



*The physiologic changes associated with aging affect the therapeutic index of chemotherapy drugs in older cancer patients.*

Kathleen Pompe. *Kloster Eberbach: Monk's Dormitory*. Digital photograph, 7" × 10".

# Chemotherapy in the Elderly: Pharmacologic Considerations

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**Background:** *The aging of the population has focused interest on the care of elderly cancer patients. A better understanding of the effects of chemotherapeutic agents on older patients with cancer will help to determine the appropriate use of chemotherapy for this age group.*

**Methods:** *The authors review recent studies and present pharmacokinetic data on several chemotherapeutic agents, particularly those that have recently become available.*

**Results:** *Agents such as gemcitabine, vinorelbine, the taxanes, anthracyclines, platinum compounds, topoisomerase I and II inhibitors, and the oral fluoropyrimidines appear to have a beneficial therapeutic index in elderly patients.*

**Conclusions:** *Careful attention to the physiologic changes associated with aging, along with dose adjustments for end-organ dysfunction (eg, renal and hepatic), is necessary to ensure the safe administration of antitumor chemotherapy to the elderly.*

## Introduction

The fastest-growing segment of the US population is composed of persons who are 65 years of age or

older. By 2030, an estimated 20.1% of the population will be 65 years of age or older. In the same period, the number of people 75 years of age or older will have tripled, and the 85-years-or-older age group will have doubled. Thus, physicians need to become familiar with the data regarding the treatment of older patients. The definition of *older* or *elderly* is somewhat arbitrary. Statistics are often based on Medicare information, thus dividing populations into groups of above and below 65 years of age. For study purposes, many studies further categorize patients as above 75 years of age.

This review focuses on the recent developments in the pharmacology of anticancer drugs in the elderly.

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As some common chemotherapy-related toxicities, eg, myelotoxicity, mucositis, and diarrhea, seem to be more prevalent and severe in the older patient population, this focus is particularly important.<sup>1</sup>

## Pharmacology

The pharmacologic changes associated with aging have received increased attention recently. Studies on hepatic drug-metabolizing enzyme activity, particularly the P450 microsomal system, show that this activity decreases by approximately 30% in healthy elderly men and women compared with younger subjects.<sup>2</sup> This reduction may result in decreased metabolism of drugs that are highly extracted by the liver (ie, gemcitabine, docetaxel, paclitaxel, vinorelbine, and the anthracyclines).

Age-related changes in renal excretory function include a decrease in the glomerular filtration rate (GFR) by approximately 1 mL per minute for every year over 40 years of age. The decline in GFR with age translates into pharmacokinetic alterations of drugs that are excreted by the kidneys. Due to the physiologic decline in renal function with age, chemotherapeutic agents that are primarily renally excreted must be used with care in the elderly. Therapeutic decisions involving the elderly, particularly the frail elderly, should be made with the knowledge that standard doses may be too toxic. Current characteristics of the frail elderly

include age over 85 years, dependence in one or more activities of daily living, three or more comorbid conditions, and the presence of one or more geriatric syndromes.<sup>3</sup> These traits render some therapeutic approaches inappropriate for this age group. Dosing modifications for these physiologic declines have been suggested (Table 1). The method of chemotherapy dosing and scheduling is undergoing reevaluation.<sup>4</sup> Patient-specific dosing regimens and the emergence of pharmacogenetics will alter dosing schemes.

## Specific Drugs

### *Antimetabolites*

Gemcitabine is a pyrimidine antagonist that is cell-cycle specific. Its dose-limiting toxicity is hematologic. Gemcitabine is approved for the treatment of pancreatic cancer and has significant activity in bladder, breast, and lung cancer.<sup>5,6</sup> To determine the activity of single-agent gemcitabine in previously untreated patients with metastatic transitional cell cancer, gemcitabine was given at a dose of 1,200 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle. Two studies showed overall response rates of 28%<sup>6</sup> and 24.3%.<sup>7</sup> An analysis of four trials involving 329 evaluable patients with non-small cell lung cancer reported response rates of 20%. When patients were divided into two groups, those aged below 70 years and those 70 years and older, the response rates were 19% and 25%, respectively.<sup>8</sup> When gemcitabine is combined with cisplatin, response rates increase (eg, 75% for bladder cancer). However, myelosuppression increases significantly with neutropenia and thrombocytopenia, requiring a 25% permanent dose reduction of cisplatin,<sup>6</sup> which may make this combination difficult for some elderly patients. As a single agent, gemcitabine generates minimal toxicity in elderly patients, and the side-effect profile does not seem to be affected by patient age.<sup>8</sup>

Methotrexate has been a component of therapy in a variety of malignant disorders. The primary route of elimination (44%-100%) is the renal excretion of unchanged drug. Patients with decreased creatinine clearance or advancing age are susceptible to increased toxicity. The presence of third-spaced fluid can extend low levels of methotrexate concentrations, thus leading to increased stomatitis and myelosuppression. Leucovorin rescue as well as dose modifications based on renal function are strongly encouraged in elderly patients. In a study that compared younger and older patients receiving oral methotrexate for rheumatoid arthritis,<sup>9</sup> the elimination half-life measures of the free and total methotrexate were greater in the older age group. The total clearances of free and total methotrex-

Due to copyright restrictions, Table 1 has been removed from this online article.

Please refer to the printed version found in *Cancer Control Journal*, V7, N6, to view this table.

Table 2. — Topotecan Dosing Recommendations for Patients with Renal Impairment

Creatinine Clearance	Minimal Prior Therapy	Extensive Prior Therapy
> 60 mL/min	1.5 mg/m <sup>2</sup> /day	1.5 mg/m <sup>2</sup> /day
40-59 mL/min	1.5 mg/m <sup>2</sup> /day	1.0 mg/m <sup>2</sup> /day
20-39 mL/min	0.75 mg/m <sup>2</sup> /day	0.5 mg/m <sup>2</sup> /day
< 20 mL/min	Not established	Not established

From O'Reilly S, Armstrong DK, Grochow LB. Life-threatening myelosuppression in patients with occult renal impairment receiving topotecan. *Gynecol Oncol.* 1997;67:329-330. Reprinted with permission.

ate were inversely proportional to age. Methotrexate clearance declines with decreasing creatinine clearance, and smaller doses should be used in elderly patients and in those with renal impairment.

Fluorouracil (5-FU) causes some increased toxicity, particularly stomatitis, in elderly patients. In an adjuvant trial of a 5-FU/folinic acid combination,<sup>10</sup> patients over 70 years of age experienced more grade 3/4 mucositis than did the younger group (19% vs 11%, respectively;  $P=.02$ ). No other toxicity differences were noted.

Oral fluoropyrimidines are being developed to increase the therapeutic index and to improve convenience and flexibility of dosing. Capecitabine, a precursor of 5'-deoxy-5-fluorocytidine, is metabolized by carboxylesterase, cytidine deaminase, and intratumoral thymidine phosphorylase to 5-FU. It has activity in breast and colorectal cancer and is associated with palmar-plantar erythrodysesthesia as seen with a continuous 5-FU infusion. In a breast cancer trial of postmenopausal women,<sup>11</sup> minimal toxicity was reported. A trial to evaluate the tolerability and potential advantages of tegafur plus uracil (UFT) in elderly patients with colorectal cancer<sup>12</sup> reported a response rate of 16.9% with mild toxicity as a single agent and 29% when combined with leucovorin. The toxicity was acceptable to elderly patients. The dihydropyrimidine dehydrogenase (DPD) inhibitor eniluracil combined with oral 5-FU will not be further developed.<sup>13</sup> DPD is a major component of 5-FU elimination by reducing 5-FU to dihydrofluorouracil. An average of 77% of 5-FU was excreted unchanged in urine in patients receiving the combination of 5-FU and eniluracil.<sup>14</sup> This may increase the susceptibility to fluoropyrimidine toxicities in the elderly with decreased renal function, and other drugs with this property will be developed.

### Purine Analogues

Fludarabine (F-araAMP) undergoes dephosphorylation in plasma to 2-fluoro-araA with subsequent intra-

cellular activation to F-araATP. Rapid dephosphorylation to 2-fluoro-araA occurs with renal excretion. Most elimination half-life periods have ranged from 6.9 to 12.4 hours. Patients with renal dysfunction have been reported with values of up to 23.9 hours. Total body clearance is related to both serum creatinine level and creatinine clearance. The 24-hour urinary excretion has averaged 60% of administered dose. Accordingly, the severity of fludarabine-related neutropenia was found to be directly related to total body clearance, area under the curve (AUC), and half-life.<sup>15</sup> Dose adjustments may be necessary in patients with renal impairment to equalize drug exposure.<sup>16</sup> It is uncertain whether greater clinical toxicity will result without dose modification.

### Topoisomerase Inhibitors

Topotecan is a topoisomerase I inhibitor that is approved for the treatment of recurrent or refractory ovarian cancer. It has activity in small-cell lung cancer and has some promising anti-leukemia effects.<sup>17,18</sup> Topotecan has a half-life of 3 hours, with renal clearance accounting for 30% of the drug elimination, as well as substantial biliary concentration. Topotecan dose modifications are not required for patients with hepatic dysfunction and normal renal function but are required for patients with moderate but not mild renal impairment. For patients with moderate renal dysfunction, the recommended starting dose of topotecan is 0.75 mg/m<sup>2</sup> per day for 5 days every 3 weeks (50% dose reduction). Life-threatening myelosuppression can occur otherwise. A specific dose modification based on creatinine clearance has been recommended, particularly for elderly patients (Table 2).<sup>19</sup>

CPT-11 (irinotecan) has been approved for the treatment of 5-FU refractory colorectal cancer. It has recently shown activity in glioblastoma multiforme.<sup>20</sup> The major metabolite is 7-ethyl-10-hydroxycamptothecin (SN-38), which is approximately 1,000 times more potent than CPT-11 as an inhibitor of topoisomerase I. It is further conjugated by uridine diphosphate glucuronosyl transferase (UDP-GT) to form SN-38G. The major toxicity of CPT-11 is delayed diarrhea. Late diarrhea is associated with intestinal accumulation of SN-38. The biliary concentration of SN-38 may be predictive of gastrointestinal toxicity. A biliary index has been proposed as a surrogate measure of SN-38 in the bile and may correlate with severity of toxicity. A retrospective analysis<sup>21</sup> has shown that advanced age may be associated with a greater frequency of delayed diarrhea. Analysis of age on pharmacokinetics has shown the mean CPT-11, SN-38, SN-38G  $C_{max}$ , AUC<sub>0-24</sub>, and biliary index val-

ues in patients 65 years of age or older were within 3% of those observed in patients less than 65 years of age. Response rates were also similar. Reduced starting doses were not required for patients older than age 65.<sup>21</sup>

Etoposide, the topoisomerase II inhibitor used most often in geriatric patients, is useful for those with refractory non-Hodgkin's lymphoma, lung cancer, and ovarian cancer.<sup>22</sup> Patients with impaired renal function have decreased drug clearance rates; therefore, dosage should be reduced in proportion to the reduction in creatinine clearance. Oral etoposide has a bioavailability of 50%, with substantial inter- and intra-patient variability. It is not affected by food or concurrent intravenous chemotherapy. Myelosuppression and mucositis are the predominant toxicities. A Cancer and Leukemia Group B study on the pharmacology of oral etoposide showed that increasing age correlated with higher etoposide concentration and free etoposide.<sup>22</sup> This model predicted toxicity but not response. Care must be taken in using this medication in elderly patients with a poor performance status. These factors suggest that this population is at higher risk for grade 4 toxicity.<sup>22</sup>

### *Vinca Alkaloids*

Vinorelbine is a semisynthetic vinca alkaloid with less neurotoxicity than the older compounds in this group. It is approved for the treatment of metastatic non-small cell lung cancer and has activity in breast<sup>23</sup> and ovarian<sup>24</sup> cancer. Studies suggest that a dose of at least 20 mg/m<sup>2</sup> per week may be required for a response. Vinorelbine is particularly useful in elderly patients due to its favorable toxicity profile. Fecal elimination accounts for the majority of drug excretion, and 11% to 21% is eliminated in the urine. Dose modification is needed only in patients with severe liver dysfunction. Sorio et al<sup>23</sup> reported that patients older than 65 years of age showed volume of distribution, terminal half-life, and systemic clearance rate that were similar to younger patients. No correlation was found with toxicity, age, or drug exposure. Therefore, dose reduction in elderly patients is not necessary.

### *Anthracyclines and Anthracenediones*

The principal long-term toxicity of anthracyclines is cardiotoxicity, which has been associated with increased occurrence in the elderly. Noninvasive monitoring has utilized the multiple uptake gated acquisition (MUGA) scan. The effectiveness of the scan during chemotherapy appears to be dependent on patient age, doxorubicin cumulative dose, and relative efficacy of the chemotherapy. It is unclear whether monitoring prevents the incidence of cardiomyopathy. Use of the

cardioprotective drug dexrazoxane or a change in schedule may allow for prolonged and safer therapy.<sup>25</sup>

Idarubicin is available in both intravenous or oral forms. The oral form has a 30% bioavailability.<sup>26</sup> The active parent compound is metabolized to an active metabolite, idarubicinol. It may have lower cardiotoxicity than doxorubicin and is well tolerated by the elderly.<sup>27,28</sup> The oral form undergoes first-pass hepatic metabolism. The plasma elimination is 5-24 hours for oral idarubicin and 13-60 hours for idarubicinol. The bioavailability is independent of age, and the pharmacokinetics are not altered in the elderly. Total body clearance is significantly reduced with renal dysfunction. Idarubicin is thought to be less cardiotoxic than doxorubicin.<sup>26</sup>

Mitoxantrone, an anthracenedione, has been utilized in acute leukemia, lymphoma, breast cancer, and prostate cancer.<sup>29-31</sup> It is useful in selected elderly patients with these disorders because mitoxantrone has a favorable toxicity profile compared with the traditional anthracyclines. Approximately 10% is eliminated renally, with the majority undergoing biliary excretion. In patients with normal hepatic function, the plasma disappearance is characterized by a rapid preliminary phase of clearance followed by a long terminal half-life of 23-42 hours.<sup>26</sup> In patients with hepatic dysfunction, this terminal half-life can be greater than 60 hours.

Epirubicin has been approved in the United States for the treatment of breast cancer. Epirubicin undergoes glucuronidation to epirubicinol, an inactive metabolite. This process does not interfere with cytotoxic activity. In trials of women with metastatic breast cancer, epirubicin was compared to doxorubicin either alone or in combination with 5-FU and/or cyclophosphamide.<sup>32</sup> There were fewer adverse events (nausea, vomiting, myelosuppression, and cardiac toxicity) with epirubicin use. Nearly twice the dose of epirubicin is needed to obtain the same incidence of cardiotoxicity that is produced by doxorubicin.<sup>33</sup> Weekly epirubicin is well tolerated in the elderly.<sup>34</sup>

Liposomes carry lipid-soluble agents to target tissue, change the pharmacokinetics of the drug, modify the toxicity, and alter the dosing schedule. Liposomal doxorubicin and liposomal daunorubicin are two approved formulations. Liposomes show uptake predominantly into cells of the reticuloendothelial system, with liver and spleen being responsible for clearance of the drug from the circulation. In preclinical studies,<sup>35,36</sup> a doxorubicin liposome formulation containing polyethylene-glycol showed a long circulation time in plasma, an enhanced accumulation in tumors, and a superior therapeutic activity over free drug. Most of the

administered dose was cleared from the plasma in 45 hours. Nearly 100% of the drug detected in plasma was encapsulated. Liposomal doxorubicin has shown activity in refractory ovarian cancer and breast cancer with acceptable toxicity.<sup>35,36</sup> Hand-foot syndrome occurs with this drug, but mucositis, alopecia, and cardiac toxicity are markedly diminished compared with doxorubicin. The reduced toxicity of this class of drugs may be particularly beneficial in elderly patients with anthracycline-sensitive diseases.

Drug resistance to anthracyclines is usually related to increased membrane intracellular efflux mediated by glycoprotein P-170. P-170 protein is coded for by the MDR-1 gene, which confers additional resistance to vinca alkaloids, actinomycin D, and epipodophyllotoxins. The incidence of drug resistance increases in elderly patients with leukemia.<sup>37</sup>

### *Taxanes*

Clinical trials have shown that paclitaxel has significant activity in ovarian, breast, and lung cancer. Metabolism can be affected by changes in liver function and by drugs that are also substrates for the cytochrome P450 (CYP)2C8 and (CYP)3A4 isoenzymes.<sup>2</sup> The effect of age on pharmacokinetics and pharmacodynamics is being studied in an ongoing trial. Thus far, no differences have been noted in the different age cohorts (55 to 64 years, 65 to 74 years, and 75+ years).<sup>38</sup>

Hourly and weekly regimens of paclitaxel may be more tolerable than and are currently being explored in a variety of disorders.<sup>39</sup> The repetitive dosing of dexamethasone must be monitored for significant toxicity in elderly patients. Peripheral neuropathy can occur with the use of other neurotoxic drugs such as cisplatin. Amifostine may be beneficial in the prevention of this toxicity.<sup>40</sup>

Patients with hepatic dysfunction present a particular concern. A phase I and pharmacokinetic study of 3- and 24-hour infusion paclitaxel has been performed in patients with liver dysfunction.<sup>41</sup> Patients were treated in three cohorts: (1) aspartate aminotransferase level greater than twofold normal and bilirubin level  $\leq 1.5$  mg/dL, (2) bilirubin 1.6 to 3.0 mg/dL, and (3) bilirubin  $\geq 3.1$  mg/dL. The dose-limiting toxicity was due to neutropenia, fever, fatigue, and mucositis. Paclitaxel must be used at these reduced doses: cohort I -  $< 135$  mg/m<sup>2</sup>, cohort II -  $\leq 75$  mg/m<sup>2</sup>, and cohort III - 50 mg/m<sup>2</sup>. While not specific for elderly patients, these guidelines can help to avoid serious toxicity.

Docetaxel is approved for treating breast cancer and has activity in non-small cell lung cancer and

ovarian cancer.<sup>42</sup> In combination with estramustine, docetaxel has shown benefit in patients with metastatic prostate cancer.<sup>43</sup> Docetaxel AUC has been shown to be a significant predictor of time to treatment failure in non-small cell lung cancer. Docetaxel clearance is a strong independent predictor of both grade 4 neutropenia and febrile neutropenia. Pharmacokinetic behavior is not believed to be altered by age or gender.<sup>44</sup> Hepatic dysfunction can increase hematologic toxicity. Patients with elevated hepatic enzymes have a 27% reduction in docetaxel clearance and are at a higher risk of neutropenic sepsis. Hepatic dysfunction was associated with an increase in both the percentage of cycles of therapy during which febrile neutropenia occurred and the number of patients suffering documented infection and severe (grade 3/4) stomatitis. The incidence of toxic death also increased in patients with moderate hepatic impairment.<sup>45</sup> Dose modifications similar to those of paclitaxel are recommended. Patients with liver metastases and normal liver function do not require dose modification.<sup>46</sup>

A recent study noted a cumulative dose of 400 mg/m<sup>2</sup> as the strongest predictor of the time to onset of fluid retention in patients not receiving prophylaxis.<sup>46</sup> One commonly used prophylactic regimen consists of 8 mg given orally twice daily for 4 days. Weekly regimens that are similar to paclitaxel but possibly less toxic are being developed.<sup>47</sup>

### *Platinum Compounds*

Cisplatin was the first antitumor compound to be studied extensively. Cisplatin is believed to be activated intracellularly by generation of a positively charged, aquated complex having the activity of a bifunctional alkylating agent. It binds directly to DNA, inhibiting its synthesis by altering the DNA template via the formation of intrastrand cross-links. The mechanism of action of platinum II complexes is due to displacement reactions that cause stable binding of the compound to DNA, RNA, proteins, or other molecules. The cytotoxic effects lack cell-cycle specificity.<sup>48,49</sup>

After an intravenous bolus injection, the removal of cisplatin from the circulation is triphasic.<sup>49</sup> The half-life of the first phase, the  $t_{1/2\alpha}$ , is 20 to 30 minutes and represents the removal of the drug that is not protein bound. The half-life of the second phase,  $t_{1/2\beta}$ , is 48 to 67 minutes and is primarily a function of removal from the circulation. These two phases depend on adequate renal function since 90% of cisplatin that is excreted is removed by the kidneys as a combination of glomerular and tubular secretion. The third phase of removal,  $t_{1/2\gamma}$ , is 24 hours and represents removal of the drug that is protein bound.<sup>49</sup> This is the major means of clear-

Table 3. — Examples of Clinical Uses of Alkylating Agents

Drug	Clinical Use
Cyclophosphamide	Breast, non-Hodgkin's lymphoma, small-cell lung cancer
Melphalan	Multiple myeloma
Chlorambucil	Chronic lymphocytic leukemia
Thiotepa	Breast, non-Hodgkin's lymphoma, intrathecal therapy, intravesical therapy
Nitrosoureas	Brain tumors, multiple myeloma
Busulfan	Chronic myeloproliferative disorders
Ifosfamide	Sarcoma, non-Hodgkin's lymphoma

ance of cisplatin that is covalently bound to plasma and other proteins.

The major toxicities are renal insufficiency with magnesium wasting, nausea and vomiting, peripheral neuropathy, auditory impairment, and myelosuppression. Reducing severe nausea and vomiting with antiemetic regimens has allowed easier administration of cisplatin therapy, thus improving the quality of life of patients. Ondansetron, granisetron, and dolasetron are antiemetics of the serotonin (5-hydroxytryptamine<sub>3</sub>) type 3 receptor antagonists. While they differ slightly in binding affinity and pharmacokinetic profiles, they are highly effective.<sup>50,51</sup>

The nephrotoxicity of cisplatin has led to hesitation in using this effective drug in elderly patients.<sup>52</sup>

However, acute nephrotoxicity has been reduced to 5% with various hydration regimens.<sup>53,54</sup> A limited number of clinical studies have described cisplatin toxicity in the elderly.<sup>55-58</sup> These studies are primarily retrospective, but they indicate that the elderly do not experience excessive cisplatin toxicity. Although a selection bias exists in these trials, a patient older than 70 years of age with no significant comorbidity and a good performance status should tolerate approximately 60 mg/m<sup>2</sup> of cisplatin without significant difficulty.<sup>52</sup> Amifostine (WR-2721) may provide some protection against cisplatin-induced nephrotoxicity, neurotoxicity, and ototoxicity,<sup>59</sup> which may improve the therapeutic index in the elderly patients. There is also some evidence that amifostine may protect against bone marrow suppression.<sup>49,59</sup>

Cisplatin is active in numerous solid tumors, including ovarian, bladder, lung, and head and neck cancers and germ cell tumors.<sup>49</sup> Many of these are common tumors in the elderly. The usefulness of cisplatin in hematologic malignancies is primarily limited to the treatment of refractory aggressive lymphomas.<sup>60,61</sup>

Carboplatin has a mechanism of action similar to that of cisplatin. The combination of paclitaxel and carboplatin produces less thrombocytopenia than would be expected from the same AUC of carboplatin used as a single agent.<sup>62</sup> The combination of paclitaxel and carboplatin can be safely administered to elderly patients.<sup>63</sup> The Cockcroft-Gault<sup>64</sup> and Calvert<sup>65</sup> formulas, which take

Table 4. — Characteristics of Alkylating Drugs

	Cyclophosphamide	Chlorambucil	Melphalan	Carmustine
Dose/schedule (mg/m <sup>2</sup> )	400-2000 IV 100 p.o. q.d.	1-3 p.o. q.d.	8 p.o. q.d. × 5d	200 IV/150 p.o.
Oral bioavailability	100%	50%	30%	?
PK (half-life, hrs)	3-10 (parent) 1.6 (aldophosphamide) 8.7 (phosphoramidate mustard)	1.5 (parent) 2.5 (phenylacetic acid)	1.5 (parent) + dose needs to be reduced with renal dysfunction	0.4
Metabolism	1. Microsomal hydroxylation 2. Hydrolysis to phosphoramidate mustard and acrolein 3. Excretion as inactive products	Chemical decomposition to active phenyl acetic acid and to inert products	Chemical decomposition to inert products	Chemical decomposition to active and inert products
Toxicity (hematologic)*	Acute, platelets spared	Acute	Delayed, nadir at 4 weeks	Delayed, nadir 4-6 weeks

\* Toxicities common to alkylating agents are alopecia, pulmonary fibrosis, leukemogenesis, infertility, teratogenesis; cyclophosphamide may cause cardiac toxicity and inappropriate antidiuretic hormone secretion.

From Tew KD, Colvin M, Chabner BA. Alkylating agents. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice*. 2nd ed. Philadelphia, Pa: Lippincott-Raven; 1996:297-332. Reprinted with permission. <http://www.com>

Table 5. — Spectrum of Activity of Newer Chemotherapeutic Agents in Solid Tumors

Agent	Bladder	Brain*	Breast	Colon	Lung	Ovary	Prostate
Gemcitabine	×		×		×	×	
Docetaxel			×		×	×	×
Paclitaxel	×		×		×	×	
Vinorelbine			×		×	×	
Oral fluoropyrimidines			×	×			
Topotecan					×	×	
Irinotecan		×		×	×		
Liposome**			×			×	

\* glioblastoma multiforme  
\*\* liposomal anthracyclines

into account renal function changes with age and a targeted AUC, allow for accurate and safe dosing.

### Alkylating Drugs

Alkylating agents act through the covalent bonding of alkyl groups to cellular molecules. They alkylate DNA through the formation of reactive intermediates that attack nucleophilic sites. These drugs play an important role in chemotherapy in many combination regimens.<sup>66</sup> Alkylating drugs are particularly valuable in treating elderly patients because they are available in oral forms (eg, chlorambucil, melphalan, cyclophosphamide, carmustine) and have relatively little acute toxicity. Tables 3 and 4 list characteristics of some of the alkylating drugs. Specific studies of the pharmacokinetics of these drugs in elderly patients have not been reported except as noted.

Ifosfamide requires biotransformation of the cytochrome P450 mixed-function oxidase system to an active metabolite, 4-hydroxy-ifosfamide, that is subsequently transformed to an active cytotoxic compound (isophosphoramidate mustard).<sup>67</sup> Ifosfamide has a broad spectrum of activity in both solid tumors and malignant lymphomas. A review by Baker and Grochow<sup>67</sup> reported a positive correlation between age and the elimination half-life of the drug. The median half-life of the inactive parent compound in patients less than 60 years of age was 3.9 hours compared with the median value of 6 hours in those over 60 years of age. There was no correlation between age and total plasma clearance, renal clearance, or nonrenal clearance. It was suggested that the observed difference was due to distribution into body fat. This prolongation of the half-

life is not associated with increased toxicity.<sup>67</sup> Therefore, dose modification based on age alone does not seem to be necessary.

### Conclusions

The elderly comprise the largest age group of patients for the medical oncologist. Many recently approved drugs have an improved therapeutic index and a broad range of activity for the elderly (Table 5). These drugs have particularly affected the treatment of solid tumors such as lung, bladder, prostate, and breast cancers. The introduction of newer agents for colorectal cancer, especially the oral medications, will allow a broader spectrum of patients to derive benefit from chemotherapy, particularly patients with a poorer performance status.

The elderly remain underrepresented in clinical trials.<sup>68</sup> More studies are needed regarding toxicity, drug metabolism, and drug effect for this population. Also, more effective methods are needed to guide decision making to determine the appropriate therapy for this group. These methods should consider comorbidity, performance status, and geriatric functional assessment.<sup>69</sup>

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