

# ADVANCES IN GERIATRIC ONCOLOGY

Perspectives on the Care of Elderly Patients With Solid Tumor and Hematologic Malignancies

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## Pharmacokinetics and Pharmacodynamics in the Elderly

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### **H&O** What are the primary concerns regarding pharmacokinetics in the elderly?

**SL** In general, for most drugs used to treat cancer in the elderly, there are no differences in pharmacokinetics based on age alone. Differences that occur are usually due to physiologic changes often associated with aging, such as changes in renal function. End-organ dysfunction also affects pharmacokinetics, but this concern is not limited to the elderly. For drugs and drug metabolites that are excreted renally, caution should be exercised because even small changes in renal function can lead to significant toxicity. Renal function is traditionally factored into dosing of methotrexate, but it should be considered with many other drugs including topotecan, capecitabine, and cytarabine. With carboplatin, for example, doses are always modified according to a formula for glomerular filtration such as the Cockcroft-Gault formula, but this dose modification is not thought of as reflecting age-related changes in pharmacokinetics. The Cancer and Leukemia Group B (CALGB) studied the changes in pharmacokinetics in the elderly seen with paclitaxel, and the changes in area under the curve, which were found not to be clinically significant. Despite increasingly widespread drug exposure with age, elderly patients did not have adverse outcomes with the standard dose. Studies with docetaxel likewise did not find clinically relevant changes in pharmacokinetics in the elderly. Overall, I believe an issue of greater concern in the elderly is drug pharmacodynamics.

### **H&O** Why are the pharmacodynamic effects of drugs an important concern in the elderly?

**SL** Dose for dose, drugs that do not have different pharmacokinetics in the elderly as compared to younger

patients can have different toxicities. Myelosuppression in the elderly is an important concern; also, with fluoropyrimidines, mucositis can be severe in the elderly. These effects can be difficult to predict. This is an area in which measures of frailty, performance, and functional assessment, using modified criteria for geriatric assessment, are important. A useful way to think of pharmacodynamic effect is as a measure of performance and functional status. Performance status is the most relevant measure for most patients. These assessments in terms of pharmacodynamics are still in early stages for the elderly, but much research has been undertaken in this regard. Generally speaking, there are few reasons to modify dosing based purely on age. If an elderly patient has an adequate performance status, the dose that would be used in a younger patient should be used, unless there is evidence of organ dysfunction such as renal dysfunction.

### **H&O** Are there specific concerns regarding measuring renal function in the elderly?

**SL** Yes. Serum creatinine should not be used as a measure of renal function in the elderly because of variations in muscle mass. The elderly tend to lose muscle mass, which can decrease the accuracy of the calculation. The Cockcroft-Gault formula is not perfect, but it does provide a reasonable guide for dosing. There are other formulas, such as Jelliffe, which need to be evaluated to determine which would be most appropriate.

### **H&O** What are important directions of research regarding pharmacokinetics or pharmacodynamics in the elderly?

**SL** How to predict toxicity, which is based more in pharmacodynamics than pharmacokinetics, is a major area of research. It is difficult, in routine practice, to predict the side effects a patient will experience. It has been discovered that there are subtle central nervous system effects in patients with cognitive impairment. Therefore, I believe a focus of research should be patient assessment. There is ongoing research that involves assessing a patient and then following that patient to predict toxicity. Another area with room for improvement in assessment relates to supportive care. Elderly patients are subject to greater

myelosuppression, and thus, therapy with hematopoietic growth factors is often required. I believe a classic pharmacokinetic evaluation should be incorporated into geriatric assessment. Simply assessing blood counts may not be sufficient to predict toxicity. The documented efficacy of hematopoietic growth factors has led to their inclusion in guidelines published by the American Society of Clinical Oncology, but I believe further research on the assessment of the need for these drugs in the elderly is needed.

Additionally, the standard toxicity criteria used to assess the toxicity of many therapies may not be applicable to older patients. For example, a 50-year-old patient with grade 1–2 neuropathy may not experience much loss of function. An 80-year-old patient with the same grade of neuropathy may have trouble walking or driving and may fall. The common toxicity criteria incorporates function somewhat, but I believe the questions we ask patients may not be appropriate across age groups. It may be important to devise different toxicity scales, and researchers have begun to do so.

### **H&O** Are drug-drug interactions a major concern in the elderly?

**SL** Yes. Most elderly patients are already receiving 5–10 drugs before a cancer diagnosis. Polypharmacy is thus an important issue. One area of research, which may prove quite difficult, is what I would call unnecessary prescription drug use. When thinking about drug-drug interactions, it may be worthwhile to consider whether the use of certain drugs can be discontinued in elderly patients being treated for cancer, simply because the drug-drug interactions are still unknown. Additionally, compliance among the elderly is becoming more problematic with the advent of oral therapy, even with highly effective and minimally toxic agents.

### **H&O** Are the pharmacokinetics of targeted therapies different in the elderly?

**SL** This is an interesting question, but it has never been studied. Even with chemotherapies that have been in use for decades, there are scant data on the pharmacokinetics in the elderly. There have not been studies in the elderly with these newer agents. For example, trastuzumab (Herceptin, Genentech) is commonly used in the elderly today, but there are very few data regarding its cardiac toxicity in this patient population. Erlotinib (Tarceva, Genentech/OSI) may cause rash or diarrhea, but it is not associated with much end-organ toxicity; however, its pharmacokinetics in the elderly have not been thoroughly studied yet. In general, there is a paucity of data to help guide a physician on how to use these drugs in the elderly. Patients who

are 85 years old are very different from patients who are 65 years old, and the former represent the most rapidly growing patient population in the United States. I hope interest in assessing the pharmacokinetics of newer drugs in this population grows accordingly.

### **H&O** What other directions of research do you hope to see undertaken in the future?

**SL** It would be ideal if the US Food and Drug Administration, as well as agencies such as Medicare, required that drugs used in cancers most prevalent in patients over age 75 be studied in this population. For example, the average age of patients with colorectal cancer is 73 years, but the average age of patients with this disease in clinical trials is 60 years. Looking at a specific drug, bevacizumab (Avastin, Genentech) is highly effective and is contraindicated in patients with vascular problems. But is this agent safe in an 80-year-old patient with no overt vascular problems? A robust clinical trial could help answer this question.

Another area with room for improvement in geriatric research is clinical trial design. Typically, the endpoint used in clinical trials is maximum tolerated dose. Blood counts or some other measures of toxicity are used to discern what the maximum dose should be. However, in the elderly, this endpoint may be insufficient. A 75-year-old with no comorbidities and good functional status may be comparable to a 50-year-old with comorbidities. Therefore, another group of elderly patients with comorbidities and functional impairments should be used for comparison. It is possible that the latter group will experience an increase in cognitive or functional impairment on a given drug, whereas the former group will not. Because these concerns are hypothetical, it would be useful to study them in the setting of a clinical trial that has its design adjusted to address the specific needs and concerns of the elderly population.

### **Suggested Reading**

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