Pharmacology of Antineoplastic Agents in Older Cancer Patients

Review Article [1] | December 01, 2000
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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.

Age Bias in Clinical Trials

Much of what we know about drug behavior and toxicities comes from trials conducted at academic medical centers and cooperative groups. Unfortunately, older persons are inadequately represented in both randomized clinical trials and trials of new agents, thereby requiring information to be inferred from subgroup analyses with small numbers of elderly patients.

It has been shown that there is an age bias against offering treatment to older cancer patients, and that this barrier continues with entry into clinical trials.[1] Moreover, elderly patients selected for trials may differ from other older cancer patients in the community because they have met stringent entry criteria in terms of comorbidity, performance status, and prior therapy history. Thus, it is difficult to know how to apply information from such trials to the more general population of older cancer patients who may have more comorbidities and poorer functional status. Trials with broad entry criteria are needed in order to generate information that is relevant to this larger group of older cancer patients.

Multiagent Regimens With Supportive or Protective Agents

As stated by Drs. Lichtman and Skirvin, single-agent therapies and some novel agents have been well tolerated by the elderly cancer patients in whom they were studied. For certain cancers, especially hematologic malignancies, multiagent chemotherapy regimens are required for treatment. Although there is speculation of cumulative toxicity, there are limited data on the outcome of elderly patients with these regimens, and further research is needed.

However, the inclusion of supportive and cytoprotective agents that target the side effects and toxicity of chemotherapy may improve the outcome of older cancer patients receiving more complex regimens. For example, hematologic growth factors, such as granulocyte colony-stimulating factor (Neupogen), granulocyte-macrophage colony-stimulating factor (Leukine), and erythropoietin (Epogen, Procrit), have been shown to decrease the degree of myelosuppression caused by chemotherapy. By doing so, older patients may be able to receive full-dose, on-schedule treatments, thereby improving the chances of a desirable outcome.[2,3] Cytoprotective agents, such as dexrazoxane (Zinecard) and amifostine (Ethylol), have shown some benefit with cardiotoxicity and neuropathy, respectively.[4] However, these agents have not been well studied in the older cancer patient cohort.
Toxicity

As noted by Drs. Lichtman and Skirvin, published descriptions of toxicity have been very general. Toxicity is graded by a standard measurement in trials, whereby grades 3 or 4 are usually significant for citation. Traditionally, myelosuppression has been the most worrisome side effect of chemotherapy agents—one that necessitates dose modification. However, in the older person with a relatively limited reserve capacity in a number of organ systems, competing lower-grade toxicities may have an impact on recovery. For example, lower-grade mucositis, neuropathy, or fatigue may not be significant individually, but together may result in a decline of nutritional and functional status that affects physical recovery and also puts stress on both the caregiver and the patient’s social situation.

Other Antineoplastic Agents

Hormonal therapies for breast and prostate cancer are widely used. Tamoxifen (Nolvadex) and the newer aromatase inhibitors are being used in older women with breast cancer with few side effects.[5,6] Agents with alternative delivery methods, such as liposomal formulations of anthracyclines, have toxicity profiles that are different from the traditional anthracyclines; these may also be helpful in elderly patients. On the horizon are newer agents developed for specific molecular targets[7] such as STI-571, targeted against the BCR-ABL tyrosine kinase in chronic myeloid leukemia[7] which have shown promise in both response and toxicity profile.

Polypharmacy

Drs. Lichtman and Skirvin describe the use of complementary and alternative medications as commonplace in the elderly, with concern regarding drug-drug interactions. However, with more than 90% of ambulatory older persons taking at least one prescription medication (four drugs on average), the more important focus should be on polypharmacy with conventionally prescribed and over-the-counter medications.[8] This phenomenon, with an obvious parallel to the presence of comorbidity in elderly cancer patients, will likely influence the outcome of older persons when the morbidity of cancer and chemotherapy treatment is added.[9] Of course, the addition of complementary and alternative medications will further complicate the situation, and should therefore be considered as part of this evaluation.

Goals of Therapy

Ultimately, it is important to determine the goals of therapy for the older cancer patient. Treatment evaluation and discussion differ for goals of palliation, stabilization of disease, or cure. Any additional information regarding quality of life, with or without antineoplastic treatment, would be helpful. Functional status, rather than age per se, may condition patient decisions about treatment. In select older patients, curative therapy may be quite appropriate, whereas in others, palliative or supportive therapy may be more suitable.

It should not be assumed that age alone will drive such decisions from the patient’s perspective. Indeed, a comprehensive geriatric assessment may aid both the clinician and patient in making treatment choices.[10] In some instances, for example, it appears that older patients are better able to cope with the psychological stresses of cancer treatment than younger patients.[11] The application of such approaches to cancer care is still in its infancy, however, and the impact of its application on specific treatment outcomes remains to be demonstrated.

Conclusions

Although elderly cancer patients can tolerate and respond to many antineoplastic agents just as well as their younger counterparts, many questions remain regarding appropriate therapy. Further clinical trials with multiagent regimens, the incorporation of protective agents, inclusion of "less healthy" patients, and quality-of-life analyses in elderly cancer cohorts are needed to refine our knowledge.
References:


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