Personalizing Medicine in Geriatric Oncology

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ABSTRACT

Minimizing toxicity while maximizing efficacy is a common goal in the treatment of any condition but its importance is underscored in the discipline of oncology because of the serious nature of many chemotherapeutic toxicities and the risk of cancer recurrence or disease progression. The challenge of achieving an optimal therapeutic index is especially augmented in the elderly population because of age-related changes in drug-metabolizing enzymes and other pharmacogenomic alterations, which may have more pronounced effects in elderly patients, given their predisposition to altered pharmacokinetics and pharmacodynamics, resulting in increased risk of toxicity. Examples of the possible interplay of these factors will be discussed using tamoxifen, paclitaxel, codeine, and fluorouracil as starting points. Limited participation of the elderly in many cancer trials, especially trials assessing drug exposure, makes much knowledge on the interaction of these patient and environmental factors speculative in nature but presents an opportunity for future research to achieve better optimization of chemotherapeutic agents in the elderly.

INTRODUCTION

Cancer treatment is far from a one-size-fits-all endeavor. Just as the selection of treatment regimen depends on numerous factors, including type of malignancy, stage, histology, tumor genetics, and prior therapies, so does the choice for selection of treatment dosing. The factors that need to be considered for dose selection of a treatment will differ depending on the individual drug, but they commonly include age, concurrent medications, pharmacogenomic factors, comorbidities, prior therapy toxicity, and renal and hepatic function. Minimizing toxicity while maximizing efficacy is a common goal in the treatment of any condition, but its importance is underscored in the discipline of oncology because of the serious nature of many chemotherapeutic toxicities and the risk of cancer recurrence or disease progression. The practice of dosing many chemotherapeutic agents on the basis of body surface area exposure levels and outcomes for the majority of chemotherapeutic agents makes this method alone insufficient. This is especially important in populations in whom alteration in pharmacokinetic (PK) and other patient-specific factors may further yield increased risk of toxicity, such as those patients older than age 65 years.

Approximately 56% all cancers diagnosed in men and 51% of all cancers diagnosed in women are among patients who are older than age 65 years, and 70% of cancer-related deaths occur in this elderly population. The challenge of determining dosage for agents with a narrow therapeutic index (eg, many chemotherapeutics) in these patients is underscored by myriad factors, one factor being that the elderly have inadequate representation in oncology trials, especially dose-determination trials. Elderly patients are at a higher risk of treatment-related toxicity because they often exhibit alterations in drug metabolism, distribution, and excretion as well as comorbidity conditions, frequent use of concurrent medications, and other physiologic effects of the natural aging process such as decreased marrow reserves. Additional factors, such as germline mutations in drug-metabolizing enzymes and other pharmacogenomic alterations, may have more pronounced effects in elderly patients, given their predisposition to altered metabolism and risk of increased toxicity. This review will discuss clinically relevant examples of pharmacogenomic considerations related to cancer and supportive care therapies that may have greater impact in the elderly population.

PHARMACOKINETIC CONSIDERATIONS IN THE ELDERLY

Optimal dose selection of any drug depends on understanding the absorption, distribution, metabolism, and excretion of that particular agent. The
Breast cancer remains the most commonly diagnosed cancer among women in the United States; approximately 232,340 new cases are estimated for 2013 with approximately 100,000 occurring in patients 65 years of age or older. Because older women are more likely to have hormone receptor–positive disease, more than two thirds of these new cases are expected to be hormone receptor–positive and amenable to treatment with hormonal therapies such as tamoxifen and the aromatase inhibitors. Treatment for postmenopausal women with hormone receptor–positive breast cancer should include treatment with an aromatase inhibitor at some point in therapy, either as first-line therapy or sequentially after tamoxifen. A secondary analysis of the Breast International Group 1-98 (BIG 1-98) trial was performed to assess the effect of age on efficacy, toxicity, and treatment completion. Disease-free survival was improved with letrozole compared with tamoxifen to a similar degree across all age ranges; however, elderly patients 75 years of age or older in both the tamoxifen and letrozole groups were less likely to complete the trial compared with patients younger than age 65 years ($P < .001$). This discontinuation of therapy was most commonly the result of disease progression and adverse effects. That trial supported the preferred use of aromatase inhibitors in the elderly population, although it suggested that this therapy may not be tolerated by all patients, and tamoxifen still has a role in therapy. The cost difference between these two therapy options also suggests that the cheaper tamoxifen may be more available to patients on a fixed income, and tamoxifen remains the treatment of choice in countries worldwide. For these reasons, methods of optimizing tamoxifen therapy in the elderly population are of importance.

Tamoxifen is a prodrug that must be enzymatically activated to exert its antitumor effects. This occurs through a complex process that produces several primary and secondary metabolites and their isomers, each varying in their degree of activity and ultimate role in clinical response. Endoxifen is most accepted as the active metabolite. The parent drug tamoxifen is converted to N-desmethyltamoxifen primarily via CYP3A4/5, which is then further converted to endoxifen (4-hydroxy-N-desmethyltamoxifen) via CYP2D6. The antiestrogenic effects of endoxifen appear to be concentration dependent, suggesting that a threshold concentration may be needed for optimal clinical effect. More than 70 allelic CYP2D6 variants have been described, and they vary in enzyme activity and prevalence with respect to race and ethnicity. CYP2D6 genotype status can be used to classify patients’ phenotypes: ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs). Endoxifen concentrations vary with respect to CYP2D6 genotype with UM and EM patients having the highest endoxifen concentrations, followed by IM patients and then homozygous PM patients who have the lowest concentrations. Differences in endoxifen concentrations can be significant with as much as a six-fold variation seen between homozygous PM and homozygous EM patients. Because of the role of CYP2D6 and other enzymes in the ultimate production of endoxifen, concurrent drug therapy inhibiting or competing for these pathways can also reduce the production of endoxifen. This is especially important in the elderly because drugs commonly used in this population are known to inhibit CYP2D6 (Table 1). Although substrates of CYP2D6 may have fewer clinically relevant drug interaction implications, potent inhibitors of the enzyme such as
paroxetine and fluoxetine have been shown to reduce endoxifen levels in EM patients to concentrations similar to those found in PM patients. 

Awareness and potential avoidance of concurrent CYP2D6-mediated drug-drug interactions is recommended by the American Society of Clinical Oncology Clinical Practice Guideline: Update on Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer. Although CYP2D6 genotyping is not recommended, this position by the American Society of Clinical Oncology does support the importance of CYP2D6 effect on the ultimate efficacy of tamoxifen.

The relationship between CYP2D6 genotype, endoxifen, and clinical outcomes has been investigated in numerous trials with conflicting results. Approximately 14 separate trials have supported a relationship between efficacy and CYP2D6 genotype, but 15 studies have not supported this same association, leaving interpretation for premenopausal patients challenging and extrapolation to elderly patients even more difficult. One of the largest retrospective trials demonstrated that IM and PM patients had a statistically significant increased risk of disease recurrence compared with EM patients (hazard ratio, 1.40 [95% CI, 1.04 to 1.90] for IM and 1.90 [95% CI, 1.10 to 3.28] for PM). This relationship was also supported in a large meta-analysis conducted by the International Tamoxifen Pharmacogenomics Consortium, which assessed 4,973 patients treated with tamoxifen across 12 international studies. When considering data only from trials with postmenopausal women with estrogen receptor–positive breast cancer who received tamoxifen 20 mg per day for 5 years, CYP2D6 PM status was associated with decreased disease-free survival (hazard ratio, 1.25; 95% CI, 1.06 to 1.47; \( P = .009 \)).

In a recent study, the association between age and tamoxifen, endoxifen, and other metabolite concentrations was assessed in 151 hormone receptor–positive patients receiving tamoxifen 20 mg per day for at least 80 days to ensure steady-state concentrations. The median age of the patients was 57 years with a range of 32 to 85 years. No association between endoxifen and age was seen when CYP2D6 genotype was not considered \(( P = .107)\); however, this association became significant when including the 86 homozygous EM patients \(( P = .008)\). In addition, endoxifen concentrations increased with age as did interpatient range. Elucidating the relationship between age, endoxifen concentration, and other genotypes would be helpful to identify patients who may derive increased benefit from tamoxifen and the optimal dose each patient should receive. Investigation into this relationship may also help explain the higher endoxifen levels in elderly patients. Although CYP2D6 activity has been reported to decrease with age, consequently predicting for a lower endoxifen concentration, this higher concentration may be secondary to decreased renal excretion of this metabolite. 

Alternatively, given the complex nature of tamoxifen metabolism, an interaction with genotype and age may also partially explain this increase in endoxifen levels, as was seen with the antiarrhythmic drug flecainide. Flecainide exhibits age-related reduction in metabolic clearance and is believed to be primarily metabolized by CYP2D6, although other CYP isoenzymes are likely involved, including CYP1A2. Evaluation of the relationship between CYP2D6 genotype on age-related flecainide parent drug and metabolite concentrations was assessed as the metabolic ratio (MR) of parent drug to metabolites. Findings yielded a higher MR in patients 70 years of age or older overall, but when broken down by genotype, the MR was 1.6-fold greater in heterozygous EM patients and 1.5-fold greater in IM and PM patients compared with no age-related increase in homozygous EM patients. This suggests that age-related changes were most predominant in patients with the IM or PM phenotype because metabolism was compensated for by CYP1A2, whose activity has been reported to decrease with age.

The net result of age-related metabolism changes, CYP2D6 genotype, and concurrent medications, as well as compliance, on the concentrations of endoxifen and subsequent clinical efficacy is likely to vary significantly among patients. Subgroup analysis of current trials and future prospective studies that include PK analysis are needed to determine the clinically relevant interplay between CYP2D6 genotype and other factors related to the aging process in elderly patients treated with tamoxifen. In addition, future prospective studies centering on establishment of a threshold concentration of endoxifen or other markers will help individualize therapy for all patients regardless of age.

**Table 1. Clinically Relevant CYP2D6 Inhibitors to Avoid With Tamoxifen**

<table>
<thead>
<tr>
<th>Strong inhibitors</th>
<th>Bupropion</th>
<th>Cinacalcet</th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Quinidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate inhibitors</td>
<td>Amiodarone</td>
<td>Diphenhydramine</td>
<td>Duloxetine</td>
<td>Thioridazine</td>
<td>Sertraline</td>
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| Paclitaxel and docetaxel are antimitotic agents frequently used in numerous malignancies including breast, lung, ovarian, and prostate cancers, among many others. Paclitaxel is more than 97% protein bound and primarily metabolized by CYP2C8 to the major metabolite 6α-hydroxytaxol, but CYP3A4 produces the 3-hydroxy minor metabolite. The relationship between age and clinically relevant paclitaxel exposure is conflicting and complicated by the concurrent PK properties of the Cremophor EL formulation vehicle and unclear clinical importance of total paclitaxel compared with unbound drug. Most trials show a direct relationship between increasing age and exposure of parent as well as unbound drug. The relationship among three age cohorts and paclitaxel exposure and toxicity was assessed in 153 patients receiving paclitaxel 175 mg/m² once every 3 weeks. Mean paclitaxel exposure was highest in the oldest cohort of patients (75 years or older; \( P = .01 \)) compared with the younger two cohorts (ages 55 to 56 years and 65 to 74 years). Grade 3 or greater neutropenia was also highest in the oldest cohort (49%; \( P = .006 \)) compared with that in the two younger cohorts (22% and 35%, respectively). Total exposure of paclitaxel has been correlated with development of adverse effects, most commonly neutropenia and neuropathy.
elderly patients with once-per-week dosing associated with less grade 3 or greater neuropathy and neutropenia (0% and 41%, respectively) compared with a dosing schedule of once every 3 weeks (25% and 88%, respectively).37 The risk of paclitaxel-induced neurotoxicity is also influenced by comorbidities that may also cause neuropathy, such as diabetes.38,39 Although trials quantifying this relationship are limited, the relationship between age and prevalence of neuropathy that causes comorbidities may further add to the age-related increase in neuropathy occurrence.

The CYP2C8 enzyme that produces the major paclitaxel metabolite is polymorphic with the CYP2C8*3 allele being associated with increased risk of clinically relevant neuropathy.40,41 A statistically significant relationship between age 2 or greater neuropathy and the CYP2C8*3 allele was shown in a European population (P = .006).40 Each variant allele doubled the carrier’s risk of developing grade 2 or greater neuropathy from paclitaxel.40 The CYP2C8*3 variant occurs primarily in the white population, with a frequency of approximately 0.13 compared with the CYP2C8*1 wild-type allele. In vitro studies suggest decreased metabolism in carriers with the variant allele; however, clinical PK studies have not reproduced these exposure changes in human trials.32,47 In addition, there was no effect of age on the expression of CYP2C8 in vitro, but human studies are lacking to determine whether this finding translates into human effects.44 Genetic alterations in the ABCB1 (p-glycoprotein, MDR1) transporter have also been associated with neuropathy. The ABCB1 protein is primarily responsible for transporting agents out of the nervous system and back into systemic circulation and is expressed in numerous tissues, including the blood-brain barrier and hematopoietic precursor cells. Patients homozygous for the ABCB1 wild-type allele demonstrated a trend toward decreased risk of neuropathy (P = .09) as well as a statistically significant lower risk of neutropenia (as measured by the percentage decrease in absolute neutrophil count; P = .02). These results were not correlated with changes in bound or unbound paclitaxel exposure however.45

The summary of these findings is a muddled picture because of the lack of correlation between drug exposure and pharmacogenomic alterations in drug-metabolizing enzymes and transporters. In addition, not all studies have supported the association between CYP2C8 and ABCB1 genotype and toxicity.46 Differences in sex, hormonal status, paclitaxel schedule, and liver function may partially explain this lack of correlation; however, further research is needed to determine whether an interaction between age and genetics may partially explain increased paclitaxel toxicity and altered distribution in elderly patients.

**OPIOID THERAPY IN ELDERLY PATIENTS WITH CANCER**

Cancer-related pain is a common problem for patients, with approximately 50% reporting inadequate pain control, although in some trials this number has approached 83%.47 Pain management in the elderly is especially challenging, and pain frequently remains undertreated.48 This is likely multifactorial in nature and may be the result of fear of overmedication, subjective nature of assessment, lack of patient report, or patient education, along with other factors. Dosing pain medications, especially the opioids, in the elderly population should necessitate some caution because of changes in drug metabolism, especially decreased renal function, that can predispose to toxicity.49,50 Pharmacogenomic mutations can further combine with age-related metabolism effects and concurrent medications and comorbidities to confound drug and dosing selection.

Codeine is an opioid analgesic most commonly used for mild to moderate pain. Codeine undergoes CYP2D6-mediated O-demethylation to morphine, which is further metabolized via uridine 5’-diphosphogluconuroinosytransferase 2B7 (UGT2B7) and UGT1A1 to the active morphine-6-glucuronide and inactive morphine-3-glucuronide. In CYP2D6 EM patients, only 5% to 10% of codeine is converted to morphine, although this active metabolite has 200-fold more affinity for the μ-receptor than the parent drug, and thus it provides the analgesic benefits of the drug.51,52 This ratio of codeine to morphine can be shifted secondary to CYP2D6 genotype, renal clearance of morphine, morphine-6-glucuronide, and/or concurrent interacting medications.53 Patients with the UM genotype have been shown to produce more of the active metabolites but PM patients may not receive pain relief from codeine because of the lack of morphine production. The 24-hour exposure of codeine and its metabolites were compared in 12 CYP2D6 UM patients, 11 EM patients, and three PM patients, all of whom received 30 mg of the parent drug.54 Morphine area under the curve (AUC) was higher in the UM patients compared with EM patients, and the PM patients had the lowest exposure. Glucuronide metabolite concentrations were also approximately 50% higher in the UM patients compared with the EM patients, and the PM patients had quite low levels. This correlated with increased sedation because more UM patients reported sedation compared with EM patients (91% vs 50%; P = .03).54 Although this was a small trial using a low single dose of codeine, larger doses and repeated dosing may increase the risk of more serious toxicities because of increased exposure to active metabolites, and case studies have supported this.55,56 Thus, the Clinical Pharmacogenetics Implementation Consortium Guidelines strongly recommend avoiding codeine in UM and PM patients and instead using an alternative agent because of increased toxicity or decreased efficacy, respectively. Evidence is weaker supporting recommendations for IM patients, although it suggests beginning with standard dosing and then changing to an alternative if lack of efficacy is seen.54 Age-related changes affecting codeine metabolism may include decreased efficacy of CYP2D6 resulting in decreased conversion to morphine, but this may be negated by decreased renal elimination of the drug. Medication given concurrently with tamoxifen may also decrease CYP2D6-mediated metabolism to morphine. The interaction of these age-related changes with CYP2D6 genotype on efficacy and toxicity of codeine is unknown and presents an opportunity for future clinically guided research.

**THERAPEUTIC DRUG MONITORING: FLUOROURACIL**

Until more optimal data are available for empirical dosing of chemotherapy agents with a narrow therapeutic index in the elderly, techniques such as therapeutic drug monitoring (TDM) may help optimize drug dosing for select agents. TDM provides the benefit of considering all factors that may affect drug exposure, although it has several limitations that have prevented its use in standard of care, including availability of clinically useful assays, logistical concerns for
patients, and limited data correlating drug concentrations with outcomes. However, some agents are more amenable to TDM than others, including methotrexate and busulfan in which the strategy is commonly used in clinical practice. In addition, availability of a commercial test approved by the US Food and Drug Administration has also made this feasible with fluorouracil (FU).

FU remains a standard therapy either as a single agent or in combination with other chemotherapeutics, radiation, and/or targeted agents for colorectal and head and neck cancers, even in the elderly population. Capecitabine is an oral fluoropyrimidine produg that ultimately is metabolized to the active metabolite FU via thymidine phosphorylase. The metabolic fate of FU is either through an anabolic pathway mediated by thymidine phosphorylase that is responsible for the ultimate production of the active metabolite flourodeoxyuridine monophosphate and the subsequent cytotoxic activity of FU or through a catabolic pathway that results in detoxification and elimination via dihydroxyrimidine dehydrogenase (DPD). The mechanism of action by which FU exerts its cytotoxic effect is primarily through inhibition of thymidylate synthase, which ultimately leads to inhibition of DNA synthesis and repair. In addition, thymidine phosphorylase also creates the secondary metabolite fluorouridine triphosphate, which can be incorporated into RNA as a false nucleoside. Also creating the secondary metabolite fluorouridine 5'-monophosphate, which can be incorporated into RNA as a false nucleotide, ultimately resulting in irreversible DNA damage. Approximately 85% of the parent drug undergoes catabolism via DPD. Patients receiving FU who have DPD deficiency have been reported to experience increased toxicity, especially severe GI and hematologic effects. Depending on the definition of DPD deficiency, it is estimated that approximately 14% of the general population has DPD levels in the lower 70th percentile, and less than 5% have levels in the lower 95th percentile, although the frequency differs across ethnic groups. Although genetic testing for DPD deficiency is available, it is not commonly used in practice and only partially explains the variability seen in FU and metabolite concentrations. Age-related changes in FU PK parameters were not consistently demonstrated, although in general, up to one third of patients may develop severe toxicities, and half of patients receiving conventional dosing failed to respond to therapy as a result of underdosing, despite strict adherence to protocol. This indicates that individualization of FU therapy may be a worthy pursuit to optimize its use, especially in the elderly population more prone to adverse effects such as leukopenia.

Numerous trials have demonstrated a relationship between the systemic exposure of continuous-infusion FU, as measured by AUC and toxicity. The benefit of using a PK-guided approach to dosing with FU was prospectively assessed in a randomized, controlled phase III trial (mean age, 71 years). Patients were randomly assigned to either conventional FU dosing or PK-adjusted FU using a dosing nomogram to target a previously defined target AUC of 20 to 24 mg × h/L. Patients in the PK-guided arm had a higher overall response (33.7% v 18.3%; P = .004), improved median overall survival (22 v 16 months), and fewer toxic events (P = .003). Although additional trials are needed to further define the optimal therapeutic range, TDM represents an alternative to genotyping that may be helpful in optimizing therapies with complex metabolism and/or those heavily influenced by age-related or environmental factors.

In conclusion, optimal dosing of chemotherapeutic agents is a challenge in the general population because of the narrow therapeutic index, serious nature of not only the toxicities of the agents but also the disease each is aimed at treating, and pharmacogenomics differences in drug metabolizing enzymes, among other factors. Dosing in the elderly becomes even more of a challenge because of the additional factors of age-related changes in metabolism that may result in altered drug metabolism or elimination, concurrent medications, and drug affordability and adherence issues. The paucity of available data makes explaining the interplay of these factors greatly speculative in nature. However, this limitation also offers research opportunities aimed at better defining the optimal dosing of chemotherapy agents in the elderly population.

### Authors’ Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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