Pharmacology of Antineoplastic Agents in Older Cancer Patients

Review Article [1] | December 01, 2000 | Oncology Journal [2], Bladder Cancer [3], Breast Cancer [4], Lung Cancer [5], Older Patients [6], Ovarian Cancer [7], Palliative and Supportive Care [8], Prostate Cancer [9]

The fastest growing segment of the US population is the group over the age of 65 years. In the next 30 years, this group will comprise over 20% of the population. Because 60% of all cancers occur in this age group, there will be an expected rise in the total cancer burden.

Approximately 60% of all cancers occur in persons over the age of 65 years.[1] Increasing age is directly associated with increasing rates of cancer, corresponding to an 11-fold greater incidence in persons over the age of 65 years vs those under 65. Consequently, the older population comprises a majority of cancer patients.[2] Persons 65 years of age and older are the fastest-growing segment of the US population and will account for an estimated 20% of Americans by the year 2030. The over-75-year-old group will triple by 2030, and the over-85-year-old group will double in the same period. The average life expectancy of a 75-year-old person is currently 10 years, and of an 85-year-old, 6 years.[3-6] Together, these statistics outline a population that, in the future, will increasingly require specific management for various cancers.

The definition of "elderly" or "geriatric" patient groups is arbitrary and does not necessarily reflect the underlying health status of an individual. Following Medicare and Social Security regulations, the definition of "elderly" is most often based on an age over 65 years. Investigators have recently begun isolating the over-75 population for data analysis as well.[7,8] A special group, the "frail elderly" patient, is characterized by an age of 85 years or older, mild impairment of activities of daily living, significant comorbidity, and the presence of a geriatric syndrome.[8]

Treatment decisions change significantly with increasing patient age.[9,10] Older patients are more likely to be undertreated with chemotherapy because of physician fear of toxicity and lack of data supporting efficacy in this population.[11,12] Studies that have addressed chemotherapy toxicity in older patients have shown that they can tolerate such regimens as well as younger patients.[13-20] Lack of data on older persons has been a serious concern for physicians in their decision-making process. Future studies will need to incorporate more elderly patients, in order to yield meaningful data that will support evidence-based decisions. As the elderly population continues to grow, there will be an increasing need for studies, physician education, and therapies for this group.[21] This article will review the differences and similarities of older and younger populations with respect to pharmacology, toxicity, and management.

Aging

As practitioners treat more older patients, the question of whether pharmacokinetic data from patients in their 60s can be applied to patients in their 70s or 80s will become a more important issue. Throughout their lifetime, individuals experience subtle and gradual age-related changes that are difficult to identify. Older persons, compared to younger populations, typically have more disease states, take more medications, experience more adverse effects and drug interactions, and have more variability in nutritional status and underlying chronic health status that may contribute to pharmacokinetic differences.[22-24] Pharmacokinetic data on older patients are limited because only a small number of these individuals are included in studies with a wide range of patient ages. Consequently, the majority of data are inferred from the small number of older patients enrolled in trials that are not specifically targeted at an older age group.[25-27]

The pharmacokinetic and pharmacodynamic properties of various drugs may differ significantly between older and younger patients, as the result of physical, biochemical, and nutritional factors. Absorption may be affected by treatment toxicities as well by prior therapies such as surgery,
radiation, and chemotherapy. The distribution of agents may be affected by differences in body fat, muscle, and protein and by fluid differences seen most often with aging, cancer cachexia syndromes, obesity, ascites, or pleural effusions. Protein binding may be altered by hypoalbuminemia, leading to an increase in free fractions of agents. The metabolism of agents may also be affected by changes in hepatic or renal function.[22-27]

Aging, cancer, other disease states, or other medications may alter renal and hepatic metabolism and the elimination of chemotherapy agents in the elderly. Renal function typically declines in a steady fashion. Studies of hepatic drug metabolizing enzyme activity, particularly the cytochrome P450 microsomal system, show a decline in activity of approximately 30% among healthy elderly men and women, compared with younger individuals.[28] Cytochrome P450 1A2 also shows a decline in activity of 20% to 25% in healthy elderly subjects.[28,29] Due to the large metabolic capacity of the liver, age-related changes and their clinical significance are difficult to measure.

Decreases in the glomerular filtration rate (GFR) of approximately 1 mL/min for every year over age 40 are well known.[30] The age-related decrease in GFR correlates with pharmacokinetic alterations of drugs that are excreted renally. Due to the physiologic decline in renal function with age, chemotherapeutic agents, which are primarily excreted renally, must be used with extreme care in the elderly. Dose adjustments may be needed, particularly in the frail elderly, in whom chemotherapy is often contraindicated. Dosing modifications for these declines have been suggested (Table 1).[8,31,32]

**Specific Drugs**

**Antimetabolites**

**Gemcitabine:** A pyrimidine antagonist, gemcitabine (Gemzar) has a cell-cycle-specific mechanism of action. Pharmacokinetic data indicate that there are age- and gender-related differences in the metabolism of this drug. The mean clearance in men is 92.2 L/h/m²; however, in men over 65, clearance decreases to 55.1 L/h/m². Similar results have been noted in women, with a mean clearance of 69.4 L/h/m² in women under 65 vs 41.5 L/h/m² in those over 65. These differences correspond to differences in the mean half-life of gemcitabine—ie, 42 minutes in men overall vs 61 minutes in men over 65, and 49 minutes in women overall vs 73 minutes in women over 65. Despite these differences, dosing recommendations for gemcitabine are the same, regardless of age and sex. Toxicities primarily include neutropenia and thrombocytopenia.

Gemcitabine is approved for the treatment of pancreatic cancer and non-small-cell lung cancer with significant activity noted in bladder and breast cancer.[33-35] In non-small-cell lung cancer patients, four studies comprising a total of 329 evaluable patients reported a response rate of 20%. Patients under age 70 years and those age 70 years and older had similar response rates of 19.0% and 25.0%, respectively.[35]

When gemcitabine is combined with cisplatin (Platinol), response rates increase for both bladder and non-small-cell lung cancer, but significant neutropenia and thrombocytopenia occur, necessitating cisplatin dose reductions.[34] Combination therapy may be more difficult for some older patients to tolerate, but gemcitabine as a single agent displays minimal toxicity in this population.[35] Dosing modifications have been reported for hepatic and renal dysfunction.[36]

**Methotrexate:** An antifolate with a wide range of therapeutic applications, methotrexate is primarily eliminated via renal excretion, with 44% to 100% of the dose passed as unchanged drug. Patients with decreased creatinine clearance or advancing age are at risk for significant nephrotoxicity, gastrointestinal toxicity, and myelotoxicity with methotrexate therapy.[37] Additionally, patients with pleural effusions or ascites are at risk of prolonged drug elimination and toxicity due to prolonged methotrexate concentrations.

Methotrexate clearance has been shown to be inversely related to age, correlating with age-related decreases in GFR. Therefore, doses should be adjusted in older patients or in any patient with impaired renal function. Leucovorin rescue, in conjunction with dosage adjustments to minimize
Pharmacology of Antineoplastic Agents in Older Cancer Patients

Published on Cancer Network (http://www.cancernetwork.com)

toxicity, may be useful in patients with advanced age.[31]

**Fluorouracil:** An antimetabolite, fluorouracil (5-FU) is used in the treatment of solid tumors such as gastrointestinal adenocarcinoma, breast cancer, and squamous cell carcinoma of the head and neck. This drug has been combined with modulators such as leucovorin, methotrexate, cisplatin, thymidine, interferon, and allopurinol.[38]

Significant intra- and interpatient variability has been observed in 5-FU pharmacokinetics. Absorption of oral 5-FU is erratic and unpredictable, making the drug clinically useless alone. Bioavailability of 5-FU increases with increasing doses, indicating a saturable first-pass metabolism. Its unpredictable absorption may be partially due to the differences in dihydropyrimidine dehydrogenase (DPD) enzyme activity in the intestines and liver.[39,40]

Age does not affect clearance of 5-FU; however, gender does appear to play a role in clearance. Women have been shown to clear 5-FU at significantly slower rates than men, correlating with the approximately 15% lower DPD activity seen in women.[41] Since 5-FU is cleared through nonrenal mechanisms, adjustments to compensate for renal impairment are not necessary.

Fluorouracil has been infused over a multitude of schedules with little difference in efficacy noted. It has shown some increased toxicity in older patients.[42] In a trial utilizing 5-FU and folic acid, patients over age 70 years experienced more grade 3 and 4 mucositis than did younger patients (11% vs 19%; \( P = .02 \)). No additional differences in toxicity were reported.[43]

UFT (tegafur plus uracil) has been evaluated in elderly colorectal cancer patients. In one phase II trial, reported response rates were 16.9% (with mild toxicity) when UFT was used as a single agent, and 29% when it was combined with leucovorin. Older patients experienced acceptable toxicity.[44] When the DPD inhibitor eniluracil is used in combination with 5-FU, renal excretion of the agent becomes more prominent, which could necessitate dosage adjustments in cases of renal failure. An average of 77% of 5-FU is excreted unchanged in the urine of patients receiving the combination.[45] Table 2 summarizes data for some of these oral fluoropyrimidines.

**Capecitabine:** The only FDA-approved oral fluoropyrimidine, capecitabine (Xeloda) is metabolized by carboxylesterase, cytidine deaminase, and intratumoral thymidine phosphorylase to 5-FU. Activity has been noted in breast and colorectal cancer.[46] Other than the occurrence of palmar-plantar erythrodysesthesia, postmenopausal women receiving capecitabine have experienced minimal toxicity.[47] The hand-foot syndrome occurs in approximately 40% of patients given the drug. Capecitabine pharmacology is not significantly affected by age, gender, body surface area, hepatic dysfunction, or creatinine clearance.[48,49]

Administration with food had been shown to significantly affect both the area under the concentration-time curve (AUC) and maximum concentration levels (C\( \text{max} \)) of capecitabine. Pharmacokinetic and efficacy data were obtained from patients taking the medication with food.[50] In addition, administration with antacids produced minor effects on the pharmacokinetics of the agent. Administration of an aluminum- and magnesium-containing antacid (Maalox, 20 mL) did not affect time to C\( \text{max} \), or half-life in a group of patients ranging in age from 35 to 74 years. Although the C\( \text{max} \) (17% to 18%) and total AUC (7% to 10%) of capecitabine were slightly higher with coadministration of the antacid, the differences were not significant. It appears that antacid administration has no clinical effect on the agent.[50]

**Fludarabine:** Fludarabine (Fludara) is an agent used in the treatment of chronic lymphocytic leukemia and other B-cell malignancies. One of its metabolites, F-araA, is primarily eliminated renally. Data indicate an elimination half-life ranging from 6.9 to 12.4 hours; however, the half-life increases up to 23.9 hours with renal dysfunction. The 24-hour urinary excretion is 60% of the administered dose. Fludarabine-related neutropenia was found to be directly related to total body clearance, AUC, and half-life. Dose adjustments may be necessary in patients with renal impairment; however, dose-adjustment guidelines are lacking.[51,52]

**Camptothecins**
Topotecan: A topoisomerase I inhibitor that has been approved for the treatment of recurrent or refractory ovarian cancer and small-cell lung cancer, topotecan (Hycamtin) also has activity in myelodysplastic syndromes and acute myeloid leukemias. [53,54] An oral formulation of the drug, with a bioavailability of 40%, is currently undergoing clinical trials. Oral administration of topotecan has been shown to have similar pharmacokinetics to intravenous therapy, except for a longer terminal half-life of 3.9 hours. Food has been shown to delay the time to maximum concentration to 3.1 hours vs 2.0 hours in a fasting state.[55]

Renal clearance accounts for 30% of topotecan elimination; the drug has a half-life of 3 hours. 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 creatinine clearance has been recommended particularly for older patients.[56] Dosing recommendations include the standard intravenous dose of 1.5 mg/m\(^2\)/d for 5 days every 3 weeks and 0.75 mg/m\(^2\)/d for 5 days every 3 weeks in the presence of moderate renal dysfunction (Table 3).

Irinotecan: Another topoisomerase I inhibitor, irinotecan (Camptosar) has been approved for use alone in the treatment of metastatic colorectal cancer or in combination with 5-FU and leucovorin, and has activity in glioblastoma multiforme and small-cell lung cancer.[57-59] It can be given weekly or on an every-3-week basis.[60]

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 due to intestinal accumulation of SN-38. Biliary concentration of SN-38 may indicate gastrointestinal toxicity, leading to the proposal of a biliary index as a surrogate measure for predicting the severity of diarrhea. Retrospective analysis showed that delayed diarrhea increased in patients with advanced age.

Pharmacokinetic parameters such as mean irinotecan, SN-38, SN-38G, C\(_{\text{max}}\), AUC\(_{0-24}\), and biliary index values in patients aged 65 years or older are reported to be within 3% of those in younger patients. In addition, response rates do not vary with age.[61,62] It is recommended that patients over the age of 70 years and those with prior pelvic irradiation or poor performance status start at reduced doses.[60]

Anthracyclines and Anthracenediones

The anthracyclines and anthracenediones include doxorubicin, daunorubicin (Cerubidine), idarubicin (Idamycin), epirubicin (Ellence), and mitoxantrone (Novantrone). These agents have a wide variety of clinical applications in both solid and hematologic malignancies. The classic toxicity of these agents is long-term cardiotoxicity, in addition to dose-limiting toxicity of myelosuppression and stomatitis. These agents largely undergo biliary excretion and doses must be adjusted if even mild hyperbilirubinemia is present.

Cardiotoxicity is increased in both elderly and pediatric patients.[63] Cardiac function is monitored during therapy and follow-up through the multiple gated acquisition (MUGA) scan. Monitoring can detect changes in left ventricular function but may not decrease the incidence of cardiomyopathy. In order to minimize lifetime risk of cardiotoxicity, it is recommended that, in adults, cumulative doxorubicin doses be limited to 550 mg/m\(^2\) and daunorubicin doses to 500 mg/m. Dexrazoxane (Zinexcard) is a cardioprotectant for patients receiving doxorubicin that decreases the incidence of cardiotoxicity with therapy above recommended dosage limits.[64-66]

Doxorubicin/Daunorubicin: Doxorubicin is moderately protein bound, with 50% to 85% bound to plasma proteins. Anthracyclines do not cross the blood-brain barrier. The elimination of anthracyclines occurs in a biphasic or triphasic manner: The two half-life phases reported for daunorubicin are 45 minutes and 18.5 hours, and for doxorubicin, 5 to 10 minutes and 30 hours.[67,68] The anthracyclines are metabolized primarily in the liver (through the activity of the aldo-keto reductases), where they are converted into alcohol metabolites.

Daunorubicinol is the major form of daunorubicin in the plasma within 1 hour of administration (with a corresponding half-life of 26.7 hours), and doxorubicinol is the major form of doxorubicin (with a
half-life of 31.7 hours). Elimination of the parent compounds and metabolites occurs primarily through the bile or feces (40% daunorubicin, 40% to 50% doxorubicin) and the urine (14% to 23% daunorubicin, 4% to 5% doxorubicin). The anthracyclines enter into the cells through passive diffusion across the cell membrane, and through the ability to concentrate in tissues 30- to 1,000-fold over corresponding plasma concentrations.[65]

An interesting effect of obesity on the pharmacokinetics of doxorubicin was reported by Rodvold et al, who studied 21 patients receiving 50 to 75 mg/m$^2$ of doxorubicin intravenously over 60 minutes.[69] This study indicated a reduced clearance of doxorubicin in obese patients when compared with normal weight patients—891 vs 1,569 mL/min, respectively. The half-life of doxorubicin was also prolonged in obese patients—20.4 vs 13.0 hours for normal weight patients. Pharmacokinetic changes are primarily attributed to changes in clearance, since the authors found no difference in the volume of distribution. Of note, the pharmacokinetic parameters of doxorubicinol were not significantly different between groups. Unfortunately, the study did not comment on any differences in toxicity between the groups due to increased exposure to doxorubicin, and no real implications for dosing adjustment can be made from these data.

**Idarubicin:** Idarubicin is an intravenous agent primarily used in the therapy of acute nonlymphocytic leukemia. An oral formulation is currently being studied.[70] The drug is well tolerated by the elderly, with pharmacokinetics unaltered and bioavailability independent of age. The major metabolite of idarubicin, idarubacinol, is cleared renally; therefore, clearance is significantly reduced with renal dysfunction. Idarubicin is thought to be less cardiotoxic than doxorubicin.[65,71-73]

**Epirubicin:** Approved for the treatment of breast cancer, epirubicin has been compared to doxorubicin either alone or in combination with 5-FU and/or cyclophosphamide (Cytoxan, Neosar) for the treatment of breast cancer. Use of epirubicin is associated with a lower incidence of nausea, vomiting, myelosuppression, and cardiac toxicity.[74] It appears to have a larger therapeutic window than doxorubicin with regard to cardiotoxicity.[75] Elderly patients tolerate weekly doses of epirubicin well.[76]

**Liposomal Formulations:** Liposomal doxorubicin (Doxil) and liposomal daunorubicin (DaunoXome) have been approved for epidemic Kaposi’s sarcoma and have activity in malignant lymphoma, refractory ovarian cancer, and breast cancer. Liposomal formulations completely alter the pharmacokinetic, pharmacodynamic, and toxicity profiles of these agents. Hand-foot syndrome is seen more frequently with these drugs; however, mucositis, alopecia, and cardiac toxicity are markedly diminished compared with nonliposomal formulations. The reduced toxicity of this class of drugs may be particularly beneficial in elderly patients with anthracycline-sensitive diseases.[77-79].

**Mitoxantrone:** An anthracenedione, mitoxantrone has activity in acute nonlymphocytic leukemia, lymphoma, breast, and prostate cancer. It is associated with decreased toxicity and increased tolerance compared to the anthracyclines, and is therefore a good choice for an elderly patient. Approximately 10% of the drug is eliminated renally, making dose adjustments 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 over 60 hours.[65,79-81]

**Taxanes**

The clinical utility of paclitaxel (Taxol) and docetaxel (Taxotere) has been demonstrated in lung, breast, bladder, head and neck, prostate, and ovarian cancers.[82,83] Taxanes undergo hepatic cytochrome P450 metabolism through the 2C8 and 3A4 isoenzymes. Consequently, liver dysfunction and drug interactions can alter the pharmacokinetics of these agents.[28] The effect of age on the pharmacokinetics and pharmacodynamics of the taxanes is being studied; however, to date, no age-related differences have been noted.[84]

The primary toxicities associated with these agents include peripheral neuropathy and myelosuppression. Neuropathy can be particularly problematic when taxanes are combined with a platinum compound. Amifostine (Ethyol) may be able to decrease this toxicity.[85] Regimens of
paclitaxel and docetaxel administered on a weekly basis are being investigated with an eye toward improving tolerance to these agents while decreasing their toxicity.[86,87] In addition, the repetitive dosing of dexamethasone to prevent adverse reactions (ie, hypersensitivity, fluid retention) can contribute significant toxicity in elderly patients.

A study of 3- and 24-hour infusions of paclitaxel was conducted in patients with liver dysfunction.[88] Study subjects were treated in three cohorts: cohort 1 had aspartate aminotransferase levels > 2 times normal and bilirubin levels \( \leq 1.5 \text{ mg/dL} \); cohort 2 had bilirubin levels from 1.6 to 3.0 \text{ mg/dL}; and cohort 3 had bilirubin levels \( \geq 3.1 \text{ mg/dL} \). Dose-limiting toxicity was due to neutropenia, fever, fatigue, and mucositis. The study indicated that paclitaxel must be used at these reduced doses: cohort 1, \(< 135 \text{ mg/m}^2\); cohort 2, \( \leq 75 \text{ mg/m}^2\); cohort 3, 50 \text{ mg/m}^2.[89] Although these guidelines are not specific for elderly patients, they can help avoid serious toxicity.

Docetaxel clearance is a strong independent predictor of both grade 4 and febrile neutropenia. The pharmacokinetic behavior of docetaxel does not appear to be altered by age or gender. However, hepatic dysfunction can increase the drug’s hematologic toxicity and major morbidity. Patients with elevated hepatic enzymes have a 27% reduction in docetaxel clearance and are at higher risk of neutropenic sepsis. Hepatic dysfunction has been associated with an increase in the percentage of cycles of therapy during which febrile neutropenia occurred and in the number of patients suffering documented infection and severe (grade 3/4) stomatitis. The incidence of toxic death has also been found to be higher in patients with moderate hepatic impairment.[89]

Dose modifications similar to those suggested for paclitaxel are strongly recommended; however, patients with liver metastases and normal liver function do not require dose modifications.[90] In addition, a cumulative dose of 400 \text{ mg/m}^2 has been associated with fluid retention in patients not receiving dexamethasone prophylaxis.[90] The median cumulative dosage of docetaxel associated with the onset of moderate to severe fluid retention is reported at 705 to 819 \text{ mg/m}^2.

**Platinum Compounds**

**Cisplatin:** Cisplatin was the first heavy metal alkylating compound to be extensively studied. It is associated with activity in lung, cervical, head and neck, esophageal, germ-cell, and ovarian cancers.[91] This wide activity in numerous malignancies common in the elderly translates into common exposure to this agent during therapy. Triphasic elimination shows the half-life of the initial phase to be 20 to 30 minutes; the second phase half-life to be 48 to 67 minutes; and the terminal half-life, 24 hours. All three half-lives are dependent on normal renal function, because 90% of cisplatin is eliminated renally.[91]

The major toxicities of therapy include: renal insufficiency, magnesium wasting, nausea and vomiting, peripheral neuropathy, auditory impairment, and myelosuppression. Severe nausea and vomiting has been markedly reduced by premedication of patients with a serotonin receptor type 3 antagonist.[92,93] The nephrotoxicity of cisplatin has caused some clinicians to avoid use of this drug in elderly patients; however, with proper precautions, toxicity can be minimized.[24] Intravenous hydration with cisplatin therapy has reduced acute nephrotoxicity to 5%.[94,95] Moreover, retrospective analyses of clinical studies in the elderly have not revealed an excessive incidence of nephrotoxicity.[15,16,96,97] Selection bias in trials may contribute to the low incidence of toxicity, but an elderly patient with a good performance status and no comorbidity can certainly tolerate a cisplatin dose of approximately 60 \text{ mg/m}^2.[24] Amifostine may provide some protection against cisplatin-induced nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression[91,98] and may also improve the therapeutic index of elderly patients treated with cisplatin.

**Carboplatin:** Carboplatin (Paraplatin) has a similar mechanism of action to that of cisplatin, with antineoplastic activity against cervical, lung, and ovarian cancers. The drug is completely eliminated through the kidneys, and is administered via one of the most unique methods of chemotherapy dosing currently in use. The Cockcroft-Gault and Calvert formulas allow for accurate and safe dosing that takes into account renal function changes with age and a targeted AUC.[30,99]

Carboplatin exhibits biphasic elimination with an initial half-life of 1.1 to 2 hours, a final half-life of
2.6 to 5.9 hours, and creatinine clearances > 60 mL/min. The combination of paclitaxel and carboplatin is widely used to treat lung cancer and produces less thrombocytopenia than would be expected from the same AUC of carboplatin when administered as a single agent.[100] The combination of paclitaxel/carboplatin can be safely administered to elderly patients.[101]

Oxaliplatin: Oxaliplatin is a platinum coordination complex of the 1,2-diaminocyclohexane family that is currently undergoing clinical trials. The most constant side effect of the drug is a dose-related transient peripheral neuropathy; hematologic toxicity is moderate. Oxaliplatin differs from cisplatin in its lack of nephrotoxicity and from carboplatin in its mild hematologic toxicity.

The transient peripheral neuropathy associated with oxaliplatin manifests as paresthesia and dysesthesia in the extremities, triggered or enhanced by exposure to cold. These neurosensory phenomena, dependent on the cumulative dose of the drug, affect all patients who receive doses $\geq 540$ mg/m$^2$ over four cycles or more of therapy. The neurologic toxicity is also highly reversible, with 82% of patients experiencing a regression within 4 to 6 months, and 41% achieving complete recovery within 6 to 8 months.

Pharmacokinetic studies have shown that oxaliplatin can be administered at the maximum tolerated dose equally safely in patients with normal and moderately impaired renal function, without dose adjustment or hydration. Clinical trials of oxaliplatin in colorectal cancer have reported response rates of 10% in 5-FU-refractory patients, 24% when the drug is used as frontline therapy, and upwards of 46% when combined with a 5-FU/leucovorin regimen.[102]

Alkylating Agents

The alkylating agents are drugs that act through the covalent bonding of alkyl groups to cellular molecules. They alkylate DNA through the formation of reactive intermediates that attack nucleophilic sites, and they play an important role in many combination chemotherapy regimens.[103] These drugs are particularly valuable in elderly patients because they are available in oral formulations (chlorambucil [Leukeran], melphalan [Alkeran], cyclophosphamide, lomustine [CeeNu]) and are associated with relatively little acute toxicity. That said, there have been few specific studies of the pharmacokinetics of the these drugs in elderly patients (Table 4 and Table 5).

Ifosfamide: Ifosfamide (Ifex) is an alkylating agent that requires biotransformation by the cytochrome P450 mixed-function oxidase to 4-hydroxyifosfamide, which is subsequently transformed to an active isophosphoramide mustard.[104] Ifosfamide has a broad spectrum of activity in both solid tumors and malignant lymphomas. Advancing age is associated with a slower rate of biotransformation of ifosfamide, which may be attributable to altered distribution into fat.

This slowed conversion correlates with an age-related increase in the half-life—the median half-life of ifosfamide is 3.9 hours in patients under age 60 years vs 6 hours in those over age 60. However, the prolonged half-life of this agent is not associated with increased toxicity. No correlation between age and total plasma clearance, renal clearance, and nonrenal clearance has been identified. Dose modification, based on age alone, does not seem to be necessary.[104]

Temozolomide: Temozolomide (Temodar) is an oral alkylating agent that has shown significant activity in malignant gliomas, including anaplastic astrocytoma, glioblastoma multiforme, and melanoma.[105-108] It is rapidly and completely absorbed following oral administration. Peak plasma concentrations occur within 1 hour but may be delayed to 2.25 hours if taken with food. A high-fat breakfast decreases the C$_{\text{max}}$ by 32% and the AUC by 9%.[109] Temozolomide is spontaneously hydrolyzed at physiologic pH to an active metabolite. The pharmacokinetics appear consistent and unaffected by age over a reported age range of 19 to 78 years.

Women have approximately a 5% lower clearance of temozolomide than men. This small difference probably does not account for the increased incidence of grade 4 neutropenia and thrombocytopenia during the first cycle of therapy in women as compared to men. Creatinine clearances ranging from 36 to 130 mL/min/m have no effect on the clearance of temozolomide. No studies have been conducted in patients with a creatinine clearance $< 36$ mL/min/m.
Patients with mild to moderate hepatic dysfunction (Child’s Pugh class A/B) have pharmacokinetics similar to those with normal hepatic function, but patients with severe hepatic dysfunction have not been studied.[105] Although studies have failed to indicate significant differences in temozolomide pharmacokinetics, data do suggest that patients over age 70 experience an increased incidence of grade 4 neutropenia and grade 4 thrombocytopenia vs patients less than age 70.[109] Common toxicities include nausea, vomiting, headache, fatigue, constipation, myelosuppression, and convulsions.[105-108]

One study reported on the use of oral temozolomide in patients aged 32 to 78 years. Data indicated that C$_{\text{max}}$ and AUC appear to accumulate significantly during a 5-day dosing regimen. Grade 4 neutropenia and grade 4 thrombocytopenia correlated with patients who had significantly higher AUC values on both day 1 (32 vs 20 g/h/mL, $P = .0019$) and day 5 (36 vs 23 µg/h/mL, $P = .0042$) of the dosing regimen.[110]

A similar study did not identify accumulation over a 5-day dosing period.[107] In addition, one report of prior nitrosourea exposure identified a 14% lower clearance of temozolomide in patients with prior nitrosourea exposure (102.27 vs 115.22 mL/min/m$^2$, $P = .047$). Dose-limiting hematologic toxicity was seen at 250 mg/m$^2$/d in patients with no prior exposure to nitrosoureas vs 150 mg/m$^2$/d in patients with prior exposure.[111]

Other Drugs

**Etoposide:** Etoposide is a topoisomerase II inhibitor used in refractory non-Hodgkin’s lymphoma, lung cancer, germ-cell tumors, and a multitude of other malignancies.[112-116] It is typically administered intravenously, although an oral formulation is also available. Oral therapy occasionally poses problems related to absorption and tolerance.[117]

Etoposide displays biphasic or triphasic pharmacokinetic characteristics, with an initial half-life of 0.6 to 2 hours (range: 0.25 to 2.5 hours), and a terminal half-life of 5.3 to 10.8 hours (range: 2.9 to 19 hours). Absorption of etoposide varies considerably and is estimated at 50%, but can range from 25% to 75%. Absorption is dose dependent, with decreasing absorption observed at oral doses greater than 200 to 400 mg.[68,118]

Impaired renal function leads to a decrease in drug clearance rates, but, to date, definitive dosage adjustments have not been established for etoposide in the presence of renal dysfunction. Increasing age has been correlated with increased free etoposide concentrations during oral therapy. Unfortunately, efficacy does not correlate with concentrations of free etoposide, only with the occurrence of toxicity. Poor performance status may put older patients at higher risk for grade 4 dose-limiting toxicities such as myelosuppression and mucositis.[112] The use of oral etoposide has shown some response in patients who were refractory or relapsed after standard or high-dose regimens.[119,120]

Etoposide is eliminated to some degree via hepatic cytochrome P450 metabolism, but dosage adjustments based on liver dysfunction are controversial. One study of oral etoposide pharmacokinetics divided 17 hepatocellular carcinoma patients with a mean age of 65 years (range: 52 to 83) into two groups: Group 1 comprised 10 patients with a bilirubin level $\leq$ 1.2 mg/dL; group 2 comprised 7 patients with a bilirubin level $> 1.2$ mg/dL.[63] Group 2 had a significantly higher mean bilirubin, mean serum glutamic oxaloacetic transaminase (SGOT), and prothrombin time index than group 1, but no difference in albumin at baseline. There was no clinical evidence of increased toxicity in patients with hyperbilirubinemia, compared with patients with normal bilirubinemia. In this study, the pharmacokinetics of oral etoposide did not differ between patients with liver dysfunction and those with normal liver function.[121]

**Vinorelbine:** Vinorelbine (Navelbine) is a semisynthetic vinca alkaloid approved for the treatment of metastatic non-small-cell lung cancer and has activity in breast and ovarian cancer.[122-125] Vinorelbine shows decreased neurotoxicity compared to other agents in its class, with myelotoxicity as the dose-limiting toxicity. This drug’s favorable toxicity profile is particularly useful in elderly patients.
Vinorelbine is excreted primarily through the biliary tract in the feces, with minimal (11%) renal elimination. Dose modification is required for patients with liver dysfunction, particularly those with bilirubin values > 3.0 mg/dL. Patients age 65 years and older have shown similar pharmacokinetics to younger patients. Age does not correlate with toxicity of vinorelbine therapy; therefore, there is no need for dose reductions in elderly patients.[126,127]

**Thalidomide:** Developed as a sedative in the 1950s, thalidomide (Thalomid) is currently being evaluated as an antiangiogenic agent.[128] The mechanism of action of thalidomide is unknown but may involve reductions in tumor necrosis factor (TNF) levels and inhibition of basic fibroblast growth factor. TNF-alpha has been associated with erythema nodosum leprosum, AIDS, cancer, graft-vs-host disease, tuberculosis, and malaria. Additionally, thalidomide increases levels of IL-2 and interferon-gamma, augments NK-like activity, and inhibits IL-12 production.[129]

Thalidomide has shown activity in multiple myeloma and malignant gliomas,[130-132] and it has good oral bioavailability. The AUC is proportional to the dose, but at doses > 200 mg, a flattening of the peak concentration curve is noted. The C\text{max}, T\text{max}, and AUC for thalidomide may vary according to the underlying disease state.[133]

The exact mechanism of metabolism and elimination of thalidomide is not understood; however, it appears to undergo nonenzymatic hydrolysis in the plasma. Less than 0.7% of the dose is excreted in the urine as unchanged drug. The drug’s half-life averages 6 to 7 hours and seems to be similar in all groups studied. In addition, only a small amount of thalidomide metabolites may be detected in the urine at 12 to 24 hours after dosing. The pharmacokinetics of thalidomide in renal or hepatic dysfunction are unknown, but based on elimination data, large differences would not be expected. No dosage adjustments are indicated for the elderly.

**Complementary and Alternative Medicine**

Data show that at least one-third of cancer patients use some form of complementary and alternative medicine (CAM).[134,135] However, there is a significant gap in knowledge regarding alternative therapies in cancer patients, and how they may interact with more conventional therapies. Although increasing evidence indicates that CAM treatments are biologically active, more research is needed to understand potential interactions with drug metabolism and therapeutic outcomes.

St. John’s wort (*Hypericum perforatum*) has recently been reported to induce cytochrome P450 metabolism to such a degree as to affect drug concentrations in selected patients. St. John’s wort lowers the AUC of digoxin by induction of the P-glycoprotein drug transporter.[136] Induction of cytochrome P450 3A4 isoenzymes has led to decreases in indinavir (Crixivan) and cyclosporine (Sandimmune, Neoral) levels that could significantly affect patient outcomes.[137-139]

Additional drug interactions involving cytochrome P450 include the ability of various foods to alter the metabolizing potential of these drugs. Grapefruit juice is a potent inhibitor of cytochrome P450.[140] Cruciferous vegetables, charcoal-grilled beef, red wine, ethanol, and cigarette smoke can also induce the cytochrome P450 system and potentially alter the rate at which many drugs are metabolized.[141]

**Conclusions**

There is increasing recognition of the importance of geriatric oncology. The elderly comprise the largest group of patients in the medical oncologist’s practice. Many of the drugs that have been approved recently have an improved therapeutic index for the elderly as well as a broad range of activity (Table 6). This has affected, in particular, the treatment of solid tumors such as lung, bladder, prostate, and breast cancers. The introduction of newer agents, particularly oral medications, for colorectal cancer will certainly have a significant impact. This will allow a broader spectrum of patients to derive benefit from chemotherapy, particularly those with a poorer performance status.
The elderly are still underrepresented in clinical trials.[142] More studies of toxicity, drug metabolism, and drug effect need to be conducted. Also, we will need improved ways to guide our decision-making as to the appropriate therapy for this group, taking into account comorbidity, performance status, and geriatric functional assessment.[143]

References:
18. Begg CB, Elson PJ, Carbone PP: A study of excess hematologic toxicity in elderly patients treated
Pharmacology of Antineoplastic Agents in Older Cancer Patients
Published on Cancer Network (http://www.cancernetwork.com)


91. Reed E, Dabholkar M, Chabner BA: Platinum analogues, in Chabner BA, Longo DL (eds): Cancer


125. Frasci G, Lorusso V, Panza N, et al: Gemcitabine plus vinorelbine vs vinorelbine alone in elderly...


Source URL:
http://www.cancernetwork.com/printpdf/pharmacology-antineoplastic-agents-older-cancer-patients-2