Monitoring Chemotherapy in an Aging Population

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Oncology Spectrums *2001;2(3):206-213*

INTRODUCTION

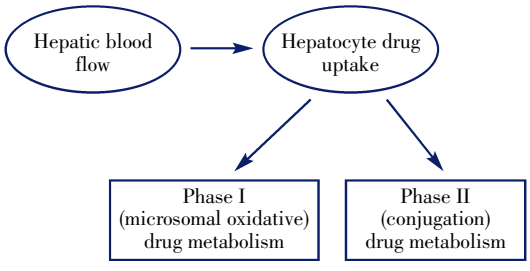
In our aging population there have been and will continue to be increases in the proportion of the population past the age of 65. It is estimated that by 2030 more than 20% of the US population (one in five persons) will be older than age 65.[1] It is well known that the elderly population is at high risk and is more susceptible to environmental and endogenous insults that initiate carcinogenic processes.[2] Along with the estimated increase in a portion of the elderly population in the coming years, a sharp increase in the incidence of cancer can also be anticipated. Older individuals tend to experience more cancer treatment-related toxicity, especially dose-dependent reactions. However, in clinical trials, chemotherapy dosing for the elderly population has not been well-evaluated. Some age-related alterations in pharmacokinetics have been documented for only a number of chemotherapy agents such as doxorubicin, daunorubicin, etoposide, ifosfamide, mitomcyin, cisplatin, and methotrexate.[3]

Age-related differences in physiology that have been well documented contribute to the increased risk of pharmacologically-related toxicity in the elderly.[4,5] Alterations in the kidney, liver, circulatory system, and body composition have the most significant impact on drug disposition. Although, in the elderly, there are changes in gastric pH and gastric blood flow, these changes do not have a significant effect on drug absorption. The decline with age in kidney function is associated with a 25–30% decrease in renal mass and a 1%-per-year decline in renal blood flow.[6] After age 40, glomerular filtration rate decreases at an estimated rate of 1 mL/min per year as a result of glomerular sclerosis.[7] Serum creatinine will not accurately represent the decline in GFR due to the simultaneous loss of muscle mass that occurs during in the aging process.[7] The decline in renal function with age has a measurable and predictable effect on drug clearance.

Drug clearance is also decreased by age-related changes in the liver. (Figure 1) Liver blood flow declines between the ages of 20 and 90 years by as much as 40%, and liver size decreases between 20–25% in a lifetime.[4,6] There are controversial reports regarding the age-related changes in the liver enzymes associated with phase I (microsomal oxidative) and phase II (conjugation) drug metabolism. Reports of age-related declines in cytochrome P450 (CYP450) 1A2, 2D6, and 3A4 activity have been made; but in many cases these data have not been reproducible. The overall decreased clearance with aging of hepatic metabolized drugs has been documented. The capability of liver enzymes to metabolize drugs may not change with age, but the actually quantity of liver enzymes may decline with age as a result of decreased liver size. In addition, reduced liver blood flow may decrease the delivery of drug through the liver enzyme system, which again may appear as a decrease in liver enzyme activity.

Serum albumin may decline with increasing age by 15–20%.[8] However, α_1-acid glycoprotein (AAG) binding to lipophilic basic drugs increases with age and in acute illness.[8] Thus, protein binding might be altered in elderly cancer patients. Drug disposition is influenced by the age-related changes in body composition. Body fat tends to increase as lean body mass and total body water decrease during the aging process.[4,6] These changes may alter the volume of distribution and clearance of some drugs.

FIGURE 1. HEPATIC DRUG METABOLISM



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In recent clinical trials, patients older than 65 years were included and stratified out in order to evaluate tolerability and response to chemotherapy. In a trial conducted by Alberts et al, the authors evaluated tolerability and response to a cisplatin and cyclophosphamide regimen and to a carboplatin and cyclophosphamide regimen in 342 elderly and adult patients with ovarian cancer.[9] The researchers found age and performance status to be significant prognostic factors in tolerability and response, the carboplatin and cyclophosphamide regimen having been tolerated better in both age groups. In another trial, which was conducted with non-Hodgkin's lymphoma patients older than age 60 years, Gomez et al evaluated the CHOP chemotherapy regimen ± GM-CSF.[10] In this trial, patients aged 61 to 69 and patients older than age 70 responded equally to the regimen but differed significantly in treatment-related toxicity. In a retrospective review by Cornelison and Reed of carboplatin dose intensity in 93 ovarian cancer patients across all age groups, age was not a prognostic factor of toxicity.[11] Patients with adequate end organ function and good performance status responded and tolerated chemotherapy equally regardless of age.

A consensus exists among the majority of the reviews regarding chemotherapy administration in the elderly population. Most researchers conclude that these patients will not tolerate chemotherapy as well as younger patients. Due to the physiological changes that occur during the aging process, elderly patients are more susceptible to toxicity as well as to altered pharmacokinetics of the chemotherapy agents. Although age-related changes in physiology have been defined, there is interpatient variability as to the extent of these changes and when these changes occur chronologically. There is considerable variability regarding the extent of changes between age 70 and 85 years, but it is generally accepted that individuals older than age 85 will have some degree of compromised organ function effecting drug disposition.[2] Still the arbitrary age of 70 is often used to classify patients as elderly even though this marker

TABLE 1. CYTOCHROME P450 DRUG METABOLISM REFERENCE[38-40]

CYP450 Isoenzyme X	1A2	2D6	2C9	3A4	
Drugs that inhibit CYP450 isoenzyme	Fluvoxamine Fluoxetine Paroxetine Nefazadone Sertraline Valproate Sulfamethazole	Fluoxetine Paroxetine Sertraline Fluvoxamine Venlafaxine Quinidine Valproate Sulfamethazole	Setraline Fluvoxamine Amiodarone Valproate Sulfamethazole	Fluvoxamine Nefazadone Venafaxine Fluoxetine Sertraline Paroxetine Erythromycin Carithromycin Amiodarone Ketoconazole Itraconazole Cimetidine Grapefruit juice Valproate Sulfamethazole	
Drugs that Induce CYP450 isoenzyme	Carbamzepine Phenytoin Primidone Rifampin Barbiturates	Carbamzepine Phenytoin Primidone Rifampin Barbiturates	Carbamzepine Phenytoin Primidone Rifampin Barbiturates	Carbamzepine Phenytoin Primidone Rifampin Barbiturates	
Drugs commonly used in the elderly that are metabolized by CYP450 isoenzyme*	Amitritpyline Imipramine Clozapine Caffeine Acetaminophen Theophylline R-warfarin	Tramadol Codeine Dextomethorphan Flecainide Encainide Propafenone Haloperidol Perphenazine Propanolol Metopropol Amitriptyline Nortriptyline Imipramine Donepezil Zafilukast	Phenytoin S-warfarin Tolbutamide Diclofenac Mefanmic acid Pirozicam Naproxen Ibuprofen	Quinidine Amiodarone Loratadine Astemizole Tamoxifen Lovastatin Atorvastatin Simvastatin Pravastin Fluvostatin Amitriptyline Imipramine Nafazodone Sertraline Diltiazem	Felodipine Nifedipine Verapamil Carbamazepine Cyclosporin Erythromycin Rifampin Omeprazole Afentanil Acetaminophen Donepezil Zafirlukast

*List is not all-inclusive

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has not been substantiated by controlled clinical trials. In many cases, being 70 years old is not necessarily a negative prognostic factor. With no better option, the common approach currently is to define elderly as older than 70 years. However, a number of trials are underway to better define drug disposition in the elderly population including identifying biological surrogate markers for defining physiological age rather than basing drug dosing on chronological age alone.

Previous literature and ongoing trials have demonstrated that organ dysfunction will alter the pharmacokinetic profile of many drugs. With chemotherapy, these alterations often contribute to an avoidable increase in treatment-related toxicity experienced by the patient. For the pharmacist, the best way to prevent elderly patients from unnecessary treatment-related toxicity is to closely monitor organ function and laboratory values. Then one can recommend appropriate dose reductions as needed while allowing those elderly patients with adequate organ function and lab values to receive the full does chemotherapy and to have the best chance for treatment success.

PHARMACOLOGY:

Doxorubicin, cyclophosphamide, gemcitabine, docetaxel and paclitaxel are among the most commonly selected agents for the adjuvant treatment of various types of cancer. Doxorubicin, cyclophosphamide, docetaxel and paclitaxel have shown great clinical benefit and improved survival outcomes for patients with cancer. Also, gemcitabine has demonstrated a significant improvement in the quality of life for pancreatic cancer patients. It is still being evaluated for the treatment of other cancers. Most clinical trials with these agents have excluded older patients based on age alone. Toxicity and tolerability have been the main limitations in using these agents in the elderly patient population. However, the studies that have included older patients include those with adequate end organ function and good performance status, and these older patients have responded and tolerated chemotherapy with these agents. Although it is well documented that end organ function declines with age, studies support the fact that we cannot assume end organ function to be defined by age alone.

Cyclophosphamide is an alkylating agent commonly used in the treatment of main solid tumors such as breast cancer and ovarian cancer as well as for the treatment of lymphomas and hematological malignancies. Cyclophosphamide is an oxzaphosphorine that requires activation by the cytochrome P450 microsomal oxidative enzyme system in the liver of its active compound, 4-hydroxycyclophosphamide. Liver conjugation enzymes metabolize cyclophosphamide to its other inactive metabolites such as acrolein and nornitrogen mustard. Acrolein is responsible for the common toxicity, hemorrhagic cystitis, associated with both cyclophosphamide and ifosfamide. The dose limiting toxicity for cyclophosphamide has been leukopenia and thrombocytopenia at higher concentrations.[12] Other common toxicities include nausea, vomiting and alopecia. Cyclophosphamide's estimated pharmacokinetic parameters are an average elimination half-life of 7 hours (with average range of 3 to 10 hours), an average total body clearance 67 to 100 mL/min, and an average volume of distribution of 0.7 L/kg.[12] Cyclophosphamide pharmacokinetics are nonlinear at higher doses, that is, 4 g/m^2. Elimination of cyclophosphamide is primarily extrarenal however, significant renal insufficiency will contribute to decreased total body clearance of cyclophosphamide and ultimately increased toxicity.

Doxorubicin is in the class of anthracycline chemotherapy agents and is one of the more commonly used antitumor agents. Doxorubicin is included in chemotherapy regimens for the treatment of numerous solid tumors and hematological malignancies including breast cancer and metastatic prostrate cancer. Metabolism of doxorubicin to its active metabolite doxorubicinol and inactive metabolite doxorubicinone, and 7-deoxydoxorubcinone occurs rapidly via cytoplasmic NADPH-dependent aldoketoreductase predominantly in red cells, and in liver and kidney tissues.[13,14] The cytochrome P450 mediated metabolism of doxorubicin p roduces the OH- radicals that are ultimately responsible for its cytotoxic activity. Doxorubicin pharmacokinetic parameters have varied dependent upon dose, duration of treatment, and in some reports age.[14] General estimated doxorubicin pharmacokinetic parameters have been reported as an average elimination half-life of 26.5 hours (31 hours for doxorubicinol), an average total body clearance of 30.2 L/H/m^2, and an average volume of distribution of 23 L/kg.[14] Elimination of doxorubicin is predominantly extrarenal with only 30% renal cleared. However, the primary metabolite of doxorubicin, doxorubicinol, is predominantly cleared renally which may be significant in profound dysfunction. The dose-limiting toxicity for doxorubicin is hematological including leukopenia, thrombocytopenia, and anemia. Other commonly reported toxicities include nausea, vomiting, alopecia, and stomatitis. The incidence of cardiotoxicity, such as congestive heart failure, has limited the total lifetime dose of doxorubicin.

Paclitaxel and docetaxel are the two members of the taxane class of chemotherapy agents. Both have demonstrated activity in a variety of cancers such as breast, ovarian, and head and neck cancers. Paclitaxel is metabolized via the cytochrome P450 microsomal oxidative enzyme system to three primary metabolites, 6_-hydroxypaclitaxel being the most predominant metabolite.[15-17] Docetaxel metabolism has also been described as being mediated by the cytochrome P450 microsomal oxidative enzyme system with similar metabolite formation, two isomeric hydroxyoxazolidinones, M1 and M3, and also the formation of M2 and oxazolidinedione (M4).[16] Elimination of paclitaxel, and docetaxel is primarily through hepatic and biliary excretion. Dose adjustment in renal insufficiency is not necessary. The estimated average elimination of paclitaxel ranges from 6 to 30 hours. Paclitaxel's average total body clearance ranges from 126 to 500 mL/min/m^2 and it has an average volume of distribution of 33 to 1,186 L/m^2.[17] The estimated average elimination of docetaxel ranges from 8 to 20 hours.

Docetaxel's average total body clearance ranges from 267 to 1163 mL/min/m^2 and it has an average volume of distribution of 33 to 1,186 L/m^2.[17] Leukopenia, neutropenia and neurotoxicity are the dose limiting toxicities for both agents. Because these products are naturally from plant extracts, allergic reactions are common but are rarely a problem with appropriate pre-treatment precautions.

The two platinum antitumor agents, cisplatin and carboplatin are the first-line agents for a number of solid tumors such as head and neck cancer and ovarian cancer. Although cisplatin and carboplatin are not metabolized in the liver by the cytochrome P450 microsomal enzymes system, there have been reports of cisplatin administration interfering with metabolism of concomitant medications including other antineoplastic agents, metabolized by the cytochrome P450 system.[18] Metabolism of cisplatin and carboplatin is highly dependent on the reactivity of platinum leaving groups. Renal elimination of carboplatin and cisplatin plays a significant role in the efficacy and toxicity of these agents. The average estimated elimination half-life of cisplatin ranges from 30 to 150 hours with an average total body clearance of 10 to 62 mL/min/m^2 and an average volume of distribution of 21 to 500 L/kg. The average estimated elimination half-life of carboplatin ranges from 1 to 7 days with an average total body clearance of 2 to 65 mL/min/m^2 and an average volume of distribution of 23 to 135 L/kg. Neuropathies are most common and are the dose-limiting toxicity for the platinum agents. The common toxicities associated with the platinum agents include leukopenia, thrombocytopenia, alopecia, nausea, vomiting, and ototoxicity. Nephrotoxicity is rare but there is an increased risk with concomitant administration of nephrotoxicity drugs such as aminoglycosides.

End organ function is directly related to the tolerability of chemotherapy because liver and renal function are instrumental to the activation, metabolism, and elimination of these agents. A loss capacity or capability of the liver to metabolize these agents or loss of renal clearance may lead to decreased efficacy or increased toxicity of chemotherapy agents. In addition, concomitant medications that either inhibit or induce the liver cytochrome P450 microsomal enzymes may influence the pharmacokinetics of the agents metabolized by cytochrome P450 enzymes. Concomitant administration of potential nephrotoxic medications may decrease renal function and this could result in decreased elimination and parent or metabolite drug accumulation. Patients should also be closely monitored for toxicity from nonchemotherapy medications administered with chemotherapy agents that may alter organ function or compete for the same paths for metabolism or elimination. (Table 1)

TOXICITY

In the elderly population, patients experience common toxicities associated with chemotherapy such as myelosuppression, cardiomyopathy, mucositis, peripheral neuropathy, delayed nausea and vomiting, and neurotoxicity. Often, these toxicities occur more frequently and are more severe in the elderly population. For older patients, underlying comorbidities such as anemia, dementia, delirium, depression, degenerative bone diseases, diabetes, and cardiovascular disease increase susceptibility to treatment-related toxicity. Before initiating new chemotherapy, discuss and define with the patient and family what is an acceptable level of toxicity. Then, prevent and limit treatment-related toxicity by advocating the use of chemoprotectants and supportive care as appropriate (Table 2).

TABLE 2. USE OF CHEMOPROTECTANTS TO REDUCE RISK OF TOXICITY

Chemotherapy Agent	Common Toxicity	Chemoprotecant
Irinotecan	Diarrhea	Loperamide
Doxorubicin	Cardiomyopathy	Dexrazoxane
Methotrexate	Myelosuppression/mucositis	Leucovorin
Paclitaxel	Myelosuppression	Growth Factors
Cisplatin	Renal/ neuropathy/ myelosuppression	Amifostine/ growth factors
Cisplatin	Anemia	Erythropoietin

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Myelosuppression

Overall, myelosuppression is the most common toxicity experienced by patients receiving chemotherapy. The elderly population has an increased sensitivity to the myelotoxic effects of chemotherapy because of the decrease in the hemopoietic reserve of pluripotent hemopoietic stem cells (PHSC) due to the aging process.[19,20] Through hemopoiesis, the PHSCs are responsible for the formation of the peripheral blood elements such as platelets, red blood cells and neutrophils. With a decreased PHSC reserve, older patients are more susceptible to myelotoxicity resulting in neutropenia, thrombocytopenia, anemia, leukopenia or even pancytopenia. As a result, they experience a delayed recovery. In the elderly population, many of the lethal cases of myelosuppression that have happened after the first course of therapy.[19] Therefore, despite the traditional guidelines, it might be advisable to implement the use of hemopoietic growth factors with the first cycle of myelotoxic chemotherapy regimens for elderly patients.

Mucositis

Mucositis is another common complication of chemotherapy that is often more severe and prolonged in elderly patients. The increased proliferation of the cells lining the gastrointestinal tract makes them more susceptible to the cytotoxic effects of chemotherapy agents such as 5-fluorouracil (5-FU) or doxorubicin. However, it is the decreased hemopoietic reserve of PHSC that contributes to the delayed recovery of mucositis in older patients.[19] Preventive and aggressive treatment of mucositis by use of oral cryotherapy (ice chips), dose and schedule selection (eg, methotrexate: decrease infusion; 5-FU: decrease dose), and early treatment of secondary infections are the best

TABLE 3. RECOMMENDED DOSE ADJUSTMENTS BASED ON HEPATIC DYSFUNCTION[34,35,37]

Chemotherapy Agent	Hepatic Laboratory Values	Recommended Dose Modification
Anthracyclines	Bilirubin 1.2–3.0 mg/dL Bilirubin 3.1–5.0 mg/d Bilirubin >5.0 mg/dL	Decrease dose 50% Decrease dose 75 % Omit dose
Vinka Alkaloids	Bilirubin 1.5–3.0 mg/dL Bilirubin 3.1–5.1 mg/dL	Decrease dose 50% Omit dose
Docetaxel	Bilirubin>Upper limit of normal (ULN) AST or ALT>1.5x ULN and Alk Phos>2.5 x ULN	Do not give Do not give
Paclitaxel	Use with caution in hepatic failure	
Etoposide	Bilirubin 1.5–3.0 mg/dL Bilirubin 3.1–5.0 mg/dL	Decrease dose 50% Omit dose
Thiotepa	Use with caution in hepatic failure	

ULN=upper limit of normal.

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TABLE 4. RECOMMENDED DOSE ADJUSTMENTS BASED ON RENAL DYSFUNCTION[36,37]

Chemotherapy Agent	Estimated Creatinine Clearance (CrCl)*	Recommended Dose Modification
Carboplatin	Any renal insufficiency	*Calvert Equation:* Total Dose=AUC X (CrCl+25)
Cisplatin	CrCl<50 mL/min	Use with caution
Cyclophosphamide or Ifosfamide	CrCl<25 mL/min	Decrease dose 50–75 %
Topotecan	CrCl<20 to 39 mL/min	Decrease dose 50%
Methotrexate	CrCl<60 mL/min	Decrease dose proportionally to decreased CrCl. Monitor levels closely.
Bleomycin	CrCl 30–60 ml/min CrCl 10–30 mL/min CrCl<10 mL/min	Decrease dose 25–50 % Decrease dose 25–50 % Decrease dose 50%
Fludarabine	CrCl<60 mL/min	Use with caution. Decrease dose proportionally to CrCl
Hydroxyurea	CrCl<60 mL/min	Use with caution. Decrease dose proportionally to CrCl
Etoposide	CrCl 15–50 mL/min	Decrease dose 25%

*Calculated with Cockcroft-Gault formula

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approaches to limiting the pain and potential infectious or nutritional complications.

Neurotoxicity

Considering the litany of neurological diseases associated with aging, it is not difficult to understand the potential debilitating effects of neurotoxic chemotherapy in the elderly. The peripheral and central nervous system experience insult and injury from agents such as the vinka alkaloids, cisplatin, taxanes, and epipodophyllotoxins. Peripheral neurotoxicity such as paresthesias, loss of touch sensitivity, decreased deep-tendon reflexes, and weakness limit the daily functional performance of elderly patients, taking away independence that can be devastating to quality of life.[21] In addition to the cognitive losses of the natural aging process that limit some patients, the potential neurotoxicity to the central nervous system from chemotherapy should be closely monitored and prevented if possible. For example, cerebellar toxicity from cytarabine has been associated with decreased renal function so an appropriate dose adjustment prior to therapy might avoid unnecessary neurotoxicity.[19]

Cardiotoxicity

The incidence of cardiotoxicity from anthracyclines has been associated with total lifetime dose, prior radiation, cardiac disease, and age. Elderly patients are predisposed to the cardiotoxicity effects of anthracyclines, most likely due to a history of chronic myocardial damage from hypertension, ischemia, and exposure to various toxins or free radicals during their lifetimes. Fortunately, with a slight adjustment of the administration of the anthracycline schedule, most of the cardiotoxicity can be limited. Also, there is the option of using cardioprotectants, such as dexrazoxane, to prevent damage to the cardiac tissue.

FIGURE 2. COCKCROFT-GAULT FORMULA FOR ESTIMATING CREATININE CLEARANCE

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{body weight (kg)}^{*}}{72 \times \text{serum creatinine mg/dL)}}$$

*Multiple by 0.85 for women

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Other Toxicity

In general, most elderly patients do not tolerate emetogenic chemotherapy well and experience delayed nausea and vomiting more frequently than do younger patients. Preventing delayed nausea and vomiting in elderly patients should be accomplished with scheduled 5Ht3-antagonist +/- dexamethasone or lorazepam rather than with metoclopromide or prochlorperazine because of the potential extrapyramidal adverse effects. Nephrotoxicity is not a common toxicity associated with cytotoxic chemotherapy but it has been reported, especially with agents such as cisplatin. The incidence of cisplatin-related toxicity, though, does not seem to increase with age.[21]

DOSE MODIFICATIONS

Hepatic dysfunction

Dose adjustments for hepatic dysfunction should be considered when administering an agent that is primarily eliminated by the liver. When reviewing a new chemotherapy prescription, it is standard routine to review the daily laboratory results. To assess for potential hepatic dysfunction, evaluate the bilirubin, liver transaminases (AST/ALT), and alkaline phosphatase values. For example, anthracyclines are eliminated from the body primarily via biliary excretion. Thus, if a patient's laboratory results show a significant increase in bilirubin (> 3.1 but < 5.0 mg/dL), that reflects a decrease in biliary excretion then a 75% reduction in the anthracycline dose would be recommended.[22,23] Other agents that require dose adjustment for hepatic dysfunction include the taxanes, etoposide, thiotepa, and the vinka alkaloids (Table 3).

TABLE 5. RENALLY ELIMINATED DRUGS COMMONLY USED IN THE ELDERLY POPULATION[36,37]

Renally Excreted Agents Commonly Used in the Treatment of the Elderly Population
Aminoglycosides
Cimetidine
Digoxin
Furosemide
Lithium
Nitrofurantoin
Penicillin
Phenobarbital
Procainamide
Quinidine
Sulfamides
Tetracycline
Cephalosporins
Ciprofloxacin
Enalaprilat
Famotidine
Fluconazole
Ofloxacin
Ranitidine

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Renal dysfunction

Because the renal pathway is responsible for both the elimination of parent drug compounds as well as numerous drug metabolites, it is important to monitor renal function by evaluating the serum creatinine and by calculating the estimated creatinine clearance (Figure 2). Often, it is not necessary to make a dose adjustment until there is a significant decrease in renal function (Table 4).[24] However, closely monitor all patients with minor decreased renal function for potential toxicity, too. Do this especially, when considering concomitant administration of other renally eliminated non-chemotherapy drugs or potentially nephrotoxic agents. (Table 5)

Drug Interactions

As recommended when dispensing a medication, especially cytotoxic agents, always screen for potential drug interactions including CYP450 metabolism inhibition or induction, protein binding displacement, competitive elimination, or altered absorption.[25] Because the elderly population is more likely to be taking concomitant medications, there is an increased risk for potential drug interactions (Table 1).

RECOMMENDATIONS FOR MONITORING CHEMOTHERAPY IN THE ELDERLY PATIENT POPULATION

1. Treat and monitor all comorbid conditions. Monitor for drug interactions with chemotherapy.
2. Advocate the prophylactic use of growth factors (G-CSF or GM-CSF) for patients older than age 70 years who are receiving cytotoxic chemotherapy.
3. Prevent and aggressively treat mucositis.
4. Be aware of increased risk for anthracycline-induced cardiotoxicity and adjust infusion duration or schedule accordingly. Consider using dexrazoxane as a cardioprotectant.
5. Closely monitor patient for peripheral neuropathy or signs of central nervous system toxicity (cognitive loss) and recommend discontinuation of offending agent if necessary.
6. Treat delayed nausea and vomiting aggressively with scheduled 5-HT_3-antagonist +/- dexamethasone or lorazepam.
7. Use caution and try to avoid the administering nephrotoxic drugs while patient is receiving chemotherapy.

8. Evaluate hepatic panel laboratory results. Assess for potential decreased biliary excretion or other hepatic dysfunction. Advise physician to adjust dose as appropriate according to recommendations (Table 4).
9. Calculate creatinine clearance with Cockcroft-Gault formula (Figure 2). Advise physician to adjust dose as appropriate according to recommendations (Table 5).
10. Assess each patient on an individual basis, not by chronological age alone to ensure that all patients receive appropriate chemotherapy with limited treatment related toxicity.

CONCLUSION

Although age-related changes in physiology have been defined, there is considerable interpatient variability regarding the extent of these differences when they occur. Currently, a number of trials are underway to better define drug disposition in the elderly population including identifying biological surrogate markers for defining physiological age rather than basing drug dosing on chronological age alone. In the past and currently, the arbitrary dose reductions based on age older than 70 years have been made in attempt to limit treatment related toxicity in the elderly population. But the age of 70 alone is not necessarily a negative prognostic factor. Until clinical trials are completed to better define surrogate markers for physiological age and drug disposition in the older population, the be approach to monitoring chemotherapy in an aging population depends upon closely monitoring organ dysfunction and on continual patient assessment for toxicity. If any treatment-related toxicity occurs, then aggressive treatment should be used to limit toxicity and to prevent any additional toxicity in future cycles of chemotherapy. Also, the older population is very likely to have co-morbid diseases that should be treated as aggressively as the cancer. Poly-pharmacy is common in the older population because of the number of comorbidities, Hence, it is important to monitor for drug-drug interactions when administering chemotherapy agents that may alter organ function, alter metabolism or clearance, or involve protein binding displacement. When close monitoring is carefully instituted, chemotherapy can be safely administered to older patients without arbitrary dose reductions or unnecessary toxicity.

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