Pharmacology of Antineoplastic Agents in Older Cancer Patients

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Drs. Lichtman and Skirvin have written an excellent review on the pharmacology of antineoplastic agents in older cancer patients. However, as in any text (often due to space limitations), one can find shortcomings, some of which will be covered in this commentary.

A key issue is that most of the pharmacologic data discussed may not have been obtained in those patients who form the majority of the elderly population—at least among those over age 75, i.e., those with comorbidities. The authors do caution us that pharmacokinetic data in older patients are limited due to the inclusion of only a small number of these patients in studies with a wide range of ages. They add that, consequently, the majority of data are inferred from trials not specifically targeted at an older age group.

Because of the inclusion and exclusion criteria in most of the cited studies, one ends up with a very special "elderly population," reflecting the more Olympian champions among the elderly rather than those seen in geriatric centers (as has certainly been the case with the European Organization for Research and Treatment of Cancer [EORTC] studies).[1] However, the authors do not repeat their caution, offering instead the remarkable sentence: "Studies that have addressed chemotherapy toxicity in older patients have shown that they can tolerate such regimens as well as younger patients." Yet, very correctly, the authors cite many instances in which this has proven to be false.

Who Is Considered Elderly?

Another problem with the term "elderly" is its arbitrary definition, related not only to insurance regulatory issues, but also to registration issues in the pharmaceutical industry. In its recommendations on studies in the geriatric population, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use suggests that the elderly population be arbitrarily defined as aged above 65 years, with a recommendation that patients above 75 years also be studied.[2] Drs. Lichtman and Skirvin discuss how similar definitions are not adequate, as the aging process is different from one person to the next.

The authors also briefly review some of the physiologic changes that can affect drug metabolism, but have no space to describe how comorbidity can be measured and how this factor may influence pharmacokinetic and pharmacodynamic results of drug usage.[3] Rather than accepting a physiologic decline of 1 mL/min of creatinine clearance per year above age 40, one might recommend that one always calculate creatinine clearance, for example, with the Cockcroft-Gault formula, which is validated for patients 75 years old or younger.[4]

Glutathione—a Forgotten Agent?

The review of the pharmacologic data of different agents includes adequate comments about the activity of these agents. The authors caution about the combination of gemcitabine (Gemzar) and cisplatin (Platinol), but surprisingly, do not cite the important Italian studies that have shown the tolerability and efficacy of the combination of vinorelbine (Navelbine) and gemcitabine in elderly patients suffering from non-small-cell lung cancer.[5]

Additionally, glutathione—a natural thiol that can prevent radiation- and chemically induced cytotoxicity—should not be forgotten. This agent is inexpensive, and, unlike amifostine (Ethylol),
which the authors cite several times, has no toxic effects. Glutathione has been given as a short intravenous infusion in doses of 1,500 to 3,000 mg/m² followed 30 to 60 minutes later by cisplatin. Less neurotoxicity and less nephrotoxicity have been seen in glutathione-treated patients who receive cisplatin-based chemotherapy.[6,7] Specific data on the use of glutathione in elderly patients are not available.

Concluding Words of Caution

The authors repeatedly state that dose reduction is not necessary on pharmacokinetic grounds—within the limits of the cited studies, of course. Healthy, older persons have a marrow mass and numbers of cultured progenitor cells similar to those of the younger population.[8] Although elderly patients admitted to hospitals are much more often anemic than younger people, their response to erythropoietin (Epogen, Procrit) is comparable.[9] These data suggest a dysregulation of hematopoiesis during aging, which, in turn, explains the increased myelotoxicity sometimes observed in elderly people. Unfortunately, we have no means of predicting the marrow reserve and degree of dysregulation for individual patients.

In summary, the article by Drs. Lichtman and Skirvin serves its purpose in describing the pharmacology of cytotoxic drugs in patients above the age of 65. However, as pointed out by the authors, it remains difficult to provide useful guidelines for the clinical use of cytotoxic agents in elderly patients.

References:

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