



Ettore "Ted" DeGrazia. *Lost Apache*. Oil on canvas, 10" × 18". Courtesy of DeGrazia Foundation.

*Age influences
pharmacokinetics
and can affect
tolerance of common
anticancer drugs.*

Pharmacokinetics of Chemotherapy in the Older Patient

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Background: *The number of individuals aged 65 years and older is growing rapidly, and the majority of cancers are diagnosed in this age group. Age-related changes in physiology can affect chemotherapy pharmacokinetics and pharmacodynamics in older patients.*

Methods: *We review the literature regarding the impact of age on the pharmacokinetics of commonly used chemotherapy drugs and discuss age-related changes in physiology and pharmacology that can affect chemotherapy tolerance in older patients.*

Results: *The data on age-related changes in chemotherapy pharmacokinetics are conflicting. While a few studies report age-related differences in chemotherapy pharmacokinetics, most found no significant difference or subtle differences in pharmacokinetics with aging. A difference in pharmacodynamics was commonly seen, however, with older patients at increased risk of myelosuppression and toxicity from age-related decline in organ function. The majority of these studies were performed in a small cohort of patients, thus limiting the generalizability of these results.*

Conclusions: *Additional studies are needed to address the pharmacokinetics and pharmacodynamics of cancer therapies in the older patient. Multicenter pharmacokinetic studies of adequate sample size, which include a thorough evaluation of physiologic factors and geriatric assessment parameters, would provide further insight into the factors affecting treatment tolerance. These studies would also help to guide appropriate chemotherapy dosing and interventions in order to maximize efficacy and minimize toxicity in the older patient.*

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Abbreviations used in this paper: GFR = glomerular filtration rate, AUC = area under the curve.

Introduction

Cancer is a disease that mostly afflicts older individuals, with approximately 60% of cancer morbidity and 70% of cancer mortality occurring in patients over 65 years of age.^{1,2} This age group is growing rapidly; by the year 2030, 1 in 5 Americans will be over 65 years of age. Despite these demographics, older patients have been underrepresented in cancer clinical trials.^{3,6} As a result, our knowledge regarding drug dosing and treatment efficacy is primarily derived from data acquired in a younger cohort of patients.

Both physicians and patients have concerns regarding the side effects of cancer therapy in the older patient.^{7,8} The data on chemotherapy tolerance in older patients in clinical trials are conflicting. Some studies report increased toxicity in older patients, while other studies report equivalent tolerability of chemotherapy in older and younger patients.⁹⁻¹³ These differences may reflect disparities in clinical trial eligibility or the heterogeneity in terms of comorbidity, functional status, or other parameters of the older population that enrolled in the trials. Only a few studies have addressed tolerance to cancer therapy in the frail older patient, in older patients with organ dysfunction, or in those with poor performance status.^{14,15} Because of the underrepresentation of these patients on clinical trials, oncologists are left with little to guide them in terms of optimal chemotherapy selection and dosing in the older patient.

Investigators are studying differences in the pharmacokinetics of chemotherapy in relation to age. In particular, they are seeking to determine if they can use pharmacokinetics or other parameters to predict who is at risk for chemotherapy-associated complications. This review focuses on studies of chemotherapy drugs that are commonly prescribed in older patients with cancer and the available data from pharmacokinetics studies relating to older patients. In addition, we review the physiologic changes with aging that might affect chemotherapy tolerance.

Pharmacology and Aging

Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace.^{16,17} The age-related physiologic decline in organ systems typically begins in the third decade of life. It is not evident at times of rest but becomes most apparent when the body is stressed.¹⁸ Both cancer and its treatment can be considered as physiologic stressors, and the age-related decrease in physiologic reserve can affect tolerance to cancer treatment.

A number of age-related changes in drug absorption, distribution, metabolism, and excretion with aging can contribute to differences in treatment tolerance

between older and younger patients. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.^{19,20} With the increased use of oral therapy, drug compliance is an important issue.²¹ As a person ages, body composition changes, with an increase in body fat and a decrease in lean body mass and total body water. The increase in body fat leads to a rise in the volume of distribution for lipid soluble drugs and a diminution in the volume of distribution for hydrophilic drugs. In the cancer population, malnutrition and hypoalbuminemia can result in an increased unbound concentration of drugs that are albumin-bound.²²

Hepatic mass and blood flow decrease with age.^{16,23} The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is controversial.²⁴⁻²⁶ In a study of 226 patients, the cytochrome P450 content in liver biopsy samples decreased by approximately 30% in patients over 70 years of age.²⁷ Phase I metabolism occurs primarily via the cytochrome P450 microsomal system and exhibits genetic variability.^{28,29}

Over a lifespan, renal mass decreases by approximately 25% to 30%, and renal blood flow decreases by 1% per year after age 50.²² The decline in glomerular filtration rate (GFR) with age is estimated at 0.75 mL/min per year after age 40; however, approximately one third of patients have no change in creatinine clearance with age.³⁰ This reduced renal function does not usually result in increased serum creatinine levels because of the simultaneous loss of muscle mass.³¹ Therefore, serum creatinine is not an adequate indicator of renal function in the older patient.

Various equations have been evaluated to estimate GFR based on the serum creatinine and other factors. The two most common equations clinically utilized are the Cockcroft-Gault equation and Jelliffe equation.^{32,33} These formulas were primarily validated in a younger group of patients without renal disease and are not as accurate in older patients.^{34,35} In a study of octogenarians, only 9% of the values obtained from a calculated creatinine clearance (via the Jelliffe and Cockcroft-Gault formulas) fell within $\pm 10\%$ of the measured 24-hour creatinine clearance values.³⁴ In another study of patients over the age of 70, the Cockcroft-Gault formula underestimated creatinine clearance in comparison to the 24-hour measured value.³¹ Marx et al³⁶ evaluated the accuracy of the Cockcroft-Gault, Jelliffe, and Wright formulas in a population of older patients with cancer. In this study, the Wright formula was the most accurate formula to calculate GFR; however, the majority of patients in this study had a GFR > 50 mL/min. In a study of patients with chronic renal disease, the modification of diet in renal disease (MDRD) equation was more accurate than other commonly used equations to cal-

culate GFR, including the Cockcroft-Gault equation and measured creatinine clearance. The MDRD equation was developed as part of the MDRD Study, and the formula takes into account the patient's serum creatinine concentration, age, sex, ethnicity, serum urea nitrogen, and albumin concentrations.³⁷

The decline in GFR with age translates into pharmacokinetic alterations of drugs or their active metabolites, which are excreted by the kidneys. Due to the physiologic decline in renal function with age, chemotherapy agents that are primarily renally excreted must be dosed with caution in older patients. Table 1 provides guidelines to help prevent the toxicity of drugs that are renally excreted. In addition, a review by Kintzel and Dorr³⁸ provides general guidelines to adjust the doses of nephrotoxic or renally excreted chemotherapy drugs in patients with altered renal function.

Polypharmacy and the Potential for Drug Interactions

Older patients are at risk for adverse drug interactions for several reasons. The risk of adverse events increases with the number of medications prescribed, and the number of medications prescribed increases with age.³⁹⁻⁴¹ Age-related changes in physiology have an impact on the pharmacokinetics and pharmacodynamics of the drugs.^{22,40} In addition, older patients may have multiple doctors prescribing medications, potentially duplicating therapy or prescribing drugs that might have adverse interactions.

The older patient with cancer is particularly at risk for adverse drug events because, in addition to chemotherapy, the patient may be taking supportive-

care medications (anticholinergics, benzodiazepines, dexamethasone) that can have exaggerated effects in an older person.^{40,41} In addition, clearance of the chemotherapeutic agent may be affected by concomitant drugs, which can lead to decreased clearance of the chemotherapy (placing the patient at increased risk for toxicity) or increased clearance (placing the patient at risk for ineffective therapy). Strategies to minimize the risk for drug-drug interactions include taking a thorough medication history (including prescribed medications, over-the-counter medications, and herbal medicines) at each visit, becoming familiar with the lists of drugs that should be avoided in older patients, eliminating any unnecessary medications, paying attention to patient adherence to prescribed medications, and coordinating care among the patient's practitioners.^{40,42}

Relationship of Age and the Pharmacokinetics of Common Chemotherapy Drugs

Several studies have been published that highlight the effects of patient age on the pharmacokinetics of different classes of chemotherapy agents (Table 2), including taxanes, vinca alkaloids, antimetabolites, topoisomerase inhibitors, anthracyclines, and alkylating agents.

Taxanes

Paclitaxel: The pharmacokinetics of paclitaxel given at 175 mg/m² over 3 hours every 3 weeks was studied by Lichtman et al⁴³ on behalf of the Cancer and Leukemia Group B. A total of 153 patients entered the study and were divided into three cohorts based on age: cohort 1 included 51 patients aged 55-64 years, cohort 2 included 56 patients aged 65-74, and cohort 3 included 46 patients aged ≥75 years. Pharmacokinetic data for the first cycle of chemotherapy were available in 122 of the 153 patients. The mean area under the curve (AUC) of paclitaxel increased ($P=.01$) and the mean paclitaxel clearance decreased ($P=.007$) across cohorts of increasing age. Older patients experienced an increased incidence of grade ≥3 neutropenia and a lower absolute neutrophil count nadir than younger patients; however, this did not translate into an increased incidence of hospitalization, fever >38°C, or receipt of intravenous antibiotics.

The results of pharmacokinetic studies of weekly paclitaxel in older patients have conflicted. Fidijs et al⁴⁴ reported on the efficacy and toxicity of weekly paclitaxel 90 mg/m² over 1 hour in 35 patients over the age of 70 (median age 76; range 70-85). Among these patients, 13 consented to pharmacokinetic sampling, and 8 had pharmacokinetic sampling performed with the 1st and 6th cycles. The authors compared the pharmacokinetic parameters from this cohort to values that

Table 1. — Preventing Toxicity of Drugs With Predominantly Renal Excretion

Hydration status should be optimized and renal function evaluated to establish possible need for dose adjustment.

Serum creatinine alone is insufficient in evaluating renal function.

More accurate tools, including creatinine clearance methods such as Cockcroft-Gault, are available and generally provide accurate indices of a patient's renal function status. However, in older patients, these equations are not as precise as in a younger population.

When dealing with extremes of obesity and cachexia or very high and low creatinine values, no single tool is completely accurate.

Within each drug class, preference may be given to agents that are less likely to be influenced by renal clearance.

Within each drug class, preference may be given to agents that are less toxic to the kidneys or for which there are ways to prevent renal toxicity.

Coadministration of known nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs or Cox-2 inhibitors, should be avoided or minimized.

Future trials should be designed to allow for the evaluation of renal function and its effect on toxicity and efficacy.

Table 2. — Selected Studies of Pharmacokinetics of Chemotherapy Drugs in Older Patients

Study	No. of Patients Participating in Study	Age Distribution	Drug	Dose and Schedule	Result
Lichtman et al ⁴³	122	Cohort 1: n = 46 Range 55–64 Cohort 2: n = 44 Range 65–74 Cohort 3: n = 32 Range 75–86	Paclitaxel	Paclitaxel 175 mg/m ² IV over 3 hrs every 3 wks	Increasing age associated with increased AUC and decreased clearance Increasing age associated with increased grade ≥ 3 neutropenia and lower absolute neutrophil count
Fidias et al ⁴⁴	13	Median 76 Range 70–85	Paclitaxel	Paclitaxel 90 mg/m ² IV over 1 hr weekly for 6 wks followed by a 2-wk break	No difference in pK in this older cohort compared with historical data from younger patients
Smorenburg et al ⁴⁵	23	Cohort 1: n = 8 Median 77 Range 70–84 Cohort 2: n = 15 Median 54 Range 22–69	Paclitaxel	Paclitaxel 80 mg/m ² IV over 1 hr weekly for 3 wks followed by a 1-wk break Paclitaxel 100 mg/m ² IV over 1 hr weekly for 3 wks followed by a 1-wk break	Older age associated with decreased clearance of unbound and total paclitaxel Despite receiving a lower dose of paclitaxel, older patients experienced similar decreases in white blood cell and absolute neutrophil count compared with younger patients
Bruno et al ⁴⁶	640	Not specified	Docetaxel	Not specified	Small decrease in clearance with age (estimated at a 7% decrease in clearance for a 71-yr-old patient)
ten Tije et al ⁴⁷	40	Cohort 1: n = 20 Median 71 Range 65–80 Cohort 2: n = 20 Median 53 Range 26–64	Docetaxel	Docetaxel 75 mg/m ² IV over 1 hr every 3 wks	No association of age with AUC or clearance Older patients more likely to experience grade 4 neutropenia and febrile neutropenia
Slaviero et al ⁴⁸	54	Median 63 Range 40–83	Docetaxel	Docetaxel 40 mg/m ² IV over 2 hrs weekly	No association of age with docetaxel clearance
Hurria et al ⁴⁹	19	Median 75 Range 66–84	Docetaxel	Docetaxel 35 mg/m ² IV over 1 hr weekly for 3 wks followed by a 1-wk break	No association of age with docetaxel clearance
Minami et al ⁵⁰	52	Cohort 1 ≥ 75 : n = 27 Median 76 Range 75–86 Cohort 2 < 75 : n = 25 Median 56 Range 39–73 Both cohorts	Docetaxel and cisplatin	Docetaxel 20 mg/m ² IV over 1 hr weekly for 3 wks followed by a 1-wk break Docetaxel 35 mg/m ² IV over 1 hr weekly for 3 wks followed by a 1-wk break Cisplatin 25 mg/m ² IV weekly for 3 wks followed by a 1-wk break	No association of age with clearance or volume of distribution Older patients received a lower dose of docetaxel and had a smaller AUC, but both groups had similar rates of neutropenia

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Table 2. — Selected Studies of Pharmacokinetics of Chemotherapy Drugs in Older Patients

Study	No. of Patients Participating in Study	Age Distribution	Drug	Dose and Schedule	Result
Sorio et al ⁵²	10	Median 70 Range 66–81	Vinorelbine	Vinorelbine 30 mg/m ² IV day 1 and 8 of every 3 wks	No age-related difference in pK No correlation between age, toxicity, and drug exposure
Gauvin et al ⁵³	12	Mean 74 Range 65–79	Vinorelbine	Vinorelbine 20–30 mg/m ² IV over 10 min weekly	Older age associated with decreased total clearance of vinorelbine Increased AUC of vinorelbine correlated with increased hematologic toxicity
Milano et al ⁵⁴	380	Median 62 Range 25–91	5-FU	5-FU 1000 mg/m ² continuous IV infusion day 1–5 and cisplatin (100 mg/m) 1 mg/min ⁻¹ IV	No association of age with 5-FU clearance Women had lower 5-FU clearance than men
Cassidy et al ⁶⁰	25	Mean 63 Range 41–80	Capecitabine	Capecitabine 2000 mg orally	No association of age with AUC or C _{max}
Bressolle et al ⁶⁵	62	Cohort 1: n = 38 Range 65–83 Cohort 2: n = 24 Range 21–45	Methotrexate	Methotrexate 7.5–15 mg IM weekly	Age inversely proportional to the clearance of free and total methotrexate
Toffoli et al ⁷²	50	Range 50–83	Etoposide	Etoposide 100 mg orally for 14 days every 3 wks; one oral dose of 100 mg was replaced with etoposide 50 mg IV over 1 hr on either day 1 or day 7	No age-related differences in pharmacokinetics when creatinine clearance was accounted for
Miller et al ⁷³	106	<50 (n = 6) 50–59 (n = 29) 60–69 (n = 42) ≥70 (n = 29)	Etoposide	Etoposide 50 mg/m ² /d orally for 21 days and cisplatin 33 mg/m ² /d IV for 3 days every 28 days for 6 courses	Older age associated with increased free and trough etoposide concentrations
Ando et al ⁷⁴	12	Median 79 Range 75–84	Etoposide	Etoposide 50mg/day [Dose level 1 (n=6)] Etoposide 75mg/day [Dose level 2 (n=6)]	No difference in pK in this older cohort in comparison to historical data from younger patients Older patients experienced greater myelosuppressive effects despite equivalent exposure
Dees et al ⁷⁷	24	Of the 44 patients included in the study: n = 11: ≥65 n = 6: ≥70 Range 35–79 24 patients participated in pK studies (age range not specified)	Doxorubicin and cyclophosphamide	Doxorubicin 60 mg/m ² IV and cyclophosphamide 600 mg/m ² IV every 21 days for 4 cycles	No age-related differences in the plasma clearance of doxorubicin and cyclophosphamide Weak correlation between age (as a continuous variable) and volume of distribution of doxorubicin Age-related decrease in nadir neutrophil count but no difference in neutropenic complications

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Study	No. of Patients Participating in Study	Age Distribution	Drug	Dose and Schedule	Result
Li et al ⁷⁸	56	Median 50 Range 12–74	Doxorubicin	Doxorubicin median dose 50 mg/m ² ; range 30–75 mg/m ²	Older age associated with lower early clearance (due to decreased distribution clearance) and lower total body clearance of doxorubicin
Graham et al ⁸⁸	25	Range 26–72	Oxaliplatin	Oxaliplatin 130 mg/m ² IV over 2 hrs	No association between age and total body clearance Clearance was correlated with renal function as measured by GFR
Jen et al ⁹⁴	445	Mean 50 Range 19–82	Temozolomide	Phase II dose: temozolomide 150 or 200 mg/m ² /d for 5 days every 28-day cycle Phase I dose: temozolomide 100 to 200 mg/m ² /d for 5 days every 28 days or 500–1000 mg/m ² as a single dose every 28 days	No association between age and pK Neutropenia and thrombocytopenia associated with age, gender, and temozolomide exposure

IV = intravenously, C_{max} = maximum plasma concentration, IM = intramuscularly, pK = pharmacokinetics.

had been reported in younger patients and concluded that the pharmacokinetics did not differ by age and the values did not change with repeated weekly dosing. Smorenburg et al⁴⁵ reported on the pharmacokinetics of weekly paclitaxel in 8 patients age 70 and older (median age 77; range 70–84) and 15 patients less than age 70 (median 54 years; range 22–69). The younger group received paclitaxel 100 mg/m² over 1 hour, and the older group received 80 mg/m² over 1 hour. The authors found that the clearance of unbound paclitaxel ($P=.002$) and bound paclitaxel ($P=.04$) was significantly lower in older patients and that clearance was inversely related to age. An approximate 50% decrease in the clearance of unbound paclitaxel was seen in older vs younger patients. Despite receiving a lower dose of paclitaxel, older patients experienced similar decreases in white blood cells and absolute neutrophil count compared with younger patients. Possible explanations for this finding include the increased exposure to paclitaxel or decreased bone marrow reserve in older patients.

Docetaxel: In a population pharmacokinetic analysis of 640 patients who received docetaxel, the impact of age on docetaxel clearance was modest, estimated at a 7% decrease in clearance for a patient 71 years of age.⁴⁶ Docetaxel clearance decreased in patients with abnormal liver function. A 27% decrease in clearance was noted among patients with elevated transaminases

(serum glutamate oxaloacetate transaminase [SGOT] or serum glutamate pyruvate transaminase [SGPT]) >1.5 × upper limit of normal) and alkaline phosphatase (>2.5 upper limit of normal). A decrease in docetaxel clearance was a strong predictor of grade 4 neutropenia and febrile neutropenia (a 50% decrease in clearance was associated with a 4.3-fold increased risk of grade 4 neutropenia and a 3-fold increased risk of febrile neutropenia). Based on this, the authors recommended no specific dose adjustments in older patients; however, dose adjustment in patients with liver impairment was recommended.⁴⁶

The pharmacokinetics and toxicity of docetaxel 75 mg/m² every 3 weeks was evaluated in a cohort of 20 patients age 65 and older (median 71 years; range 65–80) and 20 patients less than age 65 (median 53 years; range 29–64).⁴⁷ There was no significant difference in docetaxel pharmacokinetics between these two groups. In particular, there was no association between age and docetaxel clearance or age and the AUC of docetaxel. Older patients (≥65 years) were more likely than younger patients (<65 years) to experience grade 4 neutropenia (63% vs 30%) and febrile neutropenia (16% vs 0%). There was no significant difference in AUC values between patients with grade 4 neutropenia and patients with less than grade 4 neutropenia. Among the 10 patients with an AUC in the upper quartile, 3 of 6 patients >65 years experienced febrile neutropenia compared with 0 of 4 patients <65

years. The frequency of nonhematologic toxicity was similar between the older and younger patients.⁴⁷

The pharmacokinetics of weekly docetaxel was evaluated in two studies that also included the Erythromycin Breath Test, a surrogate measure of cytochrome 3A4 activity, which is the main enzyme responsible for docetaxel metabolism. In a study by Slaviero et al,⁴⁸ the pharmacokinetics of docetaxel 40 mg/m² was evaluated in a cohort of 54 patients with advanced cancer (median age 63; range 40–83). There was no significant association between age and clearance. However, there was a significant correlation between Erythromycin Breath Test results, liver function enzymes, and docetaxel clearance. Hurria et al⁴⁹ studied the pharmacokinetics and toxicity of weekly docetaxel 35 mg/m² for 3 weeks followed by a 1-week break in a cohort of 20 patients ≥65 years of age (median age 75; range 66–84). In this cohort, 19 patients were evaluable for pharmacokinetic analysis. There were no significant age-related pharmacokinetic differences in this cohort of older patients. There was a statistically significant association between decreased cytochrome 3A4 activity (as measured by the Erythromycin Breath Test) and decreased docetaxel clearance and increased AUC. However, there was no significant association between either the Erythromycin Breath Test results or docetaxel pharmacokinetic parameters and the frequency of grade ≥3 toxicity.

The pharmacokinetics and pharmacodynamics of weekly docetaxel (for 3 out of 4 weeks) in combination with cisplatin (25 mg/m² for 3 out of 4 weeks) was evaluated in 27 patients ≥75 years of age and 25 patients <75 years.⁵⁰ The younger age group received a docetaxel dose of 35 mg/m² and the older group received 20 mg/m². There was no significant difference in the clearance or volume of distribution of docetaxel in older and younger patients. In comparison with younger patients, older patients had a smaller AUC of docetaxel; however, both groups experienced similar rates of neutropenia, suggesting that older patients were more sensitive to docetaxel exposure than younger patients.⁵⁰

Vinca Alkaloids

Vinorelbine is a semisynthetic vinca alkaloid that is primarily excreted through the biliary tract. Dose modifications are recommended for patients with severe hepatic dysfunction.⁵¹ Sorio et al⁵² evaluated the pharmacokinetics and tolerance of vinorelbine in a cohort of 25 patients age 65 and older. Ten patients participated in the pharmacokinetic analysis. The vinorelbine dose and schedule was 30 mg/m² intravenously on day 1 and day 8 of an every-3-week cycle. The pharmacokinetics results were similar to those reported in younger patients, and there was no correlation between age, toxicity, and drug exposure. Gauvin et al⁵³ performed a

Bayesian estimate of vinorelbine pharmacokinetic parameters in a cohort of 12 patients with metastatic cancer who were 65 years of age and older. The vinorelbine was administered as a 10-minute continuous infusion at a dose of 20 to 30 mg/m² weekly. A high correlation was observed between patient age and decreased total clearance of vinorelbine, estimated at a 35% to 40% decrease in clearance in patients over the age of 70. A correlation between increased vinorelbine AUC and hematologic toxicity was observed.

Antimetabolites

5-Fluorouracil: Age does not affect the clearance of 5-fluorouracil (5-FU), but gender appears to play a role in both clearance and toxicity.⁵⁴ Women clear 5-FU at significantly lower rates than men and experience increased toxicity, likely secondary to lower dihydropyrimidine dehydrogenase (DPD) activity.^{54,56} Since 5-FU is primarily cleared through nonrenal mechanisms, dose adjustment in renal insufficiency is not necessary.⁵⁴ Studies have reported varying degrees of age-related toxicity to 5-FU.^{54,55} In a review of a prospective database of patients receiving adjuvant or palliative chemotherapy, patients over the age of 70 who received adjuvant 5-FU and folinic acid experienced more grade 3 and 4 mucositis than the younger group (11% vs 19%; $P=.02$).⁵⁷ In an analysis of a series of weekly 5-FU regimens, there was no difference in toxicity between younger and older patients.⁵⁸ In a meta-analysis of adjuvant therapy regimens for colorectal cancer, there was no age-related difference in chemotherapy efficacy or toxicity except older patients were at increased risk of leukopenia.⁵⁹

Capecitabine: This oral fluoropyrimidine is commonly used in the treatment of breast and colorectal cancer. The pharmacokinetics of two tablet formulations of a single oral dose of capecitabine 2,000 mg was evaluated in 25 patients between the ages of 41 and 80 years (mean age 62.6 years). There was no statistically significant difference in the pharmacokinetic parameters of capecitabine or its metabolites with age. In addition, there was no clinically significant effect of gender, body surface area, or creatinine clearance on the pharmacokinetic parameters of capecitabine and its metabolites.⁶⁰ A subsequent pharmacokinetic study in 27 patients (age range 38 to 74) with varying degrees of renal function demonstrated that patients with impaired renal function had increased systemic exposure to capecitabine metabolites and an increased risk of grade 3 or 4 toxicity.⁶¹ The authors recommend dose adjustments in patients with a creatinine clearance of 31 to 50 mL/min and advise against using the drug in patients with a creatinine clearance less than 30 mL/min.

Bajetta et al⁶² reported on the safety and efficacy of capecitabine in older women with breast cancer who were treated with capecitabine at the dose of 1,250

mg/m² twice daily on day 1 to 14 of a 21-day cycle. The inclusion criteria included that the serum creatinine be less than 1.6 mg/dL. Two toxic deaths occurred among the first 30 patients who received this dose. This led to the modification of dosing to 1,000 mg/m² twice daily, which was both efficacious and tolerable in a subsequent cohort of 43 patients. The authors postulated that these older patients were at increased risk of toxicity secondary to age-related declines of renal function, and a retrospective analysis showed that all patients on the study had mildly impaired (51 to 80 mL/min) or moderately impaired (30 to 50 mL/min) creatinine clearance. The results of these studies demonstrate that age-related declines in physiology are more instructive in determining chemotherapy dosing than age alone.

The potential for drug interactions (involving either prescribed drugs or over-the-counter medications) needs to be considered when prescribing capecitabine. For example, there is a significant pharmacokinetic interaction between warfarin and capecitabine that can lead to an exaggerated anticoagulant activity of warfarin.⁶⁵ Patients who are receiving warfarin concomitantly with capecitabine should have their INR (international normalized ratio) monitored closely so that the warfarin dose can be adjusted accordingly. In addition, caution should be exercised in prescribing capecitabine to patients who take folate vitamin supplementation. Sharma et al⁶⁴ evaluated the safety and efficacy of fixed-dose capecitabine (2,000 mg/day for 2 weeks followed by a 1-week break) in patients with advanced colorectal cancer (median age 72 years) and correlated pretreatment serum and red cell folate levels with toxicity. Patients with higher pretreatment levels of serum folate experienced greater toxicity during cycle 1 and over the entire treatment period.

Methotrexate: Methotrexate is an antifolate with a wide range of therapeutic applications. The impact of age on the pharmacokinetics of methotrexate was evaluated in a study of patients receiving methotrexate for the treatment of rheumatoid arthritis. The total clearance of free and total methotrexate was inversely proportional to age.⁶⁵ Methotrexate doses should be adjusted based on renal function. The drug is primarily eliminated renally, and therefore the clearance of methotrexate is decreased in patients with lower creatinine clearance.^{65,66} In addition, patients with pleural effusions or ascites are at risk for prolonged drug elimination and toxicity due to prolonged methotrexate concentrations. Leucovorin rescue may be useful in patients with advanced age in conjunction with dose adjustments to minimize toxicity.

Methotrexate is frequently administered in combination with other chemotherapy agents. For example, in the adjuvant treatment of breast cancer, the CMF (cyclophosphamide, methotrexate, 5-FU) regimen is commonly prescribed. In a study of postmenopausal

patients with node-positive breast cancer, the CMF regimen was associated with increased toxicity in patients aged 65 years and older compared with younger patients. In particular, older patients experienced increased grade 3 toxicity of any type, grade 3 hematologic toxicity, and grade 3 mucosal toxicity.¹³ Gelman and Taylor⁶⁷ found that age-based trends in toxicity were eliminated in the CMF regimen by modifying the cyclophosphamide and methotrexate doses based on creatinine clearance and prescribing the 5-FU at two-thirds of the standard dose.

Cytosine Arabinoside: Cytosine arabinoside (ara-C) is a major component of therapy for acute leukemias. The pharmacokinetic makeup of ara-C is characterized by rapid disappearance from plasma by deamination. Approximately 70% to 80% of a given dose is excreted as ara-U that within minutes becomes the predominant compound found in plasma. The primary determinants of toxicity are drug concentration and duration of exposure. Myelosuppression and gastrointestinal toxicity are the primary adverse effects. Neurotoxicity, including seizures, cerebral dysfunction, or acute cerebellar syndrome, occurs in 14% of patients who receive high-dose ara-C.⁶⁸ Increasing age is a risk factor for the neurotoxicity associated with high-dose ara-C. In a study of patients who received high-dose ara-C (3 g/m² every 12 hours on days 1, 3, and 5), risk factors for the development of neurotoxicity included age 40 years or older, abnormal alkaline phosphatase ($\geq 3 \times$ normal), and creatinine ≥ 1.2 mg/dL.⁶⁹ Among patients with two or more of these risk factors, 37% developed central nervous system (CNS) toxicity compared with 1% who had 0 or 1 risk factor.⁶⁹ Reducing the dose of high-dose ara-C in the setting of renal insufficiency decreases the incidence of neurotoxicity.⁷⁰ The alterations in renal function with aging contribute to the increased toxicity of high-dose ara-C in older patients.

Topoisomerase Inhibitors

Etoposide: Etoposide is a topoisomerase II inhibitor that can be administered intravenously or orally. The bioavailability of oral etoposide is approximately 50%; however, the absorption of oral etoposide is highly variable.^{71,72} Impaired renal function leads to a decrease in drug clearance rates.⁷² In a study of patients who received oral etoposide and intravenous cisplatin, increasing age correlated with increased free etoposide concentrations. The increased concentration correlated with lower neutrophil and white blood cell counts.⁷³ Ando et al⁷⁴ reported no significant age-related differences in the pharmacokinetics of oral etoposide; however, older patients experienced greater myelosuppressive effects despite equivalent exposure. Toffoli et al⁷² reported on the pharmacokinetics of oral etoposide and found that age did not correlate with increased free etoposide concentrations when creati-

nine clearance was accounted for. Etoposide is eliminated to some degree via hepatic CYP P450 metabolism, but dose adjustments based on liver dysfunction are controversial.^{75,76} The pharmacokinetics of oral etoposide in patients with liver dysfunction do not differ from patients with normal liver function.^{72,75}

Anthracyclines

Doxorubicin: Dees et al⁷⁷ evaluated the pharmacokinetics and toxicity of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² given intravenously every 21 days for 4 cycles. The 44 women in the study were 35 to 79 years of age; 11 were age 65 or older and 6 were age 70 or older. Twenty-four patients underwent pharmacokinetic analysis with cycle 1 of treatment. There was no significant age-related difference in the clearance of doxorubicin and cyclophosphamide and no significant difference in toxicity by age. However, a significant age-related decrease in nadir absolute neutrophil count was noted in older patients compared with younger patients.

The impact of age on the pharmacokinetics of doxorubicin was evaluated by Li et al⁷⁸ in a cohort of 56 patients accrued from four studies. Older patients experienced higher initial concentrations of doxorubicin. This was primarily due to a decrease in distribution clearance, which was highly correlated with age while the volume of the central compartment was not. There was a mild but significant association between age and total body clearance of doxorubicin.

Age is a risk factor for doxorubicin-related congestive heart failure (CHF). Swain et al⁷⁹ evaluated the association of age and the risk of doxorubicin-associated CHF in a cohort 630 patients who were randomized to the doxorubicin and placebo arm in three phase III studies. Patients age 65 years and older experienced a greater incidence of CHF after a cumulative doxorubicin dose of 400 mg/m² compared with younger patients.

Alkylating Agents

Cisplatin: Cisplatin is utilized in the treatment of a wide variety of malignancies including lung, cervical, head and neck, esophageal, germ cell, and ovarian cancers. The clearance is primarily dependent on renal function. The major toxicities noted with therapy include renal insufficiency, electrolyte abnormalities, nausea and vomiting, peripheral neuropathy, ototoxicity, and myelosuppression. The potential nephrotoxicity of cisplatin is a concern, but toxicity can be minimized with proper safety measures, particularly with intravenous hydration and mannitol.^{80,81} In addition, retrospective analyses of clinical studies of older patients receiving cisplatin have not revealed an increased incidence of nephrotoxicity. However, in a study of patients receiving platinum-based chemotherapy for non-small-cell lung cancer, older men were at increased

risk for developing leukopenia and neuropsychiatric toxicity, and older women were more likely to lose weight than younger women.^{82,83}

Carboplatin: Carboplatin has a mechanism of action similar to cisplatin. Carboplatin is primarily excreted in the urine, while the remainder binds to tissue proteins and is inactivated. In initial studies in the development of carboplatin when the drug dose was based on mg/m², considerable interpatient variability occurred in the degree of thrombocytopenia.⁸⁴ This led to the development of formulas to calculate carboplatin dosing that took into account systemic exposure (as estimated by the AUC). The Egorin formula took into account body size and renal function to calculate a target carboplatin dose that would achieve the desired level of thrombocytopenia.⁸⁵ The Calvert formula calculates the carboplatin dose based on the target AUC and GFR (as measured by the chromium-51 ethylene diamine tetraacetic acid [⁵¹CrEDTA] method). The Calvert formula is more widely used since it can be applied to combination therapy, however, the ⁵¹CrEDTA method to measure GFR is often replaced by a 24-hour creatinine clearance or formulas to estimate creatinine clearance such as the Jelliffe and Cockcroft-Gault formulas.^{32,84,86} These formulas to evaluate GFR are not as accurate in the older patient since they were primarily validated in a younger population. The Chatelut formula uses age, sex, weight, and serum creatinine to calculate carboplatin clearance. While this formula is easy to calculate since it does not require a calculation of GFR, it has limited applicability in older patients since serum creatinine is not an adequate indicator of renal function in this age group.⁸⁷

Oxaliplatin: Oxaliplatin is a platinum compound with activity in colorectal cancer in both the adjuvant and metastatic setting. Hematologic toxicity is moderate, but the most consistent side effect is a dose-related peripheral neuropathy. Oxaliplatin differs from cisplatin in its lack of nephrotoxicity and from carboplatin in its lower incidence of hematologic toxicity. The peripheral neuropathy often manifests as paresthesia and dysesthesia in the extremities that is triggered or enhanced by exposure to cold. In a meta-analysis of two studies of 26 patients who received oxaliplatin, of which 25 patients (age range 26–72 years) were evaluable for pharmacokinetic analysis, there was no statistically significant correlation between the clearance of ultrafiltrable platinum and age.⁸⁸ In a pharmacokinetic study of 37 patients with varying degrees of renal impairment receiving oxaliplatin, unbound platinum clearance correlated with creatinine clearance ($r = .884$).⁸⁹ However, this increased exposure in patients with renal impairment was not associated with increased toxicity. The authors concluded that dose reductions of single-agent oxaliplatin are not required if the creatinine clearance is >20 mL/min. In addition, there is no significant difference in oxaliplatin clear-

ance among patients with varying degrees of hepatic impairment.^{90,91} In a retrospective analysis of 3,742 patients enrolled on four clinical trials receiving the FOLFOX4 regimen, those who were 70 years of age or greater had slightly higher rates of neutropenia and thrombocytopenia than younger patients.⁹²

Temozolomide: Temozolomide, an oral alkylating agent, is a second-generation imidazotetrazine. It is rapidly absorbed following oral administration and is converted to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC) by a pH-dependent chemical hydrolysis. The pharmacokinetic structure is linear, with 100% oral bioavailability. Peak plasma concentrations occur within 1 hour.⁹³ Food reduces the rate and extent of temozolomide absorption. Jen et al⁹⁴ evaluated the population pharmacokinetics of temozolomide in a cohort of 445 patients included in phase I and phase II studies. Temozolomide clearance increased with body surface area. Other factors such as age, sex, height, weight, serum creatinine, estimated creatinine clearance, hepatic function, smoking status, and selected concomitant medications had little effect on pharmacokinetics. The primary dose-limiting toxicity was myelosuppression. Although there was a low incidence of thrombocytopenia and neutropenia during the first cycle, the myelosuppression tended to be associated with age, female sex, and exposure.

Relationship Between Age and Pharmacokinetics of Drugs: Phase I Clinical Trials

Borkowski et al⁹⁵ evaluated the relationship between age and clearance of nine investigational drugs on phase I clinical trials. In all but one of these trials, patient criteria included adequate hepatic function (defined as a plasma bilirubin <2 mg/dL), adequate renal function (defined as a plasma creatinine <1.5 mg/dL), and the absence of comorbid medical conditions that might increase the risk of toxicity. Of the 344 patients on these studies, 81 (23.5%) were age 65 or older, 34 (9.9%) were age 70 or older, and only 5 (1.5%) were age 75 or older. The proportion of patients who received at or above the maximum tolerated dose was similar in patients older or younger than age 65. Despite a decrease in creatinine clearance with age, there was no significant relationship between the age of the patient and the delivered dose, toxicity, or clearance rate of these drugs.

Summary and Future Directions

Results from the above studies differ as to the impact of age on the pharmacokinetics of chemotherapy drugs. A few studies report age-related differences in pharmaco-

kinetics, but most found no significant difference in pharmacokinetics with age. More importantly, however, even if there were no difference in pharmacokinetics, a difference in pharmacodynamics was commonly seen. Most often, older patients were at increased risk of myelosuppression and toxicity resulting from age-related decline in organ function. The increased use of hematopoietic growth factors has led to a shift in the toxicity profile. The dose-limiting toxicity of many regimens has shifted to nonhematologic toxicity, particularly neuropathy and gastrointestinal toxicity, which remain significant problems for older patients.

The majority of these chemotherapy studies were performed in a small cohort of patients who were eligible for a clinical trial, limiting the generalizability of these results to the population as a whole. Additional studies on the pharmacokinetics of cancer therapies in the older patient are needed; however, based on the data to date, it is likely that factors other than pharmacokinetics and chronologic age will be significant predictors of tolerance to chemotherapy.

Future pharmacokinetic studies in older patients should include a thorough evaluation of physiologic factors such as baseline renal function, hepatic function, and hemoglobin and albumin levels. In addition, studies should include an assessment of factors apart from chronologic age that independently predict morbidity and mortality in the geriatric population, such as those captured in a geriatric assessment (functional status, cognitive state, number of comorbid illnesses, nutritional state, or psychological status).^{96,97} Studies that include these parameters might provide insight into the factors contributing to tolerability of chemotherapy and lead to interventions to improve treatment tolerance in older patients.

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