



Ettore "Ted" DeGrazia. *Red Bull*. Oil on canvas, 6" × 8". Courtesy of DeGrazia Foundation.

The factors associated with increased toxicity, and the current recommendations for different chemotherapeutic agents and treatment situations are reviewed.

Tolerance to Chemotherapy in Elderly Patients With Cancer

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Background: Due to demographic changes, the number of elderly people with cancer will increase in the next decades. In the past, elderly patients with cancer were often excluded from clinical trials. Chronological age has been considered a risk factor for increased toxicity and reduced tolerance to chemotherapy.

Methods: We present a review on toxicity of chemotherapy and factors associated with toxicity in elderly patients with cancer, and we discuss chemotherapeutic agents and treatment options in treating this patient population.

Results: Age is a risk factor for increased toxicity to chemotherapy and decreased tolerance. However, few trials have been reported with adjustment for age-associated changes such as impairment of functional status and increased comorbidity, which also show an independent association with increased toxicity. Published data may include several biases, such as referral and publication bias.

Conclusions: Decision making in elderly cancer patients should be based on the results of a geriatric assessment. Patients with few or no limitations should be treated as younger patients are treated. Data with a high level of evidence are unavailable for patients showing moderate or severe limitations in a geriatric assessment.

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Abbreviations used in this paper: NSCLC = non-small-cell lung cancer, NCI CTC = National Cancer Institute Common Toxicity Criteria, CrC = creatinine clearance, GFR = glomerular filtration rate, CMF = cyclophosphamide, methotrexate, and fluorouracil, KPS = Karnofsky performance status, ECOG = Eastern Cooperative Oncology Group, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone.

Introduction

Cancer is a major health problem in the United States and other developed countries. Currently, 1 in 4 deaths in the United States is due to cancer. Cancer has surpassed heart disease as the leading cause of death for those <85 years of age. About 30% of all cancer deaths occur in patients aged ≥ 80 years and older.¹ Approximately 60% of patients diagnosed with cancer are ≥ 65 years of age. This age-associated increase in incidence of malignant tumors, together with the expected rise in the number of elderly people due to demographic changes within the next few decades, will lead to a higher absolute number of elderly patients with cancer.²

Chemotherapy is a cornerstone of cancer treatment for many tumor entities. However, it is associated with severe side effects, even when standard-dose regimens are applied. Age is considered a risk factor for increased toxicity and poor tolerance to chemotherapy.

Ageing is a heterogeneous process. Within a group of elderly patients of the same chronological age, some are fit and healthy and others are vulnerable or frail. Basing decisions on the chronological age of a patient ignores many aspects of the clinical situation. In this article, we discuss the database concerning cytotoxic treatment of elderly cancer patients, the factors associated with increased toxicity, and the current recommendations for different chemotherapeutic agents and treatment situations.

Database Limitations

Clinical trials are a major source of information for clinical decision making. However, elderly patients with cancer are often excluded from clinical trials.³⁻⁵ This exclusion is the result of an arbitrary upper age limit in the inclusion criteria. Based on data of Hutchins et al,³ the National Cancer Institute decided not to support trials with an arbitrary upper age limit. Inclusion and exclusion criteria are bequeathed from trial to trial and are not based on a high level of evidence. Elderly patients are less often referred to cancer centers, which reduces their chances of being offered participation in clinical trials.⁶ Even when elderly patients are referred to cancer centers, they are offered participation in a clinical trial less often than younger patients are.⁷ Yet, when a clinical trial is offered to elderly patients with cancer, they are as likely to participate as younger patients. Elderly cancer patients do not appear to seek clinical trials as actively as younger patients, and few are informed about the availability of clinical trials.⁸ Avis et al⁹ identified factors associated with participation in clinical trials for the treatment of breast cancer. They found that age did not influence participation, but only 4% of the participants were ≥ 70

years of age. As a consequence, the available data are mainly limited to fit elderly patients. Furthermore, the factors leading to selection of elderly patients who are treated within a clinical trial are poorly understood, and only a few trials are designed specifically for compromised elderly patients.

Definition of an Elderly Patient

Most of the trials in the past used chronological age limits to define cancer patients as elderly; 65 or 70 years of age is a commonly used limit for patients with solid tumors. Whether age is in itself a justified criterion for the use of a geriatric assessment — or whether age will become irrelevant in describing a patient after inclusion of functional status, comorbidity, or other aged-related changes — needs to be proven in future trials.

Biganzoli et al¹⁰ surveyed 277 oncologists on their attitudes toward adjuvant chemotherapy in elderly women with breast cancer. Most oncologists considered women age 70 or greater as elderly. Hotta et al¹¹ identified 48 prospective elderly-specific clinical trials for advanced non-small-cell lung cancer (NSCLC). They studied the trial design and the characteristics of 2,648 elderly patients with advanced NSCLC who participated. The median number of patients treated per trial was 36. In 44 (92%) of the 48 trials, elderly patients were identified by their chronological age, and age ≥ 70 years was the most frequently used limit for inclusion. They concluded that elderly patients were simply defined using chronological age and that the quality of elderly-specific trials was generally poor, mainly because of their small sample size.

Future trials should classify patients as fit, compromised, or frail, based on the results of a comprehensive geriatric assessment (CGA). Chronological age should be used only as a cutoff level to routinely perform a CGA if a patient has reached 65, 70, or 75 years of age.

Toxicity of Chemotherapy in Elderly Cancer Patients

It is important to distinguish between objective and subjective toxicity. Objective toxicity is rated according to defined criteria, eg, the National Cancer Institute Common Toxicity Criteria (NCI CTC). Typical symptoms related to cancer treatment and changes of laboratory results are rated within a 5-point Likert scale according to predefined cutoff levels. Subjective toxicity refers to the extent to which a patient's well-being is influenced by objective toxicity.¹² Patients with the same level of objective toxicity can show significant differences regarding the degree to which they are compromised by a treatment.

Subjective/Objective Toxicity

A number of earlier reports concluded that elderly patients do not experience a higher rate of toxicity than younger patients if doses are adjusted to renal function.¹³⁻¹⁷ However, a selection and referral bias leading to accrual of only fit elderly patients cannot be excluded. Other data reported an age-dependent increase in toxicity in elderly cancer patients.^{18,19} Patients with aggressive malignant lymphoma and those with acute myeloid leukemia are at increased risk of toxicity.²⁰ Trials specifically designed for medically compromised patients are rare.

Maintaining or improving quality of life seems more important for elderly cancer patients than for younger cancer patients. However, if there is no alternative, 70% of elderly patients are willing to undertake “strong” chemotherapy.¹² The topic of subjective toxicity seems of great importance for decision making in elderly cancer patients and should receive more attention in future research.

Increased Toxicity

Two reasons for increased toxicity in elderly patients with cancer are an increased exposure to a drug (eg, by prolonged half-life due to decreased elimination or by impaired renal function) and changes in pharmacodynamics caused by increased vulnerability of organs with age. Figs 1, 2, and 3 reflect the need to consider age-adjusted organ function, drug-interaction, and comorbidity when deciding appropriate drugs and doses for treatment. Often no clear cutoff levels are available.

Advancing age is associated with changes in pharmacokinetic parameters. Changes in distribution, excretion, and resorption can produce an increase in toxicity in elderly patients with cancer.

Distribution: The volume of distribution changes; total body water is reduced to about 50% (instead of 60%), whereas total body fat increases. Other factors associated with a change of distribution are binding of drugs to erythrocytes (eg, anthracyclines, epipodophyllotoxins, and oxaliplatin) and proteins (especially albumin). Thus, hypoproteinemia and anemia can alter distribution of drugs.

Excretion: There are two major paths of drug excretion: by the kidneys or by the liver. Renal function decreases with advancing age. This continuous process starts early in the third decade of life and is caused by a loss of active nephrons. In elderly patients, creatinine value can be false normal due to a decrease in muscle mass. Therefore, in clinical practice, measured or estimated values for creatinine clearance (CrC) should be used. The lower the CrC value, the less this is reflected by a calculated glomerular filtration rate (GFR).²¹ Various equations are available, such as Cockcroft-Gault, Jelliffe, and Wright formulae.²²⁻²⁴ Compared with others for the calculation of GFR, the Wright for-

mula is the most accurate, most precise, and least biased in elderly patients with a GFR >50 mL/min compared to the gold standard of measurement of GFR by urine collection.²⁵

Resorption: The area of the intestinal mucosa decreases with age. However, to date, no unfavorable data for orally applied cytotoxic drugs due to a decreased resorption have been reported in elderly patients.

A number of age-related changes in pharmacodynamics have been identified. Older people with acute myelogenous leukemia are more likely to express the multidrug-resistance phenotype, which causes an efflux of drugs from leukemic blasts.²⁶ Further mecha-

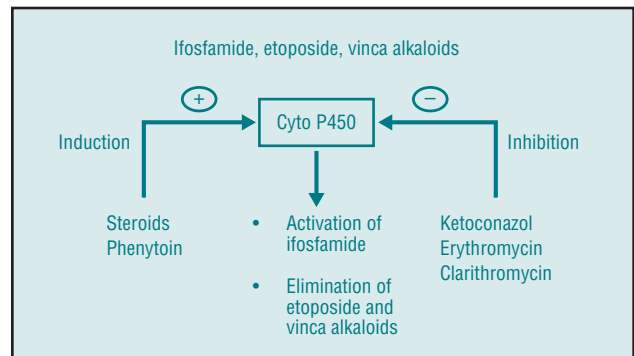


Fig 1. — Liver function and chemotherapy. This example portrays possible drug interactions involving ifosfamide, etoposide, and vinca alkaloids, thereby reflecting the need to consider age-adjusted organ function, drug interaction, and comorbidity in decision making.

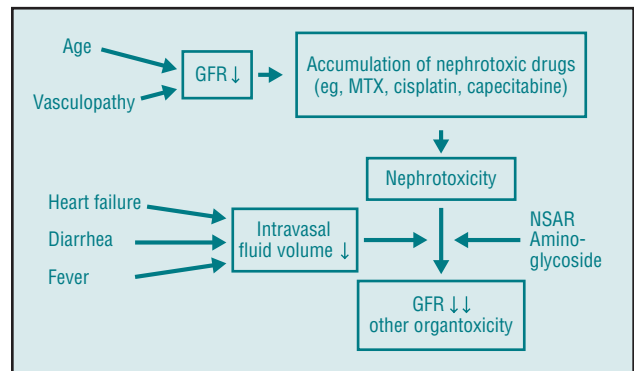


Fig 2. — Renal function, age, and chemotherapy.

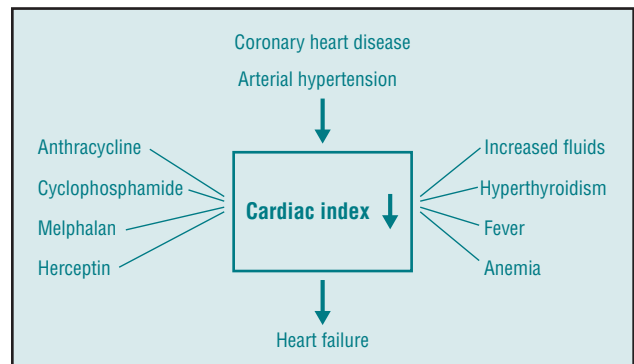


Fig 3. — Cardiac function and chemotherapy.

nisms that have been discussed in altered pharmacodynamics are reduced DNA-repair capacity, decreased apoptosis induction, higher rates of tumor hypoxia, and decreased cell proliferation.

Concept of Vulnerability

With the aging of the tissue, the time to recovery from damage is prolonged. This is true for the whole body in general and seems particularly relevant for specific tissues such as the bone marrow or the heart muscle. Methods to reliably measure vulnerability prior to treatment are largely not available.

Factors Associated With Increased Toxicity

The lack of evidence-based data and the fear of increased toxicity are the most relevant reasons for undertreatment of elderly patients with cancer. Therefore, it is important to realize which factors are associated with increased toxicity. In patients identified as being at increased risk for toxicity, the distinction between curative and palliative treatment approaches is relevant. In patients for whom definite cure is realistic, treatment risk reduction by intensification of supportive care can help to realize curative potential. In patients with a noncurative approach and increased risk of toxicity, dose reduction is justified and can help to minimize side effects.

Dranitsaris et al²⁷ developed a multivariable logistic regression model to predict which patient with breast cancer receiving adjuvant chemotherapy will experience anemia. The risk of anemia showed a negative correlation with the pretreatment hemoglobin concentrations, and this risk was reduced with successive chemotherapy cycles. The risk was also predicted by a platelet cell count of $\leq 200 \times 10^9/L$ before chemotherapy, age ≥ 65 years, type and intensity of chemotherapy, and use of prophylactic antibiotics.

Within an analysis of variance (ANOVA) model, Rogatko et al²⁸ identified 17 pretreatment factors, including performance status, alkaline phosphatase, total bilirubin, serum creatinine, and tobacco use, as significant predictors of toxicity in early-phase clinical trials. Unexpectedly, dose was not always a predictor of toxicity. Even for values within the normal range, serum bilirubin and alkaline phosphatase predicted toxicity after treatment with docetaxel, and alkaline phosphatase predicted toxicity after treatment with irinotecan. Median age was 62 (range 27–84 years).

Within a multivariate analysis, Aslani et al²⁹ identified the prechemotherapy nitrogen index (total body nitrogen expressed as a percentage of age-, gender-, and height-matched healthy patients) of <0.89 vs >0.89 as best predictor of neutropenia (index of absolute neutrophil count nadir of $<1.0 \times 10^9/L$) in women aged 26 to 77 years treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) for breast cancer.

Hargis et al³⁰ studied 847 patients receiving cisplatin-based chemotherapy on Cancer and Leukemia Group B (CALGB) protocols. Both measurement of CrC by 24-hour urine collection (CrC) and the patient's age independently provided predictive information concerning cisplatin genitourinary toxicity within a logistic regression model. Estimated CrC and serum creatinine level were inferior. Performance status was included in the analysis. Estimated CrC proved to be a poor predictor of a measured CrC value of <75 mL/min, leading to a misclassification of nearly half of the patients to a "low-risk" subgroup.

Mileshkin et al³¹ reported an increased but manageable cardiovascular toxicity during high-dose chemotherapy and autologous peripheral blood stem cell transplantation for patients aged ≥ 60 years. They analyzed the data of 40 patients with a median age of 65 years (range 60–76 years) of whom 22 were diagnosed with multiple myeloma and 18 with non-Hodgkin's lymphoma. Toxicities were similar with the exception of cardiac toxicity, which was significantly higher in patients aged ≥ 60 years vs controls (50% grade 3 vs 10%; $P < .0001$). Atrial fibrillation was the most frequent cardiovascular toxicity.

In patients with metastatic colorectal cancer, Steinberg et al³² could not find a clinical pretreatment factor associated with toxicity. The variables used for analysis of toxicity were age, treatment center, sex, tumor response, performance status, number of courses, serum glutamic oxalacetic transaminase (SGOT) level, and alkaline phosphatase and albumin measurements.

In conclusion, age is a factor associated with toxicity. Myelosuppression³³ mucositis,³⁴ cardiac dysfunction,³⁵ and central neurotoxicity³⁶ are higher in elderly patients with cancer, but not peripheral neurotoxicity.³⁷ However, most of the trials did not include a geriatric assessment to control for age-associated changes in addition to chronological age as reasons for increased toxicity.

The ability to use pretreatment factors to determine which elderly patients are at greater risk of toxicity would be valuable. Future trials need to determine regimen- and patient-specific prognostic factors in elderly cancer patients.³⁸

Geriatric assessment adds additional relevant information to Karnofsky performance status (KPS) or Eastern Cooperative Oncology Group (ECOG) status concerning survival^{39,40} and quality of life.⁴⁰ The first data regarding toxicity are being reported.

Frasci et al⁴¹ identified comorbidity as the best predictor for early termination of chemotherapy in patients ≥ 70 years of age who were treated for advanced NSCLC. Freyer et al³⁹ treated 83 patients aged ≥ 70 with advanced cancer of the ovary with chemotherapy consisting of carboplatin (area under the curve [AUC] 5) and cyclophosphamide 600 mg/m². They included a geriatric assessment prior to the start of

chemotherapy. Independent predictors of severe toxicity, defined as febrile neutropenia, neutropenia grade IV, early termination of treatment, and rehospitalization of more than 7 days, were depression ($P=.006$), dependence in activities of daily living (ADL) or instrumental ADL (IADL) ($P=.048$), and ECOG performance status >2 ($P=.026$).³⁹

These analyses show that a geriatric assessment can identify elderly patients with increased risk of toxicity. More data regarding different types of tumors and different treatment schedules are necessary.

In addition to age-related factors, individual genetic profile is increasingly being identified as a major risk factor for toxicity and response to chemotherapy. These factors will need to be considered when designing future prospective trials.⁴²

Is Toxicity Always a Bad Thing?

Often response and toxicity of chemotherapy are dose related. Therefore, toxicity and efficacy are related and could possibly allow prediction of response to treatment. Is drug-induced toxicity a good predictor of response to neoadjuvant chemotherapy in patients with breast cancer? This question was investigated by Chintamani et al,⁴³ who found that toxicity is a strong predictor of response, at least in the setting of neoadjuvant chemotherapy of patients with breast cancer.

Di Maio et al⁴⁴ analyzed data for 1,265 patients who received chemotherapy in three different randomized trials. Within a landmark analysis, they investigated a subpopulation of 436 patients who received all six planned chemotherapy cycles and who were alive 180 days after randomization. They assessed whether hematologic toxicity could be a biological measure of drug activity and therefore an indirect marker of efficacy. Hazard ratios of death were 0.65 (0.46–0.93) for patients with severe neutropenia and 0.74 (0.56–0.98) for those with mild neutropenia. Median survival after 180 days was 31.4 weeks (95% confidence interval [CI] 25.7–39.6) for patients without neutropenia, 42.0 weeks (95% CI 32.7–59.7) for patients with severe neutropenia, and 43.7 weeks (36.6–66.0) for those with mild neutropenia (severe vs mild vs no neutropenia ($P=.0118$)).⁴⁴ Klimm et al⁴⁵ analyzed the influence of sex on toxicity in 4,626 patients with Hodgkin's lymphoma of all prognostic risk groups enrolled onto the multicenter studies HD4 to HD9 of the German Hodgkin's Study Group. More acute chemotherapy-related hematotoxicity occurred in women, especially more severe leucopenia (World Health Organization [WHO] grade 3/4, 69.9% women and 55.2% men; $P<.0001$). However, this did not translate into more infections. Women had similar response rates but fewer relapses and

deaths. This led to a significantly better freedom from treatment failure (FFTF) at 66 months — 81% women (95% CI 79%–82%) and 74% men (95% CI 72%–76%). Severe leucopenia during chemotherapy was strongly associated with better FFTF for both men and women. In conclusion, several trials report toxicity as surrogate of efficacy.

Selected Chemotherapeutic Agents

This section discusses currently available information on age-related toxicity of selected cytotoxic agents. While older patients who enter trials are often not representative of the general elderly population, the published data from these trials are the only source of information available.

Cisplatin

Toxicity of cisplatin is comparatively well studied in elderly patients.⁴⁶ In their study of 400 patients, de Jongh et al⁴⁷ analyzed toxicity of weekly high-dose (70 to 85 mg/m²) cisplatin-based chemotherapy. Leukopenia was seen more frequently in combination chemotherapy with etoposide, whereas thrombocytopenia correlated with cisplatin dose and prior (platinum-based) chemotherapy. Risk factors for nephrotoxicity were older age, female, smoking, hypoalbuminemia, and paclitaxel coadministration. Neurotoxicity greater than grade 1 (in 11% of patients) was associated with prior chemotherapy and paclitaxel coadministration. Symptomatic hearing loss occurred in 15%, with anemia as a predisposing factor.

Docetaxel

In a prospective evaluation of single-agent docetaxel for treatment of cancer in patients >65 years of age compared with those <65 , no difference could be found in pharmacokinetics.⁴⁸ However, the older age group had an increased risk for grade 4 neutropenia (65% vs 30%) and a higher rate of febrile neutropenia (16% vs 0%). Differences were due to age-related changes in pharmacodynamics.

The comparison of pharmacokinetics and pharmacodynamics of a combination of docetaxel and cisplatin was in line with this result. The pharmacokinetics of docetaxel and cisplatin were the same in elderly patients (age ≥ 75 years) and nonelderly patients (age <75 years), but the elderly experienced a higher rate of neutropenia.⁴⁹ The conclusion of a variety of phase II trials on pharmacokinetics of docetaxel in elderly cancer patients was that age-related differences in clearance are negligible compared to differences in clearance due to interpatient variability in drug metabolism.⁵⁰ No geriatric assessment was performed within these trials.

Infusional 5-Fluorouracil

To determine the time course of toxicity and to analyze factors predicting toxicity relating to 5-FU administration, Tebbutt et al⁵¹ studied 1,470 patients with gastrointestinal cancers receiving 5-FU in a protracted venous infusion. Initial development of stomatitis occurred more rapidly than diarrhea or palmar-plantar erythema (PPE). Female sex, advanced age, elevated alanine transaminase and urea values, and early NCI CTC grade 1 PPE were significant independent prognostic factors for the development of stomatitis grade 2 or worse ($P<.01$). Early grade 1 diarrhea predicted more severe diarrhea in the further course of the treatment ($P<.01$). Older female patients with good performance status and impaired liver and renal function who developed early grade 1 PPE alone or in combination with diarrhea showed the highest risk of subsequent development of grade 2 or worse PPE or stomatitis during treatment with protracted venous infusion 5-FU.

Capecitabine

Age and female sex are risk factors for increased toxicity to 5-FU⁵² or capecitabine. As 5-FU and capecitabine are eliminated by renal function, dose adjustment is necessary for patients with impaired renal function. Cassidy et al⁵³ did not find an age-related increase in toxicity when controlling for renal function. Ho et al⁵⁴ conducted a population-based study to assess temporal trends in the use of systemic agents in patients ≥ 70 years of age with metastatic colorectal cancer prior to (cohort A) and after (cohort B) the approval of capecitabine. In cohort A, 39% of patients were treated with chemotherapy, and 46% of patients in cohort B received chemotherapy. The most common first-line chemotherapy regimens were single-agent 5-FU (in 66% in cohort A) and capecitabine (in 47% in cohort B). Capecitabine was the favored palliative regimen, and it was well tolerated. Both treatment cohorts demonstrated similar survival. No geriatric assessment was performed within this trial.

Fludarabine

Martell et al⁵⁵ analyzed toxicity of fludarabine 15 mg/m² daily for 5 days every 28 days in 192 previously untreated patients with chronic lymphocytic leukemia. Median age was 64 years (range 37–87 years), and the median estimated CrC was 62 mL/min (range 27–162 mL/min). Age was not associated with first-cycle hematologic toxicity or infection. However, a strong association between toxicity and estimated CrC was observed.

Gefitinib

Hotta et al⁵⁶ retrospectively analyzed toxicity, response, and survival of gefitinib in patients ≥ 75 years of age compared with patients < 75 years of age. In the older group,

adverse events were generally mild to moderate, and grade 3–4 adverse events were observed in 8 patients (9%). The objective response rate was 17% vs 21% for elderly vs nonelderly, respectively, and the median survival time (7.6 vs 9.3 months) was also comparable.

Imatinib

Imatinib is equally effective in elderly patients with chronic myeloid leukemia, but treatment is associated with a higher rate of myelosuppression, especially thrombocytopenia. Patients being treated with imatinib who are receiving levothyroxine replacement have a high likelihood of increased hypothyroidism. An adaptation of the levothyroxine replacement might be necessary.⁵⁷

Irinotecan

The single-agent irinotecan schedule and the FOLFIRI combination (folinic acid, 5-FU, and irinotecan) are active regimens with increased yet manageable toxicity as first-line treatment in patients > 70 years of age.^{58,59}

Methotrexate

Jahnke et al⁶⁰ evaluated toxicity related to high-dose methotrexate (MTX) with particular regard to age in patients with primary central nervous system lymphoma. Unless a reduced dose was required due to a decreased GFR, patients received 4 g/m² high-dose MTX followed by leucovorin rescue. A total of 154 patients (89 greater than age 61 years and 21 greater than age 70; median age = 61 years) received 619 high-dose MTX cycles. Toxicity was generally mild, with WHO grade ≥ 3 occurring in less than 10%. Differences in incidence and severity of toxicity did not reach statistical significance between patients > 60 years and those ≤ 60 years. The same was true for therapy termination due to MTX toxicity and for delayed serum MTX clearance. Dose reduction differed significantly between patients ≤ 60 years (18%) and > 60 years (44%; $P=.001$). The authors concluded that high-dose MTX is a safe treatment for patients with primary central nervous system lymphoma regardless of age, as long as dose reductions are performed according to calculated GFR before each treatment cycle.

Oxaliplatin

Oxaliplatin is safe and effective in elderly patients as a single agent and in combination therapy, eg, with capecitabine.^{61,62} Merkel et al⁶³ did not identify age as a risk factor for oxaliplatin-associated nonhematologic toxicity in patients treated with chronomodulated oxaliplatin and 5-FU and sodium folinate combination chemotherapy for advanced cancer of the gastrointestinal tract. Goldberg et al⁶⁴ recently performed a pooled analysis of safety and efficacy of oxaliplatin plus 5-FU/leucovorin (FOLFOX4) administered

bimonthly in elderly patients with colorectal cancer. The analysis included 3,742 patients with colorectal cancer (614 patients ≥ 70 years of age) from four clinical trials. Older patients experienced significantly higher grade ≥ 3 hematologic toxicity (neutropenia [43% vs 49%; $P=.04$] and thrombocytopenia [2% vs 5%; $P=.04$]). Older age was not associated with increased rates of severe neurologic adverse events, diarrhea, nausea/vomiting, infection, overall incidence of grade ≥ 3 toxicity (63% vs 67%; $P=.15$), or 60-day mortality (1.1% vs 2.3%; $P=.20$). The relative benefit of patients receiving FOLFOX4 vs controls did not differ by age for response rate, progression, or recurrence free-survival (hazard ratio [HR] 0.70 for FOLFOX4 vs control for age <70 years, 0.65 for age ≥ 70 years; $P=.42$), or overall survival (HR 0.77 for age <70 years, 0.82 for age ≥ 70 ; $P=.79$). However, among the 614 patients in the ≥ 70 age group, only 15 (1.1%) were ≥ 80 years of age.

Paclitaxel

Investigators for the Cancer and Leukemia Group B conducted a trial (CALGB 9762) to assess the pharmacokinetics and toxicity profile of paclitaxel in relation to patient age.⁶⁵ They found a significant increase in concentration vs time (AUC) and a decrease in total body clearance of paclitaxel in the cohort of patients aged ≥ 75 years compared with those aged 55 to 64 and 65 to 74 years. This translated in a higher rate of grade 3–4 neutropenia of 49% compared to 22% and 35%, respectively. The increased neutropenia did not result in adverse clinical outcomes (eg, hospitalization due to toxicity, need for intravenous antibiotics, or fever).

Smorenburg et al⁶⁶ measured the clearance of unbound paclitaxel, which was more closely related to toxicity than clearance of total drug. They found a 50% decrease in drug clearance in breast cancer patients aged ≥ 70 years compared to younger women.

In conclusion, age alone does not appear to warrant a mandatory reduction in primary dose. Weekly regimens seem especially reasonable for elderly patients; these regimens show reduced hematologic toxicity and at least comparable efficacy compared with 3-week regimens.

Thalidomide

Mileshkin et al⁶⁷ reported the data of 75 patients with a median age of 64 years (range 36–83 years) and relapsed or refractory multiple myeloma treated with thalidomide. The only predictor for response was age ≤ 65 years (38% vs 17%; $P=.043$). Multivariate analysis for overall survival showed that age >65 years (9.2 months vs >26 months; $P=.011$), raised serum lactate dehydrogenase ($P=.002$), and raised serum creatinine ($P=.007$) predicted inferior outcome. Predictors of toxicity were not reported.

Topotecan

Garst et al⁶⁸ investigated the safety and efficacy of topotecan in older patients with relapsed small-cell lung cancer (SCLC) within a retrospective analysis of 5 large topotecan trials. Patients aged ≥ 65 years were compared to patients <65 years. In all 5 trials, patients received topotecan 1.5 mg/m² per day as a 30-minute intravenous infusion on days 1 through 5 of a 21-day cycle. Topotecan was similarly well tolerated in both age groups, with generally manageable hematologic toxicity. The incidence, duration, and onset of severe hematologic toxicities did not vary significantly with age. Grade 4 neutropenia was reported in 72% of the younger patients and in 77% of the older patients. Grade 4 leukopenia was reported in 32% of the younger patients and in 31% of the older patients. Grade 4 thrombocytopenia was less common in younger patients. Nonhematologic toxicities, median time to progression, and overall survival were comparable between groups.

Molecularly Targeted Agents

Townsend et al⁶⁹ analyzed the frequency of adverse events in patients treated with molecularly targeted agents in two different age groups, <65 years and ≥ 65 years. A total of 401 patients from 19 different studies who received 1,252 treatment cycles were analyzed. The authors concluded that older patients seem to tolerate molecularly targeted therapies either alone or in combination with chemotherapy as well as younger patients. Thus, age alone should not be a barrier to the administration of targeted agents.

Special Diseases and Treatment Situations

Breast Cancer

A difficult clinical decision in treating elderly women with breast cancer involves whether to use adjuvant chemotherapy. Most women at risk for recurrence will not experience an advantage with chemotherapy. The number of patients needed to treat to prevent one breast cancer-associated death increases with age due to the higher risk of death that is not related to breast cancer in this age group. Yet, most treated women will experience some kind of toxicity. Data on the treatment of women aged >70 years are limited.⁷⁰ The recommendation of the 9th St. Gallen Conference did not include any decision based on patient age.⁷¹

Several reports have been published with recommendations on the treatment of elderly women with advanced breast cancer.^{72–74} Brunello et al⁷⁵ reviewed the treatment of 260 elderly patients (mean age 75.6 years, range 70–97 years) with histologic diagnosis of early breast cancer. Conserving surgery was performed

in 54.6% of patients, nodal dissection in 84.6%, and sentinel node biopsy in 5.8%. Tumor size was pT2-3 in 45.4% of patients, grading was G3 in 27.3%, hormonal status was negative in 16.9%, and lymph nodes were involved (N+) in 36.1%. Of 188 patients presenting with one or more risk factors (pT2-3, G3, N+, and negative hormonal status), 48.4% were not offered adjuvant chemotherapy (compared with 7.2% in the control group), 39.8% of these patients had nodal involvement (compared with 4.3% of controls, $P < .0001$), and hormonal status was negative in 22.7% (compared with 0.0% of controls, $P = .0002$). In patients receiving non-anthracycline-based chemotherapy, 20 elderly patients (25.9%) were unable to complete the planned number of cycles (compared with 4.7% of controls, $P = .0002$). The 2-year disease-free survival was significantly decreased in N+ patients with negative hormonal status compared with the other elderly patients (49.9% compared with 90.9%, $P = .0006$).⁷⁵

Studies on the tolerability and efficacy of adjuvant chemotherapy for older women are limited. Crivellari et al¹⁹ treated postmenopausal women with operable N+ breast cancer either with tamoxifen alone for 5 years or with tamoxifen plus 3 consecutive cycles of classic CMF. Efficacy and toxicity data were analyzed separately for the two age groups. Women ≥ 65 years of age ($n = 76$) had higher grades of toxicity compared with women < 65 years of age ($n = 223$) ($P = .004$). More women in the older age group experienced grade 3 toxicity of any type compared with younger women (17% vs 7%), including grade 3 hematologic toxicity (9% vs 5%) and grade 3 mucosal toxicity (4% vs 1%). Older patients received less than their expected dose of CMF compared with younger postmenopausal women ($P = .0008$). The subjective burden of treatment based on quality-of-life measures was similar in younger and older patients. In older patients, the 5-year disease-free survival rates were 63% for CMF plus tamoxifen and 61% for tamoxifen alone (HR 1.00; 95% CI 0.65-1.52; $P = .99$). In younger patients, the corresponding 5-year rates were 61% and 53% (HR 0.70; 95% CI 0.53-0.91; $P = .008$). In a retrospective analysis, Hurria et al⁷⁶ reported the relationship of age to toxicity in adjuvant treatment for breast cancer. Their study included 132 patients aged ≥ 65 years with primary invasive breast cancer who received one of three different chemotherapy protocols: CMF, doxorubicin and cyclophosphamide (AC), or AC plus paclitaxel or docetaxel (AT-T). Mean age was 70 years, and comorbidity as measured by the Charlson comorbidity index was low: 83% of patients had a score of 0, 12% had a score of 1, and 5% had a score of 2. Patients who received anthracycline-based regimens were more likely to experience grade 3 or 4 toxicity ($P = .01$), required hospitalization more often ($P < .001$), and/or developed febrile neutropenia more frequently ($P < .001$). Treatment delays due to

myelosuppression were more common in patients receiving CMF compared to the other regimens ($P < .001$). The type of chemotherapy regimen (anthracycline compared to CMF) was a better predictor for toxicity than increased age or comorbidity score.

A multivariate analysis by Muss et al⁷⁷ showed that smaller tumor size, fewer positive lymph nodes, more chemotherapy, and tamoxifen use were all significantly related to longer disease-free and overall survival ($P < .001$). There was no association between age and disease-free survival. Overall survival was significantly worse for patients aged ≥ 65 years ($P < .001$) because of death from causes other than breast cancer. Thirty-three deaths (0.5% of all patients) were attributed to treatment, and older women had higher treatment-related mortality. Older and younger women derived similar reduction in breast cancer mortality and recurrence from regimens containing more chemotherapy, implying a dose-efficacy relationship in this situation.

Colorectal Cancer

The decision process on adjuvant chemotherapy in colon cancer differs from that of breast cancer. Eighty percent of recurrences arise within the first 2 to 3 years after resection. The number needed to treat is lower than in breast cancer. Randomized data that include a substantial group of patients 80 years of age are not available, but the available data on 5-FU imply a benefit on reduction of recurrence rate independent of age.⁷⁸ Population-based analyses reported an undertreatment of elderly patients.^{79,80} Treatment recommendations for patients with metastatic colorectal cancer have been reported elsewhere.⁸¹

In their study of adjuvant chemotherapy in patients with stage II or III carcinoma of the colon, Sargent et al⁸² analyzed the treatment results and toxicity in 3,351 patients treated within seven randomized phase III trials with postoperative 5-FU plus leucovorin (five trials) or 5-FU plus levamisole (two trials). The most common toxicities were nausea or vomiting, diarrhea, stomatitis, and leukopenia. Adjuvant treatment had a significant positive effect on both overall survival and time to tumor recurrence. The 5-year overall survival rate was 71% for those who received adjuvant therapy compared with 64% for the untreated group. No significant interaction was observed between age and the efficacy of treatment. Those aged > 70 years did not experience a higher incidence of toxic effects except for leukopenia in one study. Fata et al⁸³ reviewed all patients in their tumor registry with stage II and III adenocarcinoma of the colon who underwent potentially curative resection for their disease. A group of 120 patients underwent complete resection and received 5-FU-based adjuvant chemotherapy. In a Cox regression model, age was not a predictor of disease-free survival ($P = .633$) or overall survival ($P = .900$). Furthermore, there was no correla-

tion between toxicity and age. Iwashyna et al⁸⁴ used the data of a prospective, nonrandomized, population-based cohort study of 3,357 elderly Medicare beneficiaries who had undergone resection of stage III colon cancer. At 5 years, 52.7% of those treated (95% CI 49.6%–55.6%) and 40.7% of the matched untreated controls (95% CI 38.1%–43.4%) were alive. The authors concluded that the survival benefit of adjuvant 5-FU demonstrated in participants of randomized controlled trials is also evident in elderly patients in the community. Importantly, the survival benefit did not diminish with increasing patient age. Sunderarajan et al⁷⁸ analyzed data of 4,768 patients >65 years of age with stage III colon cancer. Only 32% of patients aged 80 to 84 years and only 10% of patients aged >85 years in whom adjuvant 5-FU-based chemotherapy would have been indicated received treatment. The efficacy of chemotherapy did not differ according to age. Neugut et al⁸⁵ analyzed the effect of duration of adjuvant chemotherapy in stage III colon cancer within the Surveillance, Epidemiology, and End Results (SEER) database. Among 1,722 patients who received 1 to 7 months of 5-FU-based chemotherapy, factors associated with receiving less than 5 months of treatment included older age, being unmarried, and prevalence of comorbid conditions. Among the 1,579 patients who survived 8 months or more, those who received 5 to 7 months of treatment (1,091 patients, 69.1%) had lower overall mortality (HR 0.59; 95% CI 0.49–0.71) and colon cancer-specific mortality (HR 0.53; 95% CI 0.43–0.66) than those patients who received inadequate therapy with only 1 to 4 months of treatment. André et al⁸⁶ included patients up to the age of 75 years in the Multicenter International Study of Oxaliplatin/5-FU-LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial. A subgroup analysis reported decreased effectiveness of the FOLFOX4 regimen (oxaliplatin, leucovorin, and 5-FU) in patients aged >65 years compared to younger patients. Differences in toxicity were not reported. The X-ACT trial⁸⁷ (capecitabine vs bolus 5-FU/leucovorin as adjuvant therapy for colon cancer) revealed a favorable toxicity profile for capecitabine compared to bolus 5-FU/leucovorin regimen in patients with stage III colon cancer. No differences in toxicity according to age were seen. A separate analysis of efficacy of treatment has not been reported.

Lung Cancer

Systematic reviews on the treatment of elderly patients with lung cancer have been published recently.⁸⁸⁻⁹⁰ This section focuses on aspects of treatment and toxicity reported in recent literature.

Small-Cell Lung Cancer

Ludbrook et al⁹¹ retrospectively analyzed 174 patients with limited-stage SCLC. Patient and treatment charac-

teristics, disease response, relapse, and survival were compared among three age cohorts — <65 years (n = 55, 32%), 65 to 74 years (n = 76, 44%), and ≥75 years (n = 43, 25%) — and according to Charlson comorbidity scores 0, 1, and ≥2. Patient factors that significantly differed with age were functional status classified by Eastern Cooperative Oncology Group performance status and the number of comorbidities. Combined modality chemoradiotherapy was given in 86%, 66%, and 40% of patients ages <65 years, 65 to 74 years, and ≥75 years, respectively ($P < .0001$). The use of thoracic irradiation was comparable among the age cohorts ($P > .05$), but incidence of the use of chemotherapy varied significantly, with less intensive regimens, fewer cycles, and lower total doses being more common with advancing age ($P < .05$). Prophylactic cranial irradiation was performed in 41 patients, only 3 of whom were >70 years. Overall response rate to primary treatment significantly decreased with advancing age: 91% in patients <65 years, 79% in those aged 65–74 years, and 74% in patients aged ≥75 years ($P = .014$). Treatment toxicity and relapse patterns were similar across all age cohorts. Overall 2-year survival rates were significantly lower with advancing age: 37%, 22%, and 19% ($P = .003$), with corresponding median survivals of 17, 12, and 7 months among patients aged <65, 65 to 74, and ≥75 years, respectively. On multivariate analysis, age and Charlson comorbidity scores were not significantly associated with treatment response and survival. Independent prognostic factors favorably associated with survival were good performance status, normal lactate dehydrogenase, absence of pleural effusion, and ≥4 cycles of chemotherapy, again implying a dose-efficacy relationship independent of patient age.

Non-Small-Cell Lung Cancer

On the basis of current evidence, an expert panel recommended that single-agent chemotherapy should be the standard arm against which experimental treatments are tested in future randomized trials that include patients with advanced NSCLC, performance status ≥2, and/or advanced age.⁹²

The number of patients with a performance status of ≥2 increases with age. When performance status is included into decision making, the question remains whether patient age should still be regarded an independent factor. Baka et al⁹³ compared two treatment schedules of gemcitabine in 174 patients with NSCLC stage IIIb and IV and impaired KPS (≤70). Primary objectives were changes from baseline KPS and palliation of symptoms. Patients were randomly assigned to receive gemcitabine 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle (3w4) or gemcitabine 1,500 mg/m² on days 1 and 8 of a 21-day cycle (2w3). There was significant early attrition due to disease progression; only 61.5% of patients were alive at 2 months. KPS signifi-

cantly improved from baseline to precycle 3 in both arms, with a trend in favor of the 3w4 regimen for duration and faster onset of improvement. Eight of 17 quality-of-life variables assessed showed an improvement of more than 10%. Response rate, survival, and duration were similar in both arms. Hesketh et al⁹⁴ reported treatment results of patients aged >80 years with advanced NSCLC treated within two trials, and they compared the results to patients aged 70 to 79 years. The disease control rate (partial response + stable response) was encouraging (53%), and toxicity was comparable to the younger patient group. Survival was worse in the group of patients who were more than 80 years of age, with a performance status of 0-1 with 7 months, compared to fit younger patients (11 months) but identical to younger patients with a poor performance status (≥ 2). Maione et al⁹⁵ analyzed the data from the Multicenter Italian Lung Cancer in the Elderly Study (MILES) trial to find potential predictors of survival. Pretreatment global quality of life and IADL scores, but not ADL and comorbidity, showed significant prognostic value for survival of elderly patients with advanced NSCLC who were treated with chemotherapy. Results for toxicity were not reported. The MILES data did not find a superior efficacy of gemcitabine plus vinorelbine compared to either of the two agents used alone.⁹⁶ Belani et al⁹⁷ compared the incidence of NCI CTC grade 3-4 toxicity between subgroups of younger patients and elderly patients treated with docetaxel plus platinum combinations vs vinorelbine plus cisplatin for first-line treatment of advanced NSCLC. Elderly patients showed a moderate increase in asthenia, infection, and pulmonary toxicities across both treatment arms. Diarrhea and sensory neurotoxicity were specifically more frequent in cisplatin-containing arms. Most hematologic toxicities occurred with similar incidences in elderly and younger patients, although neutropenia was slightly more frequent in elderly patients. Schild et al⁹⁸ reported equal benefit but significantly more grade 4 toxicity for fit elderly patients with stage III NSCLC who received combined modality treatment. Grade 4 toxicity occurred in 62% of patients younger than age 70 years compared with 81% of older patients ($P=.007$). Grade 4 hematologic toxicity occurred in 56% of the younger patients compared with 78% of older patients ($P=.003$). Grade 4 pneumonitis occurred in 1% of the younger patients compared with 6% of the older patients ($P=.02$).

Prostate Cancer

In patients with hormone-refractory prostate cancer, a 3-weekly docetaxel chemotherapy regimen is regarded as standard treatment for fit patients. Subgroup analysis did not find differences for patients aged <65 years, 65 to 74 years, and >74 years and for those with a KPS

>70 and <80.⁹⁹ However, a possible selection process in the trial cannot be ruled out.

Advanced Oesophago-Gastric Cancer

Trumper et al¹⁰⁰ analyzed data from patients enrolled in three randomized, controlled trials assessing 5-FU-based combination chemotherapy in advanced oesophago-gastric cancer. Of the 1,080 patients enrolled, 257 (23.8%) were aged ≥ 70 years. There were no significant differences in the incidence of grades 3/4 toxicity between the two cohorts. Objective and symptomatic response rates as well as failure-free and overall survival were not significantly different. In a multivariate analysis, independent prognostic factors for survival were performance status and locally advanced disease but not age. Patients aged ≥ 70 years with oesophago-gastric cancer obtained similar benefit without increased toxicities from palliative chemotherapy with respect to symptomatic response, tumor regression, and survival.

Ovarian Cancer

Gronlund et al¹⁰¹ compared the toxicity and efficacy of intravenous second-line treatment for elderly (>65 years) and younger patients with epithelial ovarian carcinoma. Of 286 consecutive patients with primary epithelial ovarian carcinoma, 102 received second-line treatment with either topotecan 1.0 mg/m² per day for 5 days every 3 weeks or paclitaxel 175 mg/m² and carboplatin (AUC 5) every 3 weeks. In a multivariate Cox analysis, independent significant factors for overall survival included performance status at the time of first-line treatment (0 vs 1-2; $P=.013$; HR 2.12), performance status at the time of second-line treatment (0 vs 1-2; $P=.004$; HR 2.47), and response to second-line treatment (complete and partial vs no change and progressive disease; $P<.001$; HR 4.38). Age (<65 years vs >65 years) yielded no independent information ($P=.90$). No differences in the rate of treatment delay, neutropenia grade 4, thrombocytopenia grade 3-4, or hypersensitivity reaction to either cytostatic agent were observed between the groups ($P>.05$).

Hodgkin's Disease

Engert et al³³ performed a retrospective analysis of the German Hodgkin's Study Group database to determine clinical risk factors, course of treatment, and outcome in elderly patients compared to younger adults. Among 4,251 patients included in the study, 372 (8.8%) were ≥ 60 years of age. Acute toxicity during chemotherapy was generally higher in the elderly patients, particularly severe infections (grade 3 or 4; 15% vs 6%), which correlated with an increased incidence of leukopenia in elderly patients (grade 4; 8% vs 23%). As a result, significantly fewer elderly patients received the intended dose of chemotherapy (75% vs

91%). The survival analysis showed a markedly poorer treatment outcome after 5 years for elderly patients (65% vs 90%).

Malignant Lymphoma

In a landmark trial in the treatment of elderly patients with diffuse large-cell lymphoma by the Groupe d'Etude des Lymphomes de l'Adulte, standard CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) was compared to CHOP plus rituximab in patients aged 60 to 80 years. The addition of rituximab to the CHOP regimen increased the complete response rate and prolonged event-free and overall survival in elderly patients with diffuse large B-cell lymphoma and did not result in a clinically significant increase in toxicity.¹⁰² In a report from the German High-Grade Non-Hodgkin's Lymphoma Study Group of patients aged 61 to 75 years with aggressive non-Hodgkin's lymphoma, the toxicity of CHOP-14 (given every 2 weeks) and CHOP-21 (given every 3 weeks) was similar to that seen in patients <60 years.¹⁰³ However, the addition of etoposide (CHOEP-21 and particularly CHOEP-14) was more toxic. The dose-dense CHOP protocol was more effective than the classic CHOP version. The RICOVER-60 trial¹⁰⁴ (rituximab with CHOP for patients aged 61 to 80 years with diffuse large B-cell lymphoma stage I-IV) evaluated CHOP-14 plus rituximab vs the dose-dense CHOP-14 protocol. The trial was stopped early due to superiority of the CHOP-14 plus rituximab arm.

Febrile Neutropenia

Kuderer et al¹⁰⁵ analyzed factors associated with in-hospital mortality and hospital length of stay with febrile neutropenia in 41,779 adult cancer patients. Overall, in-hospital mortality was 9.5%. Patients with no major comorbidities had a 2.6% risk of mortality. In patients with one major comorbidity, the risk of mortality was 10.3%, whereas those with more than one major comorbidity had a $\geq 21.4\%$ risk. Independent major risk factors for inpatient mortality included invasive fungal infections, gram-negative sepsis, pneumonia and other lung disease, and cerebrovascular, renal, and liver disease. Age was not an independent factor. Main predictors for hospital length of stay of 10 days or longer included leukemia, invasive fungal infections, other types of infection, and several comorbid conditions.

Colony-Stimulating Factors of Granulopoiesis

Hematotoxicity is more common in elderly patients. Chemotherapy is associated with a higher rate of infection, more hospitalizations, and a higher mortality in older patients.¹⁰⁶ Lyman et al¹⁰⁷ analyzed factors associated with failure to achieve dose intensity of chemotherapy in aggressive non-Hodgkin's lymphoma. Dose reductions of $\geq 15\%$ occurred in 40% of patients, and treatment delays of ≥ 7 days occurred in 24% of

patients, resulting in 53% of patients receiving a relative dose intensity (RDI) of less than 85% of the minimum 6 cycles. Reduced RDI was more prevalent in older patients, with 60% of patients greater than 60 years of age receiving an RDI of less than 85% compared to 44% in those younger than 60 years of age. Multivariate analysis identified several independent predictors for reduced RDI, including age >60 years, advanced disease stage, poor performance status (ECOG ≥ 2), and no prophylactic colony-stimulating (CSF) use. Interestingly, age was no longer a significant risk factor in patients who received prophylactic CSF.

Reviews and guidelines on the use of G-CSF and erythropoietin in elderly patients with cancer have been published elsewhere.¹⁰⁸ In conclusion, it has been demonstrated convincingly that the use of growth factors can help to maintain dose intensity and/or reduce hematotoxicity in elderly patients.

Conclusions

Trials that systematically include functional status and comorbidity as part of a geriatric assessment are rare. In trials where functional status and comorbidity have been assessed, age did not show a significant correlation with toxicity. Most trials reporting an age-associated increase in toxicity have not controlled for age-associated changes such as functional impairment, decline in organ function, and comorbidity. To date, no prospective trial has been conducted assessing the need of a geriatric assessment for the care of elderly cancer patients receiving chemotherapy. However, a geriatric assessment may help to classify elderly patients into different groups: those who can be treated similarly to younger patients, those who are vulnerable and need modified therapy, and those who are frail and cannot tolerate cytotoxic therapy. Cutoff levels to define these three patient groups will most likely depend on the underlying tumor entity and the kind and intensity of therapy that will be used.

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