $P < 0.001$ ).

This disparity was seen in all types of cancer except lymphoma. The greatest underrepresentation was in breast cancer—women older than 65 account for 49% of all patients with breast cancer nationwide but only 9% of the subjects in those trials ( $P < 0.001$ ).<sup>74</sup> Other research has shown that older women are less likely to be actively recruited to participate in clinical trials even if they meet all eligibility requirements.<sup>75</sup>

Although those elderly patients who meet the inclusion criteria for clinical trials may be healthier than the elderly population in general, undertreatment has still been the rule rather than the exception, resulting in a poorer outcome than that in younger patients who are given standard treatment. For example, older patients with aggressive lymphoma were less likely to be treated for cure and were less likely to survive for 5 years.<sup>76</sup> Patients with stage III colon cancer who were not treated with chemotherapy after surgery were older than those who were treated with chemotherapy (mean age, 78.7 vs 70.4 years;  $P < 0.01$ ).<sup>77</sup> A review of data from 1652 patients with lung cancer in the United Kingdom who were seen consecutively found that older patients tended to receive less aggressive diagnosis and treatment, with correspondingly poorer outcomes.<sup>78</sup> Another study of survival in elderly patients with cancer found that inadequate treatment and a more advanced stage of disease at the time of the diagnosis were two of the main predictors of a poor outcome.<sup>79</sup>

These findings indicate that clinical bias often results in a less aggressive approach to diagnosis and treatment in elderly patients and that underrepresentation of the elderly in clinical trials both reflects and reinforces these biases.

## Summary

Cancer in the elderly is a growing clinical problem, because the population is aging and the incidence of many cancers increases with age. In the absence of comprehensive data on treatment in the elderly, the belief persists that the elderly derive less benefit and suffer greater toxic effects from chemotherapy than younger patients. Consequently, undertreatment is common, resulting in poorer outcomes.

Age itself, however, is not predictive of outcome. The CGA helps distinguish between elderly patients who should be treated with standard chemotherapy with intent to cure and those who should be treated



with palliative therapy only. While frailty, as defined by the presence of multiple comorbidities and severely impaired functional status, is clearly associated with poorer outcomes, elderly patients who are otherwise healthy and fit derive the same benefits from standard chemotherapy as younger patients and, except for being more susceptible to myelosuppression, do not have greater toxic effects.

The routine use of G-CSF as primary prophylaxis has been recommended in patients aged 70 or older who are treated with combination chemotherapy at standard dose intensity. Reducing the incidence, severity, and duration of chemotherapy-induced neutropenia with prophylactic G-CSF helps maintain standard chemotherapy dosing in elderly patients who may be particularly prone to myelotoxic effects. Facilitating the use of standard-dose chemotherapy in elderly patients can help them obtain the same benefits of treatment that younger patients obtain.

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