Pharmacology of Chemotherapy in the Older Cancer Patient

Lodovico Balducci, MD, and Claudia Beghé, MD

The magnitude of therapeutic complications in elderly or frail patients with cancer can be related to estimates of individual functional reserve.

**Background:** The incidence of cancer among the elderly population is increasing. The aging process can deplete functional reserve of many organ systems and thus affects the treatment goals for this age-group.

**Methods:** The pharmacologic consequences of the aging process on elderly cancer patients are reviewed, and guidelines are suggested for assessing and treating this patient population with antitumor drugs.

**Results:** Individualized management of the older cancer patient reflects the results of a comprehensive geriatric assessment. Factors that affect treatment decisions include estimates of the extent of treatment toxicity, the impact of treatment on quality of life, estimates of life expectancy, and the influence of age on pharmacokinetic parameters.

**Conclusions:** Management of older patients with cancer includes individual assessments that consider the effects of aging on the pharmacodynamics, therapies, and complications of treatment for this population. Treatment can be made safer and more effective by adjusting chemotherapy dosage, maintaining hemoglobin levels, and using hemopoietic growth factors when appropriate.

**Introduction**

The incidence of cancer in the older-aged person is increasing, with 50% of all neoplasms occurring in persons over 65 years of age. Aging involves a progressive depletion of the functional reserve of multiple organ systems that may influence the pharmacology of antineoplastic drugs. This process is poorly reflected by chronological age, but rather it occurs at different rates in different individuals. Thus, the management of the older cancer patient involves the estimate of individual functional reserve.

This article reviews some of the pharmacologic consequences of aging and provides general guidelines for the assessment and the treatment of the older person with cancer.

**Pharmacokinetics**

Age may affect most pharmacokinetics parameters, including absorption, volume of distribution, hepatic drug metabolism, and excretion (Table 1).

### Table 1. — Influence of Age on Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effects of Age</th>
</tr>
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<tbody>
<tr>
<td>Absorption</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>• decreased gastric motility and secretions</td>
</tr>
<tr>
<td></td>
<td>• decreased splanchnic blood flow</td>
</tr>
<tr>
<td></td>
<td>• decreased absorptive surface</td>
</tr>
<tr>
<td>Volume of distribution (Vd)</td>
<td>Decreased for water-soluble agents</td>
</tr>
<tr>
<td></td>
<td>• decreased water content</td>
</tr>
<tr>
<td></td>
<td>• decreased serum albumin</td>
</tr>
<tr>
<td></td>
<td>• decreased hemoglobin</td>
</tr>
<tr>
<td>Hepatic drug metabolism</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>• decreased liver volume</td>
</tr>
<tr>
<td></td>
<td>• decreased hepatic blood flow</td>
</tr>
<tr>
<td>Excretion:</td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td>Probably unchanged</td>
</tr>
<tr>
<td>Renal</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>• decreased glomerular filtration rate</td>
</tr>
</tbody>
</table>

Diminished drug absorption may reduce the effectiveness of oral agents, but more information is needed on this issue. A new interest in drug absorption has been stimulated by the recent development of new oral antitumor agents such as capecitabine, tegafur, and oral cisplatin.
The volume of distribution (Vd) is a function of body composition, serum albumin, and hemoglobin. A progressive increase in body fat and a decline in body water generally occur up to age 85. These changes tend to restrict the Vd of water-soluble drugs and expand that of fat-soluble compounds. After 85 years of age, a progressive depletion of fat often occurs as well, and organ atrophy is a common finding. Hemoglobin is a parameter of special interest, because the levels of hemoglobin may be modulated by epoetin. The majority of antineoplastic agents, including anthracyclines, anthracenediones, epipodophyllotoxins, and taxanes, are bound to red blood cells. A reduction in the concentration of hemoglobin may result in increased serum concentration of free drug and increased toxicity.

The decrement in renal excretion of drugs is the most predictable pharmacokinetic change, and the glomerular filtration rate (GFR) declines consistently with age. It is important to remember that compounds excreted through the bile may give rise to active and toxic metabolites excreted through the kidneys (Table 2). Thus, renal insufficiency may enhance the toxicity of drugs that are primarily eliminated with the bile.

### Table 2. Renal Excretion of Antineoplastic Agents

<table>
<thead>
<tr>
<th>Drugs completely excreted through the kidneys:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Carboplatin</td>
</tr>
<tr>
<td>Bleomycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs partially excreted through the kidneys:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epipodophyllotoxins</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
</tr>
<tr>
<td>Taxanes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs producing active or toxic metabolites excreted through the kidneys:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Cytarabine (high doses)</td>
</tr>
</tbody>
</table>

Kintzel and Dorr have proposed a formula to adjust the dose of antineoplastic agents to the GFR. The most reliable measurement of the GFR can be obtained with the formula recently proposed by Levey et al. However, the pharmacokinetics of drugs cannot be completely predicted by changes in the GFR. Gurney showed how the area under the curve (AUC) of the same drug may vary up to sevenfold in patients of comparable size receiving the same dose of medications. Borkowski et al. showed that the renal clearance of dichloromethotrexate declined with the age of the patient, but the total clearance of the drug did not. This observation suggests that yet unknown excretory mechanisms may compensate for the decline in renal function.

### Pharmacodynamics

Pharmacodynamic changes may affect both the toxicity and the effectiveness of antineoplastic agents.

The ability of aging cells to catabolize drugs or to buffer the toxic effects of drugs may become more limited than in young cells. Stein et al. reported that the toxicity of fluorinated pyrimidines was more prevalent and more severe in older individuals and ascribed this phenomenon at least in part to a reduced intracellular concentration of dihydropyrimidine dehydrogenase. Rudd et al. reported that cisplatin-induced DNA adducts persisted for more than 80 hours in the circulating monocytes of persons over 70 years of age but were cleared in less than 20 hours in younger individuals.

Age may also be associated with tumors that are resistant to chemotherapy. The prevalence of leukemic cells expressing the multiple drug resistance gene (MDR-1) is 67% among persons over age 60 but only 17% among younger persons. In addition, anoxia of neoplastic cells and reduced cell proliferation may also reduce the effectiveness of cycle-active drugs. It is well known that cytotoxic chemotherapy is less effective in older individuals with acute myelogenous leukemia, non-Hodgkin’s large-cell lymphomas, ovarian cancer, and possibly breast cancer. These changes in sensitivity may be explained at least in part with pharmacodynamic changes.

### Therapeutic Complications

A more restricted functional reserve may enhance the susceptibility of normal tissues to antineoplastic chemotherapy (Table 3).

### Table 3. Complications of Chemotherapy That Are More Common and Severe in Older Individuals

- Myelosuppression
- Cardiomyopathy
- Mucositis
- Neurotoxicity
- Delayed nausea and vomiting
- Thrombocytopenia
- Anemia

The incidence and severity of myelotoxicity caused by moderately toxic chemotherapy increase dramatically after age 70. In this respect, the study of patients with large-cell non-Hodgkin’s lymphoma who were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy is particularly instructive. Armitage and Potter reported a 30% chemotherapy-induced death rate. Gomez et al., Zinzani et al., and Bastion et al. all reported that the incidence of grade 3 and 4 neutropenia and neutropenic infections more than doubled after age 70. To a lesser extent, thrombocytopenia and anemia were also more common. It is also well known that the risk of death during induction chemotherapy is higher among patients with acute myelogenous leukemia who are 60 years of age or older. In this case, however, the disease may also be responsible for a restriction in hemopoietic reserve.

The incidence of chemotherapy-induced mucositis is more common and more severe after age 65. The elderly may be predisposed to this complication by a number of factors, including reduced ability to catabolize fluorinated pyrimidines, reduced reserve of mucosal stem cells, and increased proliferation of surface mucosal cells. Whereas...
The incidence of immediate nausea and vomiting seems to decrease with the age of the patient, the risk of delayed nausea seems to increase with chemotherapy. The issue of peripheral neuropathy has become particularly compelling, as this complication may be dose-limiting for two drugs of common use, cisplatin and paclitaxel.

The cerebellar complications of cytarabine in high doses are due to the accumulation of the toxic metabolite ara-uridine (ara-U), which is excreted through the kidneys. Increased incidence of cerebellar toxicity with age may be associated more with a decline in GFR than with a reduction in the functional reserve of the cerebellum. Cognitive complications of chemotherapy are increasingly recognized and may be particularly severe in older individuals whose cognitive function is already compromised. Unusually, the nephrotoxicity of cisplatin does not appear to be more common among the aged. Seemingly, a decline in tubular reabsorption parallels the decline in GFR and results in decreased exposure to the drug.

Evaluation of the Older-Aged Patient With Cancer

The individualized management of the older-aged patient with cancer is based on the answers to the following questions: (1) Will the patient die of cancer or with cancer? (2) Will the patient suffer cancer-related morbidity? (3) Is the patient able to handle the toxicity of treatment? These questions can be answered with a multidimensional assessment that accounts for the diversity of the older population (Table 4).

Although chronological age is a poor reflection of physiologic age, two age landmarks have been identified: age 70, beyond which the incidence of age-related changes increases sharply, and age 85, when the last stage of life (frailty) begins. No laboratory test, including serum concentration of interleukin (IL)-6, cysteine/thiolic groups ratio, or serum osmolarity, offers an adequate assessment of age. The comprehensive geriatric assessment (CGA) allows the practitioner to establish some landmarks (eg, frailty, life expectancy, risk of complications) in the diverse panorama of the older population. The following components identify patient determinants and establish guidelines for the practitioner:

- The CGA defines patients considered to be frail, including those age 85 and older, those dependent in one or more activities of daily living (ADLs), patients with three or more comorbid conditions, and patients with one or more geriatric syndromes. The frail person has no functional reserve and is susceptible to the most negligible stress. Frail patients are clearly not candidates for any form of treatment other than palliation.

- Estimates of life expectancy are developed based on functional status, the number of comorbid conditions, cognition, depression, and the presence of geriatric syndromes.

- Patients at high risk for complications of cytotoxic chemotherapy are recognized. They include patients who are dependent in one or more instrumental activities of daily living (IADLs) and those with poor social support (eg, those who live alone or whose main caregiver is an older spouse).
Unrecognized medical problems such as malnutrition or hidden diseases may be revealed by a CGA and properly treated. This intervention may minimize the complications of cancer treatment.

Guidelines for the Management of Older Patients With Cancer

A number of reasonable guidelines aimed at making the treatment of older patients both safe and effective may be drawn from this brief review:

1. The first doses of chemotherapy should be adjusted to the GFR, according to the formula of Kintzel and Dorr, in all patients age 65 and older. As the pharmacokinetics of drugs cannot be completely predicted from GFR, successive doses should be escalated or decreased according to the severity of treatment toxicity.

2. Hemoglobin should be maintained to a level of 12 g/dL with epoetin alfa.

3. Hemopoietic growth factors (G-CSF or GM-CSF) should be routinely used in persons 70 years of age and older who are receiving moderately toxic chemotherapy (eg, CHOP, cyclophosphamide/doxorubicin, or docetaxel/doxorubicin for breast cancer; carboplatin/paclitaxel for non-small cell lung cancer). If no neutropenia is reported with the first treatment, the use of growth factors may be stopped in successive treatments.

4. The dominant goal of treating frail patients is palliation (Figure). Palliation may include some mild form of chemotherapy, including single-agent gemcitabine, navelbine, mitoxantrone, and low-dose taxanes. The management of pain in older individuals with narcotics or nonsteroidal agents may be associated with serious complications including nausea, constipation, and delirium. In patients who are reluctant to take analgesic medications because of these complications, chemotherapy may represent effective palliation.

A number of research projects are recommended for the treatment of older cancer patients, including (1) exploring alternative mechanisms of drug excretion and determining a simple approach to predict the AUC of drugs in older individuals, (2) analyzing the value of new antidotes to drug toxicity, including dextrazoxane for cardiomyopathy, keratinocyte growth factor for mucosal protection, IL-11 for thrombocytopenia in older individuals, and amifostine for nephroprotection, myeloprotection, and neuroprotection, and (3) studying the role of new agents — especially oral fluorinated pyrimidines and the liposomal derivatives of anthracyclines and cisplatin — in the management of the older and frail patients.

References


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