International Society of Geriatric Oncology Chemotherapy Taskforce: Evaluation of Chemotherapy in Older Patients—An Analysis of the Medical Literature

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ABSTRACT

The elderly comprise the majority of patients with cancer and are the recipients of the greatest amount of chemotherapy. Unfortunately, there is a lack of data to make evidence-based decisions with regard to chemotherapy. This is due to the minimal participation of older patients in clinical trials and that trials have not systematically evaluated chemotherapy. This article reviews the available information with regard to chemotherapy and aging provided by a task force of the International Society of Geriatric Oncology (SIOG). Due to the lack of prospective data, the conclusions and recommendations made are a consensus of the participants. Extrapolation of data from younger to older patients is necessary, particularly to those patients older than 80 years, for which data is almost entirely lacking. The classes of drugs reviewed include alkylators, antimetabolites, anthracyclines, taxanes, camptothecins, and epipodophyllotoxins. Clinical trials need to incorporate an analysis of chemotherapy in terms of the pharmacokinetic and pharmacodynamic effects of aging. In addition, data already accumulated need to be reanalyzed by age to aid in the management of the older cancer patient.

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INTRODUCTION

The fastest-growing segment of the US population comprises persons 65 years and older. The average person of 65 years can expect to live another 15 years and remain functionally independent for most of that time. The 75- and 85-year-old have an average life expectancy of 10 and 6 years, respectively, and they will often function independently the majority of that time. We can expect an increase in the number of older cancer patients. There has been a general exclusion of the elderly from clinical trials, particularly those involving chemotherapy. This has led to a paucity of data available to the clinician to make rational treatment decisions. One of the earliest analyses of chemotherapy was performed by Begg et al, who reviewed the Eastern Cooperative Oncology Group experience. Although their article is one of the most quoted concerning age and toxicity, it is 20 years out of date, and the drugs mentioned are used infrequently. The epidemiologic change and its effect on medical oncology practice, which was first recognized by Yancik et al, is now upon us. This article is a review of the chemotherapy data to assist clinicians to make important treatment decisions for the older patient.

METHODS

An electronic medical subject headings search of the available literature was done through MEDLINE using the PubMed interface for clinical articles. The following key words were searched for in the databases: age, metabolism, elderly, geriatrics, cancer, and chemotherapy. A person of 65 years or older was defined as elderly. The articles were analyzed by a task force organized by the International Society of Geriatric Oncology (SIOG; Genolier, Switzerland). SIOG has recently published guidelines for dose modification of chemotherapy in elderly patients with renal insufficiency. This article is an attempt to provide some evidence-based guidelines for the treatment of older patients. Most publications reflect a retrospective subset analysis, in which older patients make up a fraction of patients. Generally, patients were reported to not have a significant comorbidity and may not be truly representative of the average patient seen in practice. There is very little prospective pharmacokinetic data. Many papers focus on toxicity, which reflects pharmacodynamic changes in the older patient, but it also can be related to changes in pharmacokinetics.

In addition to age, there have been a number of publications regarding end-organ dysfunction. Although this is not specifically for the elderly, the data can be used for this purpose, as older patients have a higher incidence of comorbidity and end-organ dysfunction. The presence of these factors leads to the heterogeneity of effect and toxicity seen clinically. Because of the overall lack of data, particularly for patients...
older than 80 years, the clinician will continue to have the task of extrapolating data to fit the individual patient. Clinical judgment will always be important. Modification of toxicity and appropriateness of dosing also will be affected by the use of hematopoietic growth factors and change in the schedule of drug administration.12 Older patients should have the full benefit of these agents, as age is a risk factor for myelotoxicity.13,14 The assessment of renal function is extraordinarily important in dosing chemotherapy. There is a controversy over which formula is the most accurate in assessment of renal function.15-18 Table 1 presents some of the pharmacokinetic changes with aging. The National Comprehensive Cancer Network (Philadelphia, PA) guideline for the management of older cancer patients is an important resource (www.nccn.org). It is hoped that the knowledge of age-related issues with the chemotherapeutic agents would lessen the incidence and adverse consequences of toxicity in older patients.19

**ALKYLATING AGENTS**

Alkylating agents have been the foundation of therapy for decades. Their main dose-limiting toxicity (DLT) is the hematotoxicity. There is a large interindividual variability in terms of bone marrow reserves. Metabolism represents the main route of elimination for most compounds. Hepatic enzymatic processes are often involved and may alter with increasing age. As examples, cyclophosphamide and ifosfamide undergo a 4-hydroxylation catalyzed by cytochromes P450 of the CYP3A and CYP2B subfamilies. Nonenzymatic processes that are less subject to large interindividual variability metabolize some other alkylating agents, such as melphalan and temozolomide.20 For cyclophosphamide, cytotoxic and adverse effects correspond to metabolites rather than to parent compounds, so changes in metabolism related to age could have a great effect on efficacy and toxicity.

**Melpahan**

Melphalan is administered to elderly patients for treatment of multiple myeloma. Drug excreted and unchanged in the urine represents about one third of the administered dose.21 A positive correlation has been observed between melphalan area under the curve (AUC) and the degree of renal insufficiency.22,23 However, renal insufficiency did lead to a limited decrease in melphalan clearance compared with the interindividual variations in systemic clearance.24,25

High-dose chemotherapy is being increasingly used for the treatment of multiple myeloma when autologous transplantation is considered.26 The dose of 200 mg/m² by intravenous infusion has become a standard. Higher toxicity, mainly myelosuppression, has been observed in patients older than 70 years.26-29 Dose reduction is recommended related to declining renal function.27 For elderly patients with multiple myeloma ineligible for high-dose chemotherapy, melphalan may be given orally (0.25 mg/kg) with prednisone (2 mg/kg) for 4 days according to 6-week cycles adapted to renal guidelines.28 Retrospective analysis showed a correlation between hematological and infectious toxicity and renal insufficiency in patients treated with oral melphalan and prednisone. Dose modification is not recommended due to age alone. Dose modification for declining renal function is recommended.

**Cyclophosphamide**

Metabolism of cyclophosphamide to active metabolites is initiated by cytochrome P450 (subfamily 3A and 2B) mainly in the liver. Formation of the final metabolites, phosphoramide mustard and acrolein, require another enzymatic process and spontaneous reactions. An accumulation of toxic alkylating metabolites is expected in renal insufficiency, justifying a dose reduction of 20% to 30%, depending on the degree of the renal insufficiency.30 There is preclinical indication that cyclophosphamide is metabolized slower in the elderly, but there are no clinical data to confirm this. There are no pharmacokinetic differences based on age alone.31 Cyclophosphamide is often administered in combination with other chemotherapeutics, such as anthracyclines or methotrexate and fluorouracil (FU) for treatment (cyclophosphamide, methotrexate, and FU) of breast cancer. A nonrandomized, small prospective study in patients older than 70 years with metastatic breast cancer concluded that the dose of cyclophosphamide, methotrexate, and FU in patients older than 70 years should not exceed 75% of the standard dose.32 In a larger study of the same population, requirement of dose reductions was correlated with creatinine clearance (CrCl), but not with age.33 Cyclophosphamide and methotrexate dose were calculated using a linear function of CrCl, and FU was given at two thirds of the usual dose. These doses resulted in no significant age trends in almost all toxicity, response, and time to treatment failure.

Also the combination of cyclophosphamide/doxorubicin for the treatment for breast cancer was evaluated.34 There was moderate evidence of an age-related decrease in nadir absolute neutrophil count. Pharmacokinetic analyses did not demonstrate age-related...
differences in either cyclophosphamide or doxorubicin plasma exposure, but only the pharmacokinetics of the parent drug (unchanged cyclophosphamide) was explored. Overall, regarding the modest effect of age on toxicity, Dees et al concluded that healthy older patients should not be denied adjuvant chemotherapy on the basis of age alone. There is no solid evidence in elderly cancer patients for systematic dose reduction of cyclophosphamide based on age alone.

### INTRAVENOUS FLUOROPYRIMIDINES

The fluoropyrimidines are one of the most widely used class of agents in the medical treatment of solid malignancies. There are marked intraindividual variations in plasma levels of the parent drug and metabolites, and toxicities can vary widely among individuals. In the elderly, these drugs are often arbitrarily reduced in dosage. There is no pharmacokinetic basis for dose modification based on age alone. However, there may be significant age related toxicities.

**Studies Suggesting an Effect of Age on Toxicity**

Stein et al reported increased toxicity with age in a phase III trial of the Gastrointestinal Tumor Study Group treatment of metastatic colorectal cancer. This was based on a logistic regression analysis using age, gender, treatment, performance status, and length of therapy. Analyses by Tsalic et al and Zalcberg et al showed similar findings. These conclusions also are supported by data derived from a meta-analysis of six randomized trials of patients with colorectal carcinoma, with a total of 1,219 patients comparing infusional FU with bolus FU. Older patients and those with poorer performance status had significantly higher risks of diarrhea, mucositis, nausea, and vomiting, and older female patients had the highest incidence of nonhematologic toxicity. Grade 3 or greater hematologic toxicity was seven times more common with bolus FU (31% vs 4%, P < .0001).

**Studies Suggesting Age Is Not Determinant of Toxicity**

An overview of seven phase III trials involving FU with either leucovorin or levamisole showed that no interaction between age and outcome could be identified. Age older than 70 years correlated with the occurrence of treatment-related leucopenia with borderline significance. In an attempt to minimize the bias of patient selection for protocol study, Delea et al retrospectively examined a 5% sample of Medicare patients who had undergone colorectal surgery. There was no difference in the incidence of hospitalization, but drug dosage and comorbid conditions were not identified. In a retrospective analysis of clinical trials testing FU, leucovorin, oxaliplatin (FOLFIRI 4), older age was not associated with an increased overall incidence of grade 3 or greater toxicity or 60-day mortality, except there was a higher incidence of grade 3 neutropenia and thrombocytopenia. The benefit of FOLFIRI 4 did not differ by age. In an intergroup study with adjuvant FU for high-risk stages II and III colon cancer, the secondary analysis of this trial demonstrated that the elderly are as likely to tolerate and benefit from adjuvant chemotherapy as are younger patients. In an evaluation of the Surveillance, Epidemiology and End Results Medicare–linked database for resected stage III colorectal cancer, adjuvant FU was well tolerated, even among the very old patients without a major comorbidity. A retrospective analysis of European trials has showed that fit elderly patients experience equivalent benefit and toxicity as younger patients.

Data have been published giving conflicting results as to whether intravenous fluoropyrimidines are more toxic in elderly patients. A main determinant of this difference is the schedule used. It is clear that the weekly FU regimen is better tolerated than the monthly regimen. Infusional therapy likely has a more favorable toxicity profile. Intravenous fluoropyrimidines should be given by a weekly schedule or by the published infusional regimens. The data suggests no reason to reduce the dose for intravenous fluoropyrimidines, unless there is severe renal dysfunction or comorbidity.

### CAPECITABINE

The pharmacokinetics of capecitabine are not affected by age in patients with normal renal function. Studies have compared capecitabine with FU in patients with a median age of older than 60 years. From this literature, it appears that capecitabine at the recommended dosage of 1,250 mg/m² twice daily for days 1 to 14 every 21 days is better tolerated than FU administered as per Mayo Clinic schedule (425 mg/m² days 1 to 5 every 28 days), with hand-foot syndrome being more common in the capecitabine therapy and myelosuppression more common in the FU therapy. Studies in elderly breast cancer patients showed that the dose of capecitabine might be reduced from 1,250 mg/m² to 1,000 mg/m², with equal efficacy but reduced toxicity. Feliu et al studied prospectively 51 patients who had advanced colorectal cancer and were older than 70 years, with doses adjusted based on CrCl. Only 12% of patients experienced grade 3 or 4 treatment-related adverse events, such as diarrhea, hand-foot syndrome, and thrombocytopenia. No treatment-related deaths were reported. The median dose-intensity was 88% ideal dose. Sharma et al studied the effect of fixed dose oral capecitabine 2,000 mg twice daily on days 1 through 14 every 3 weeks in patients with advanced colorectal cancer with a median age of 72 years. Grade 2 and 3 treatment-related toxicities were diarrhea at 34%, fatigue at 27%, stomatitis at 15%, and hand-foot syndrome at 22%. The median overall survival was 11.2 months, and the response rate was 28%. The patients with higher pretreatment levels of serum folate experienced greater treatment toxicities during the entire treatment period (P = .04).

The toxicities reported could be just a consequence of impaired renal function that occurs with aging. In a prospective evaluation, Cassidy et al have found that patients with moderate renal impairment at baseline (estimated CrCl 30 to 50 mL/min) experienced a higher incidence of grade 3 or 4 toxicities. Therefore, the authors recommended a lower starting dose in patients with moderate renal impairment at baseline (calculated CrCl 30 to 50 mL/min) and a contraindication in patients with severely impaired CrCl at baseline (< 30 mL/min). For patients with normal or mildly impaired renal function at baseline, the standard starting dose is well tolerated. This is similar to the recommendations of the SIOG task force on renal insufficiency. The dose of capecitabine should be adjusted to CrCl, and a starting dose of no more than 1,000 mg/m² twice daily be strongly considered.
Oxaliplatin

The kidneys eliminate approximately 30% to 50% of the drug. Clearance of total and free platinum is decreased in patients with renal impairment. However, in studies of patients with mild-to-moderate renal impairment (glomerular filtration rate [GFR] > 20 mL/min), no increased toxicity was seen.\(^{50,60}\) Clearance of ultrafilterable platinum after administration of oxaliplatin is not influenced by impairment of hepatic function, sex, or age.\(^{61}\)

Oxaliplatin is principally used in patients with colorectal cancer. Principal DLTs are peripheral neuropathy and bone marrow suppression. Few studies have been performed specifically in the elderly population. The retrospective meta-analysis of 3,742 patients (614 patients ≥ to 70 years), performed by Goldberg et al,\(^{45}\) of patients receiving FOLFOX 4 was mentioned previously. A retrospective review of 44 patients with a median age of 78 years concluded that treatment in this population was feasible with manageable toxicity.\(^{62}\)

The combination of oxaliplatin and capcitabine has been studied in patients older than 70 years. No relationship was seen between response and patient age, Eastern Cooperative Oncology Group performance status, or the ability to perform activities of daily living (ADL)\(^{63,64}\). The rate of neurotoxicity secondary to oxaliplatin-based chemotherapy has not been shown to be any greater in the elderly than in younger patients. A bifractionated protocol (oxaliplatin day 1 and 2) was developed in an attempt to minimize this adverse effect. Grade 3 sensory neuropathy occurred in 6% of patients. ADL and IADL scores did not change significantly during treatment.\(^{62}\) Other trials with oxaliplatin combinations in patients older than 70 years showed acceptable toxicity and efficacy.\(^{66-68}\)

Cisplatin

Cisplatin has triphasic elimination with a half-life of the initial phase of 20 to 30 minutes, second-phase half-life of 48 to 67 minutes, and a terminal half-life of 24 hours. Cisplatin pharmacokinetics is dependent on normal renal function due to the contribution of renal elimination for cisplatin.\(^{70}\) However, the nonreversible plasma protein binding of cisplatin also should be considered as an important elimination process, as only the unbound plasma cisplatin concentrations represent the active fraction. Plasma protein binding of cisplatin is larger than that of other platinum compounds (eg, carboplatin). Thus, the impact of the renal function on cisplatin pharmacokinetics is limited in comparison with these other compounds. Age is an independent and significant predictor of the AUC of the free ultrafilterable platinum fraction and total plasma platinum, with a higher AUC with increasing age.\(^{71}\) The maximum concentration of ultrafilterable platinum fraction has been shown to correlate significantly with nephrotoxicity.\(^{72}\)

Renal function should be considered as a major pharmacodynamic parameter for cisplatin, as renal insufficiency represents the major toxicity, together with magnesium wasting, nausea and vomiting, peripheral neuropathy, auditory impairment, and myelosuppression. Severe nausea and vomiting has been markedly reduced by the use of adequate antiemetic treatment regimens. Intravenous hydration has reduced acute nephrotoxicity to 5%.\(^{73}\) Retrospective analysis of clinical trials has not reported an undue incidence of nephrotoxicity related to age. Thus, cisplatin is a viable option in highly selected elderly.\(^{74-78}\)

Cisplatin should not be used in renal dysfunction, and one should be aware that a significant proportion of elderly patients have decreased renal function. The high incidence of age-related hearing loss should also be considered. Cisplatin should be used at the lower range of dosage (eg, 60 mg/m\(^2\)) and preferably at a reduced infusion rate (eg, during 24 hours) to avoid excessive toxicity in elderly.\(^{7}\) Hydration must be monitored carefully to prevent fluid overload. The concomitant use of other potentially nephrotoxic drugs should be avoided.

Carboplatin

Carboplatin has a similar mechanism of action compared with cisplatin, with antineoplastic activity against cervical, lung, and ovarian cancers that is more or less comparable with cisplatin. Carboplatin is completely eliminated through the kidneys, and it has one of the most unique methods of dosing. The Cockcroft-Gault, Calvert, and Chatelut formulas allow for accurate and safe dosing, taking into account renal function changes with age and a targeted AUC.\(^{79-81}\)

Carboplatin exhibits biphasic elimination with an initial half-life of 1.1 to 2 hours and a final half-life of 2.6 to 5.9 hours, with CrCl more than 60 mL/min. Because of the low incidence of nonhematologic toxicity, it can replace cisplatin in the palliative setting, or in case adverse effects of cisplatin are problematic. There is no data to support dose reduction based on age alone. The Calvert formula should be used for dosing, and the AUC choice should be based on disease-specific efficacy data.

Anthracyclines

Anthracyclines are part of most chemotherapeutic regimens for the treatment of many malignancies encountered in the elderly.\(^{82-85}\) Toxicity that is observed more frequently is a form of cardiomyopathy that manifests itself during the therapy with doxorubicin in the greatest part of the cases,\(^{86}\) and it has been reported that the incidence of congestive heart failure following treatment with anthracyclines increases progressively with age after 70 years, these results are confirmed by a multivariate analysis.\(^{87-89}\) This may explain why many elderly patients are either excluded from anthracycline treatment or receive less-aggressive chemotherapy. For anthracyclines, some studies suggest that the drug’s peak concentration correlates with efficacy, whereas toxicity is most likely a function of both peak and exposure.\(^{90-93}\) This has to be taken into account if we consider that the peak concentration seems elevated in the elderly.\(^{32,96}\)

One pharmacokinetic analyses of doxorubicin did not demonstrate age-related differences in either cyclophosphamide or doxorubicin plasma exposure.\(^{35}\) Doxorubicin is 70% protein bound, and consideration should be given for dose reduction in patients with hypoalbuminemia.\(^{32}\)

The AUC of daunorubicinol, a metabolite of daunorubicin, manifests itself during the therapy with doxorubicin in the greatest toxicity that is observed more frequently is a form of cardiomyopathy that manifests itself during the therapy with doxorubicin in the greatest part of the cases,\(^{86}\)

The limited sampling strategies developed for several anthracyclines would facilitate the implementation of pharmacokinetic studies.\(^{101-104}\)
In one study, variability in clearance could be attributed to sex and also to age in women.99 If severe renal impairment leads to a decrease in epirubicin clearance, no dose reduction guidelines have been proposed. The pharmacokinetic profile of epirubicin is modified in case of hepatic impairment.105,106 Dosing modifications based on ASTs levels have been proposed.100,107,108 There is concern about cardiotoxicity, and this should be monitored carefully. In older patients with normal cardiac function and reasonable functional status, anthracycline therapy can be tolerated and effective.109-112 The use of the cardioprotectant dexrazoxane should be considered particularly in patients with a prior exposure to anthracyclines.113

**Liposomal Anthracyclines**

Liposomal formulation completely alters the pharmacokinetics, pharmacodynamics, and toxicity profile of these agents. Hand-foot syndrome is seen more frequently with these drugs; conversely, myelosuppression, mucositis, alopecia, and cardiac toxicity are markedly diminished compared with nonliposomal formulations.114 The reduced toxicity of this class of drugs may be particularly beneficial in older patients with anthracycline-sensitive diseases and ovarian cancer.115-121

**Mitoxantrone**

Mitoxantrone, an anthracyclene, which has decreased toxicity and increased tolerance as compared with the anthracyclines, might be a good choice, but efficacy might be somewhat inferior to other anthracyclines in breast cancer. However, in prostate cancer, it is a valid and approved drug.122 Approximately 10% is eliminated by the kidney, making a dose adjustment for renal failure unnecessary. In patients with normal hepatic function, a terminal half-life of 23 to 42 hours can be observed; however, with hepatic dysfunction and hyperbilirubinemia, the terminal half-life can be more than 60 hours.123,124

**Antimicrotubule Agents**

**Vinca Alkaloids**

Vincristine is excreted primarily by the liver and requires dose reduction, or even avoidance, in liver failure.125-127 There are no data for dose modification based on age alone. Relevant for the elderly is that important drug interactions have been reported (eg, with nifedipine, resulting in increased systemic exposure).128

Vinorelbine is a semisynthetic vinca alkaloid and causes less neurotoxicity than the older compounds in this group. It is highly bound to human platelets (78%),129 and thrombocytopenia seems to correlate with increased hematological toxicity, probably due to an increased unbound fraction, although high inter- and intraindividual variability in AUC (20% to 65%) can be present.130 Vinorelbine undergoes substantial hepatic elimination, but dose modification might only be necessary in patients with severe liver dysfunction, when the liver volume has been replaced by the tumor by more than 75%.131 There are conflicting data on the effect of age on pharmacokinetics of intravenous vinorelbine.132-134 In the largest study, CrCl and hepatic clearance were independent factors of vinorelbine clearance, whereas age was not.134 Several studies in breast and lung cancer and non-Hodgkin’s lymphoma show that full-dose vinorelbine (eg, 25 to 30 mg/m² weekly with rest points) has a very favorable tolerance profile,132,133,135 and improved quality of life has been demonstrated in a large phase III trial in non-small-cell lung cancer (NSCLC) in the elderly (median age of 74 years).136 Although there are conflicting data on the impact of age on vinorelbine exposure, several trials show that vinorelbine is generally well tolerated in elderly cancer patients. There is no evidence that dose modification is required on the basis of age.

**Taxanes**

**Paclitaxel.** The majority of paclitaxel is protein bound (97%), and it is extensively metabolized in the liver by the cytochrome P450 system and excreted in bile, more specifically by the cytochrome P450 isozymes CYP2C8 and CYP3A. Awareness of drug interactions is needed when given concomitantly with drugs metabolized by the same pathways (eg, ketoconazole).137 It is preferable not to use paclitaxel in liver dysfunction because of significantly increased AUC and toxicity (mostly neutropenia),8,125 but if it is necessary, the dose should be greatly reduced. Table 2 shows the available data on paclitaxel pharmacokinetics in elderly patients. A Cancer and Leukemia Group B trial showed a modest but significant decrease in clearance of total paclitaxel with increasing age without adverse sequelae.140

**Table 2. Studies on Paclitaxel Pharmacokinetics in Elderly Cancer Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage</th>
<th>Patients</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias et al, 2001143</td>
<td>NSCLC 90 mg/m² 6 to 8 weeks during 1 hour</td>
<td>35, 70-85</td>
<td>No difference</td>
<td>Historic controls</td>
</tr>
<tr>
<td>Nakamura et al, 2000180</td>
<td>NSCLC 210 mg/m² every 3 weeks during 3 hours</td>
<td>28, 70-75; 92, &lt; 70</td>
<td>CI total paclitaxel, 168 mL/min/m², 162 mL/min/m²</td>
<td>Unbound fraction not measured</td>
</tr>
<tr>
<td>Smorenburg et al, 2003141</td>
<td>Breast cancer, 80 to 100 mg/m² every week and 3 and 4 weeks during 1 hour</td>
<td>8, &gt; 70; 15, &lt; 70</td>
<td>CI unbound, paclitaxel, 124 L/h/m², 247 L/h/m²; CI Cremophor EL increases with age</td>
<td></td>
</tr>
<tr>
<td>Lichtman et al, 2006140</td>
<td>Various cancers, 175 mg/m²/week</td>
<td>32, &gt; 75</td>
<td>Cl total paclitaxel, 8.2 L/h/m², 9.3 L/h/m², 11.0 L/h/m²</td>
<td>Unbound fraction not measured; in &gt; 75 years increased neutropenia, but no increase in other toxicity end points</td>
</tr>
</tbody>
</table>

NOTE. Cremophor EL; BASF, Mount Olive, NJ.

Abbreviations: NSCLC, non-small-cell lung cancer; CI, clearance.
decrease seems partly induced by decreased clearance of the formulation vehicle Cremophor EL (BASF, Mount Olive, NJ).\textsuperscript{141} Moreover, unbound paclitaxel might be a better predictor of clinically relevant exposure than total paclitaxel. Many studies have shown the feasibility and efficacy of administering paclitaxel in elderly patients with various cancer types. Both weekly and 3 weekly regimens have been studied. The every 3 weeks regimen can be used in fit elderly patients, such as those with ovarian and bladder cancer.\textsuperscript{142} There is a preference for weekly administration in some patients, particularly breast cancer, as this causes less hematological toxicity without loss of efficacy,\textsuperscript{143-145} possibly as a result of the more effective antiangiogenic activity in this fractionated regimen.\textsuperscript{146} A recent trial in neoadjuvant breast cancer therapy even showed improved efficacy of weekly versus every-3-weeks paclitaxel.\textsuperscript{147}

There are somewhat conflicting data on the impact of age on paclitaxel clearance. Moreover, the importance of unbound versus total paclitaxel clearance is not fully determined. However, several trials indicate the feasibility of both every 3 weeks and weekly paclitaxel in elderly patients. There is no basis for a dose reduction based on age alone for any standard dose or schedule.

**Docetaxel.** The majority of docetaxel is protein bound (94%), and it is extensively metabolized in the liver by the cytochrome P450 system (CYP3A4) and excreted in bile, resulting in increased toxicity when administered to patients with impaired liver function.\textsuperscript{8} There is a large interpatient variability in exposure (AUC) and drug clearance. Hepatic CYP3A4 is by far the strongest predictor of total docetaxel clearance, and together with albumin/\textalpha{}1-acid glycoprotein (AAG) accounts for 72% of the interpatient variation in clearance.\textsuperscript{148} In serum, docetaxel is extensively bound to albumin, lipoproteins, and AAG. Indeed, the latter is the main determinant of docetaxel serum binding variability. There have been attempts in elderly patients to predict variation in AUC of docetaxel through correlations with plasma AAG or urinary cortisol ratio.\textsuperscript{149} Table 3 presents the available pharmacokinetic data of docetaxel in elderly patients. Many studies have investigated the efficacy and toxicity of docetaxel in relation to age, mainly in breast cancer,\textsuperscript{150-152} lung, and prostate\textsuperscript{124} cancer. In a specific phase I trial in elderly cancer patients treated with docetaxel every 3 weeks, maximum-tolerated dose was not reached at 80 mg/m\textsuperscript{2}. Conversely, another phase I trial in elderly breast cancer patients was stopped after four patients at the first level of 75 mg/m\textsuperscript{2} every 3 weeks because of excessive toxicity. The Japanese population might be more vulnerable due to ethnic differences in metabolism; the maximum-tolerated dose in a Japanese phase I trial was 30 mg/m\textsuperscript{2}/wk. As with paclitaxel, weekly dose docetaxel regimens have being investigated, and they seem to decrease toxicity without loss of efficacy, except maybe in prostate cancer where 3 weekly might be slightly more effective than weekly docetaxel.\textsuperscript{124} Neutropenia was limited with weekly regimens, but fatigue was often invalidating. Various dosages (eg, 20 to 35 mg/m\textsuperscript{2} weekly or 60 to 100 mg/m\textsuperscript{2} every 3 weeks) and regimens (rest weeks at various time points) have been used.

There is no significant data to support dose modification of docetaxel based on age alone. Docetaxel pharmacokinetics is at most only minimally influenced by age. Any age-related changes are minimal compared with interpatient variability in metabolism. However, elderly patients are somewhat more vulnerable to adverse effects, but also here, interpatient variability is larger than age-related variability. Improvement in predicting unbound docetaxel clearance and toxicity by pharmacogenomic-based treatment optimization will hopefully improve correct dosing for the (elderly) cancer patients. In principal, standard regimens of docetaxel can be used (eg, 30 to 35 mg/m\textsuperscript{2} weekly or 60 to 100 mg/m\textsuperscript{2} every 3 weeks) and regimens (rest weeks at various time points) have been used.**

### Table 3. Studies on Docetaxel Pharmacokinetics in Elderly Cancer Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Dosage</th>
<th>Patients</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno et al, 1998\textsuperscript{181}</td>
<td>Various diseases</td>
<td>Various dosage</td>
<td>640</td>
<td>All ages</td>
<td>Cl total docetaxel, decreased 7% in elderly (older than 70 years)</td>
</tr>
<tr>
<td>ten Tije et al, 2005\textsuperscript{182}</td>
<td>Various</td>
<td>75 mg/m\textsuperscript{2} every 3 weeks</td>
<td>26</td>
<td>65</td>
<td>Cl total docetaxel: 30.0 L/h, 31.0 L/h</td>
</tr>
<tr>
<td>Minami et al, 2004\textsuperscript{183}</td>
<td>NSCLC</td>
<td>Docetaxel every week and 3 and 4 weeks plus cisplatin low dose</td>
<td>27*</td>
<td>75</td>
<td>No difference</td>
</tr>
<tr>
<td>Slaviero et al, 2004\textsuperscript{184}</td>
<td>Various</td>
<td>40 mg/m\textsuperscript{2}</td>
<td>54</td>
<td>Median 63; range 40-83</td>
<td>No difference</td>
</tr>
<tr>
<td>Hurria\textsuperscript{185A}</td>
<td>Various</td>
<td>35 mg/m\textsuperscript{2} every week and 3 and 4 weeks</td>
<td>20</td>
<td>65</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Abbreviations: Cl, clearance; PK, pharmacokinetics; NSCLC, non–small-cell lung cancer.

\*Dosage of 20 mg/m\textsuperscript{2}.

\*Dosage of 35 mg/m\textsuperscript{2}.

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**PURINE ANTIMETABOLITES: FLUDARABINE

The elimination half-life of this drug ranges from 6.9 to 12.4 hours. The total body clearance of this agent is related to both the serum creatinine and the CrCl. After initial dephosphorylation, the subsequent metabolite, 2-fluoro-araA, is eliminated primarily by renal excretion, with approximately 60% of the administered dose excreted in the urine within 24 hours after administration.\textsuperscript{153} Dose modifications...
based on varying degrees of renal dysfunction have been proposed.\textsuperscript{7,154,155} The most significant toxicities with fludarabine are related to the therapy-related myelosuppression, as well as the impact on cellular immune function. The severity of fludarabine-related neutropenia is related not only to the total body clearance of this agent, but also to AUC and half-life. In a large trial of chronic lymphatic leukemia patients, no association was found between age and the incidence of either hematologic toxicity or infection during the first cycle of fludarabine therapy. However, patients with an estimated CrCl of less than 80 mL/min had an increased risk of toxicity during their treatment course,\textsuperscript{156} and a majority of elderly patients will fall in this category.

In numerous series of patients with chronic lymphocytic leukemia, older patients tended to have shorter survival with the same incidence of toxicity.\textsuperscript{157-160} The other two purine analogs, 2-chlorodeoxyadenosine and deoxycoformycin, are also used in the treatment of hematologic malignancies, albeit less commonly than fludarabine. Data on these agents in an elderly population is likewise limited, but therapy-related myelosuppression and subsequent infectious complications remains the primary toxicities, as with fludarabine. Fludarabine may be used efficaciously and safely in an older patient population, but supportive measures are important. Response rates tend to be lower in these older patients as compared with a younger cohort. Dose reductions are recommended in the setting of reduced CrCl, in an effort to limit treatment-related toxicities.

### CYTIDINE ANALOGS

**Cytarabine**

Cytarabine is rapidly metabolized in the liver to inactive metabolites, and 90% to 96% is excreted in the urine.\textsuperscript{161} It is recommended that this agent be used with caution and at reduced doses in patients with either hepatic or renal insufficiency. Dose reductions are required when using high-dose therapy with this agent, due to the increased risk for CNS toxicity and intrahepatic cholestasis.\textsuperscript{7}

**Gemcitabine**

Pharmacokinetic data indicate that small age- and sex-related differences exist. These differences corresponded to differences in mean half-life for men at 42 minutes versus 61 minutes in the group of patients older than 65 years, and women at 49 minutes versus 73 minutes in the group of patients older than 65 years. Despite these differences, dosing guidelines are the same based on age and sex for gemcitabine. Toxicities primarily include neutropenia and thrombocytopenia. Dosing modifications for hepatic and renal dysfunction have been reported.\textsuperscript{9} Gemcitabine as a single agent displays minimal toxicity in older patients.\textsuperscript{163}

### ANTIMETABOLITE

**Methotrexate**

Increased toxicity also has been observed in elderly patients receiving low-dose, long-term methotrexate.\textsuperscript{162} Excretion is almost entirely by the renal route and is inhibited by nonsteroidal anti-inflammatory drugs, cephalosporins, and several other drugs. The methotrexate half-life and clearance have been shown to be significantly prolonged in older patients,\textsuperscript{162} and the dose should be adjusted in the elderly population according to renal function.\textsuperscript{7} An alternative dosing formula has been proposed: adjusted dose = normal dose $\times$ CrCl ÷ 70.\textsuperscript{34}

**Pemetrexed**

Pemetrexed is primarily excreted unchanged in the urine (70% to 90% in the first 24 hours). It is contraindicated in patients with CrCl less than 45 mL/min. In patients with impaired renal function pemetrexed plasma clearance positively correlated with GFR, which resulted in increased drug exposures. Pemetrexed 600 mg/m$^2$ was well tolerated (with vitamin supplementation) in patients with GFR of more than 80 mL/min. In patients with GFR 40 to 79 mL/min, a dose of 500 mg/m$^2$, along with vitamin supplementation, was tolerated.\textsuperscript{11} It is active as a second-line therapy for NSCLC with a favorable toxicity profile in older patients.\textsuperscript{164,165} Further studies are needed to determine dosing in renally impaired patients.

### HYDROXYUREA

The metabolism of the oral agent hydroxyurea is not well established, but it is thought to be excreted predominantly in the urine. The primary toxicity of this agent is myelosuppression, although mild GI adverse effects are also common. Although dose reductions have been recommended in the setting of both hepatic and renal insufficiency, these have not been clearly delineated.

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**Table 4. Age-Related Analysis of Irinotecan**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aparicio et al, 2003\textsuperscript{157}</td>
<td>Various oxaliplatin or irinotecan combinations</td>
<td>66, Median 78</td>
<td>42% grade 3 or 4 toxicity</td>
</tr>
<tr>
<td>Chau et al, 2004\textsuperscript{158}</td>
<td>FU-resistant patients; irinotecan monotherapy</td>
<td>339, 21% &gt; 70</td>
<td>No increased toxicity; same efficacy</td>
</tr>
<tr>
<td>Sastre et al, 2005\textsuperscript{159}</td>
<td>First-line irinotecan/CIV FU</td>
<td>85, ≥ 72</td>
<td>Valid alternative in older patients in good condition</td>
</tr>
<tr>
<td>Souglakos et al, 2005\textsuperscript{160}</td>
<td>First-line FOLFIRI</td>
<td>30, Median 76</td>
<td>Active with acceptable toxicity</td>
</tr>
<tr>
<td>Rosati et al, 2006\textsuperscript{161}</td>
<td>Second-line weekly irinotecan</td>
<td>23, ≥ 70</td>
<td>Activity; careful toxicity monitoring</td>
</tr>
</tbody>
</table>

Abbreviations: FU, fluorouracil; CIV, continuous intravenous infusion; FOLFIRI, fluorouracil, leucovorin, and irinotecan.
Topotecan

Topotecan is a topoisomerase I inhibitor approved for the treatment of recurrent or refractory ovarian cancer and small-cell lung cancer, and it has activity in myelodysplastic syndromes and acute myeloid leukemias. Topotecan renal clearance accounts for 30% of its elimination, and it has a half-life of 3 hours. Topotecan clearance is related to serum creatinine level and age. A close relationship also was observed between topotecan clearance and CrCl. Dose adjustments are required in patients with moderate renal impairment. Severe myelosuppression can occur if dose adjustments are not made. A specific dose modification based on CrCl has been recommended, particularly for older patients. Weekly regimens seem to be effective with decreased risk of hematological toxicity.

Irinotecan

Irinotecan is a topoisomerase I inhibitor approved for the treatment of metastatic colorectal cancer alone or in combination with FU and leucovorin. It has activity in glioblastoma multiforme, NSCLC and small-cell lung cancer, and gastric, esophageal, and pancreatic cancer. It can be given as a weekly and every 3 weeks dose. The weekly and once every 3 week regimen showed similar efficacy and quality of life. Patients age 70 years or older independently predicted occurrence of grade 3 and 4 diarrhea. Treatment with the every 3 week schedule was associated with a lower rate of grade 3 and 4 diarrhea. SN-38, the major metabolite of irinotecan, is approximately 1,000 times more potent than the parent compound. The major toxicity of irinotecan therapy is delayed diarrhea and myelosuppression. Late diarrhea may be caused by intestinal accumulation of SN-38. The biliary concentration of SN-38 may be predictive of gastrointestinal toxicity, leading to the proposal of a biliary index as a surrogate measure to predict the severity of diarrhea. Delayed diarrhea was increased in patients with advanced age. Pharmacokinetic parameters—such as mean irinotecan, SN-38, SN-38G, maximum concentration AUC0-24, and biliary index values in patients 65 years or older—were within 3% of those in younger patients. In addition, response rates do not vary based on age. It is recommended that patients older than 70 years, patients with prior pelvic irradiation, or those with poor performance status start at reduced doses. There is no data to support a specific dose modification. Table 4 presents the studies of elderly patients with irinotecan.

Table 5. Age-Related Analysis of Etoposide

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage</th>
<th>Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toffoli et al, 2001</td>
<td>100 mg × 14 days every 3 weeks</td>
<td>50</td>
<td>50 to 83</td>
</tr>
<tr>
<td>Miller et al, 1997</td>
<td>50 mg/m² × 21 days and cisplatin</td>
<td>106</td>
<td>27 to ≥ 70</td>
</tr>
<tr>
<td>Ando et al, 1999</td>
<td>Two dose levels: 50 mg/d and 74 mg/d</td>
<td>12</td>
<td>Median 79</td>
</tr>
</tbody>
</table>

Abbreviation: PK, pharmacokinetics.

Etoposide

Etoposide is a topoisomerase II inhibitor used in the treatment of many malignancies, including refractory non-Hodgkin’s lymphoma, lung cancer, germ cell tumors. It is typically given through the intravenous route, although oral therapy also is used. Oral therapy occasionally poses problems with absorption and tolerance. Etoposide displays biphasic or triphasic pharmacokinetic characteristics with an initial half-life of 0.6 to 2 hours (mean, 0.25 to 2.5), and a terminal half-life of 5.3 to 10.8 hours (mean, 2.9 to 19). Etoposide absorption is highly variable and estimated at 50%, but ranging from 25% to 75%. Impaired renal function leads to a decrease in drug clearance rates. Increasing age has been correlated to increased free etoposide concentrations during oral therapy correlating with leukopenia. Poor performance status may place older patients at a higher risk for grade 4 DLTs, such as myelosuppression and mucositis. Etoposide is eliminated to some degree via hepatic CYP P450 metabolism, but dosage adjustments based on liver dysfunction are controversial. The pharmacokinetics of oral etoposide in patients with liver dysfunction do not differ from patients with normal liver function. Table 5 presents data on elderly patients receiving etoposide. Etoposide is a useful drug in elderly patients. The route of administration and dose adjustments need to be carefully considered. There is more variability in the pharmacokinetics and toxicity of oral etoposide compared with the intravenous route. As a result of this variability, oral etoposide may appear to be less effective and more toxic. In elderly patients receiving etoposide, a small dose reduction and careful monitoring is advised, even with normal organ function.

Authors’ Disclosures of Potential Conflicts of Interest

The authors have indicated no conflicts of interest.

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