Pharmacology of Antineoplastic Agents in Older Cancer Patients

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People over the age of 65 are a fast-growing segment of the US population, and with the incidence of cancer increasing with age, the challenges of treating older cancer patients are also on the rise. Drs. Lichtman and Skirvin present a comprehensive review of the antineoplastic agents used in elderly cancer patients. They highlight the important factors of chemotherapy pharmacology in elderly cancer patients, with emphasis on the impact of physiologic changes—especially renal clearance—in dosing and toxicity. In addition, descriptions of significant toxicities are provided. The following additional issues should be considered.

Drs. Lichtman and Skirvin are to be congratulated for their extensive review of what is known about the pharmacokinetics of chemotherapy drugs used in elderly patients. As their article indicates, detailed knowledge is usually available regarding the influence of hepatic and renal function on the pharmacokinetics of chemotherapy drugs.

Renal function clearly needs to be taken into account in every older patient who is scheduled to undergo chemotherapy with a renally excreted drug. The serum creatinine level can be misleading, and one should systematically calculate the creatinine clearance. For example, a 121-lb, 80-year-old woman with a creatinine level of 80 µmol/L (1.1 mg/dL) has a creatinine clearance of 35 mL/min. The Cockcroft-Gault formula is a rapid and practical way to assess this clearance.

Metabolism of Chemotherapy and Age

As the authors mention, the activity of cytochrome P450 decreases with age. The age-related effect on the metabolism of chemotherapy is, however, difficult to assess, since it is usually confounded by the concomitant use of numerous medications. Indeed, a study of children with acute lymphoblastic leukemia receiving anticonvulsants recently demonstrated that concomitant medications influence the outcome of chemotherapy.[1] In that study, anticonvulsant therapy had a deleterious effect on event-free survival (hazard ratio = 2.67; \( P = .0009 \)), hematologic relapse (hazard ratio = 3.40; \( P = .0006 \)), and central nervous system relapse (hazard ratio = 2.90; \( P = .047 \)) in B-cell acute lymphoblastic leukemia. The clearance of teniposide (Vumon) and methotrexate was accelerated, but not that of cytarabine.

The problem is further illustrated by survey findings at a tertiary cancer center program (Moffitt’s Senior Adult Oncology Program), where 58% of patients aged 70 and older were taking four or more different medications (Table 1). Drug interaction studies are presently lacking in the elderly, although they would be highly informative for clinical practice and could be of great help in improving control of efficacy and toxicity.

Pharmacokinetic and Pharmacodynamic Issues

As Drs. Lichtman and Skirvin also state, multiple other elements, such as body composition (the proportion of fat increases with age), nutritional status, anemia, or comorbidities, can affect the pharmacokinetics and pharmacodynamics of antimitotic agents in older cancer patients. Another consequence of aging is the decrease of functional reserve.

Typically, phase I/II studies with pharmacokinetics run for a short number of cycles. However, it appears that older cancer patients are less likely than their younger counterparts to successfully
tolerate a long duration of chemotherapy.[3,4] Older cancer patients are also more likely to rapidly decompensate when they experience complications from treatment. Dehydration from diarrhea or infections are more likely to result in hospitalizations, deconditioning, or delirium. There is a clear risk of generating long-term functional dependence,[5] and therefore, prevention, early recognition, and treatment of complications should be aggressively undertaken.

An interesting design that is beginning to appear in the literature is a split phase II study, with predefined groups of younger and older patients, in order to compare pharmacokinetic and pharmacodynamic issues. The authors mention one of their own studies that was conducted with the CALGB.[2] Another example of such a study was conducted with the folfox 2 regimen (leucovorin [folinic acid], fluorouracil, and oxaliplatin).[6] This design has a high potential for eliciting useful information, as it ensures the entrance of a balanced number of younger and older patients into the study. Much work remains, however, in identifying the few key variables that provide the most relevant information for discriminating between young and old patients in the small collectives typically used in such studies.

Limitations of Pharmacokinetic Studies

A limitation of pharmacokinetic studies is that they are mostly conducted as single-agent trials. Many commonly used regimens are multidrug schedules, with pharmacokinetic and pharmacodynamic interactions that can be difficult to evaluate. The extrapolation of data from study patients to patients with several comorbidities is also difficult. Therefore, another possible approach is to try to select patients on the basis of pretreatment criteria—ideally with models that are valid across several treatment regimens. Having a predictive toxicity score analogous to the American Society of Anesthesiologists (ASA) score would be very helpful.

Our program conducted a pilot study of such an approach,[7] and the Eastern Cooperative Oncology Group Subcommittee on Aging is working on further development of this project. In the meantime, extrapolating relevant information from general oncologic studies remains the main resource for oncologists treating older patients. In this, the article by Drs. Lichtman and Skirvin provides a very helpful source of information.

References: