Management of Cancer in the Older Person: A Practical Approach

LODOVICO BALDUCCI, MARTINE EXTERMANN

Senior Adult Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

Key Words. Cancer · Elderly · Older person · Geriatric assessment · Pharmacokinetics

ABSTRACT

The management of cancer in the older aged person is an increasingly common problem. The questions arising from this problem are: Is the patient going to die with cancer or of cancer? Is the patient able to tolerate the stress of antineoplastic therapy? Is the treatment producing more benefits than harm?

This article explores a practical, albeit evolving, approach to these questions including a multidimensional assessment of the older person and simple pharmacologic interventions that may ameliorate the toxicity of antineoplastic agents. Age may be construed as a progressive loss of stress tolerance, due to decline in functional reserve of multiple organ systems, high prevalence of comorbid conditions, limited socioeconomic support, reduced cognition, and higher prevalence of depression. Aging is highly individualized: chronologic age may not reflect the functional reserve and life expectancy of an individual. A comprehensive geriatric assessment (CGA) best accounts for the diversities in the geriatric population. The advantages of the CGA include:

A. Recognition of potentially treatable conditions such as depression or malnutrition, that may lessen the tolerance of cancer treatment and be reversed with proper intervention;
B. Assessment of individual functional reserve;
C. Gross estimate of individual life expectancy; and
D. Adoption of a common language to classify older cancer patients.

The CGA allows the practitioner to recognize at least three stages of aging:

A. People who are functionally independent and without comorbidity, who are candidates for any form of standard cancer treatment, with the possible exception of bone marrow transplant.
B. People who are frail (dependence in one or more activities of daily living, three or more comorbid conditions, one or more geriatric syndromes), who are a candidate only for palliative treatment; and
C. People in between, who may benefit from some special pharmacological approach, such as reduction in the initial dose of chemotherapy with subsequent dose escalations.

The pharmacological changes of age include decreased renal excretion of drugs and increased susceptibility to myelosuppression, mucositis, cardiotoxicity and neurotoxicity. Based on these findings, the proposal was made that all persons aged 70 and older, treated with cytotoxic chemotherapy of dose intensity comparable to CHOP, receive prophylactic growth factor treatment, and that the hemoglobin of these patients be maintained ≥12 gm/dl. The Oncologist 2000;5:224-237

INTRODUCTION

In the US, 50% of all malignancies occur in persons aged 65-95 [1-3]. With the increase in the older population, it is expected that 60% of all cancers will be detected in elderly patients in the next two decades [2]. The issues of geriatric oncology include: Is the patient going to die with cancer or of cancer? Is the person going to suffer the complications of cancer during his/her lifetime? Is the patient able to tolerate the treatment safely? Will the treatment provide more benefits than harm? We explore these issues.

Correspondence: Lodovico Balducci, M.D., Senior Adult Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida 33612, USA. Telephone 813-979-3822; Fax: 813-972-8468; e-mail: Balducci@moffitt.usf.edu Website: http://www.moffitt.usf.edu Received March 31, 2000; accepted for publication May 17, 2000. ©AlphaMed Press 1083-7159/2000/$5.00/0

using cytotoxic chemotherapy as a model because cytotoxic chemotherapy has a wider array of side effects than other forms of cancer treatment.

This review consists of two parts: A) pharmacologic consequences of age, and B) individualized management of the older cancer patient. Aging is highly individualized in terms of life expectancy, functional reserve, social support, and personal preference [3]. To be effective, treatment plans need to account for this diversity.

Cancer Chemotherapy and Age

Aging is associated with a progressive decline in the functional reserve of multiple organ systems [3, 4]. This may influence pharmacokinetics (PK) and pharmacodynamics of antineoplastic drugs and reduce the tolerance of normal tissues for treatment complications [4, 5].

PK of Aging

Whereas the majority of PK parameters (Fig. 1) may change with aging, the most consequential changes involve volume of distribution (Vd) and renal excretion of drugs [4, 5].

The Vd is a function of body composition, serum albumin, and red blood cell concentration. With aging, the Vd of water-soluble drugs decreases as a result of decline in total body water; drop in albumin and hemoglobin concentration may further restrict the Vd of these agents and enhance their toxicity. The incidence and prevalence of anemia increases with age, especially after 65 [6-9]. Anemia may be particularly relevant for treatment with anthracyclines, taxanes, and epipodophyllotoxins that are heavily bound to red blood cells [5, 10-13]. The correction of anemia with erythropoietin may be particularly beneficial to older individuals, as anemia is the only component of Vd that can be manipulated.

A decline in glomerular filtration rate (GFR) is one of the most predictable changes associated with age [4, 5]. This decline may lead to enhanced drug toxicity through two mechanisms:

A. Reduced excretion of active drugs, such as methotrexate, bleomycin, or carboplatin, or

B. Reduced excretion of active metabolites whose parent compounds are not excreted through the kidneys. Examples of these metabolites include idarubicinol from idarubicin, or daunorubicinol from daunorubicin [5, 14-16].

The effects of GFR decline on the management of older persons with cancer were highlighted by the study of Gelman and Taylor [17]. In a retrospective analysis these authors demonstrated that the toxicity of a combination of cyclophosphamide, methotrexate and fluorouracil (CMF) was minimized, without reduction of the antineoplastic activity, when the doses of methotrexate and cyclophosphamide were adjusted to the GFR in women aged 65 and over.

As one acknowledges the effects of renal function on cancer chemotherapy, one must also realize that the PK of drugs are variable and the area under the concentration time curve may not be fully predictable from the GFR. For example, Borkowski et al. [18] studied the renal and plasma clearance of dichloromethotrexate in patients aged 70 and older and in younger subjects. Whereas the renal clearance of the drug declined with age, the plasma clearance did not, which is surprising because dichloromethotrexate is completely excreted through the kidneys. This observation suggests alternative forms of drug disposition when the GFR declines. Thus, we cannot support a recommendation that the dosage of antineoplastic agents be adjusted to the renal function in all older individuals.

Age may influence the hepatic metabolism of drugs, but the consequences of this change on cancer chemotherapy are largely unknown [5], partly because the study of this parameter is complex. The hepatic metabolism of drugs is a function of the hepatic blood flow [19] of the rate of drug extraction by the hepatocytes, and of the hepatocyte mass, in addition to the intracellular concentration and activity of drug-metabolizing enzymes [20]. Two types of drug-metabolizing reactions occur within the liver [20]. Type 1 reactions are oxydo-reductive reactions, that may generate both active and inactive metabolites of drugs, and involve the P450

Figure 1. PK and pharmacodynamic parameters.
cytochrome system. These reactions are influenced by other medications, such as barbiturates or cimetidine, that may augment or diminish the concentration and activity of the P450 enzymes. Type II reactions are conjugative reactions, that give origin to water-soluble compounds excreted through the bile or urine. Some of the age-related changes in liver function include:

- Decline in hepatic blood flow and hepatic mass [4].
- Decline in the intracellular activity of P450 cytochrome enzymes. This decline is particularly pronounced in the so-called “frail patients” (see below) [21, 22]. Compounds that require intrahepatic activation, such as oxophosphorines (cyclophosphamide and ifosfamide), should be avoided in frail patients.
- The risk of hepatic drug interactions may increase in older individuals as polypharmacy becomes more common with age [23].

Recently it was shown that the metabolites from type II reactions may maintain some of the activity of the parent compounds. For example, the 6 glucuronide of morphine maintains opioid activity, and the half-life of this metabolite, which is excreted through the kidneys, may become more prolonged in older individuals, which explains in part the increased sensitivity of the older person to opioids [24-26].

**Pharmacodynamics**

Pharmacodynamic changes may influence both the toxicity and antineoplastic activity of cytotoxic agents [5].

Rudd et al. reported cisplatin-induced DNA adducts were cleared from circulating monocytes in 24 h in individuals aged 50 and younger, and in more than 90 h in individuals aged 70 and older [27]. Delay in DNA repair may cause enhanced toxicity in older individuals. Another mechanism of increased toxicity may involve a delay in intracellular drug catabolism. For example, the concentration of dehydroxydiprimidine dehydrogenase that catabolizes fluorinated pyrimidines, may be reduced in the elderly [28].

Pharmacodynamic changes may cause resistance to cytotoxic chemotherapy in older individuals. At least three mechanisms of multidrug resistance have been suggested in the aged. The prevalence of myeloblasts expressing the p-glycoprotein increases in patients with acute myelogenous leukemia aged 60 and older [29]. The p-glycoprotein is encoded by the multidrug resistance (MDR-1) gene, and is responsible for extruding natural anticancer agents (antibiotics, plant derivatives) from the tumor cells.

Tumors occurring in older individuals may be more likely to manifest resistance to apoptosis because these neoplasms may develop from senescent cells that are unable to undergo apoptosis [30]. Resistance to apoptosis is another mechanism of multidrug resistance because all cytotoxic agents kill neoplastic cells through apoptosis. Tumors occurring in older individuals may manifest poorer oxygenation, due to compromised angiogenesis [31]. Hypoxia may be responsible for resistance to alkylating agents and radiation therapy.

**Susceptibility of Normal Tissues to the Toxicity of Antineoplastic Drugs**

The susceptibility of older tissues to the complications of cytotoxic agents may be enhanced by at least three mechanisms:

- Decreased stem cell reserve that may compromise the recovery of tissue losses (Fig. 2). This mechanism may be responsible for the complications concerning rapidly renewing tissues, including the hemopoietic tissue and mucosas [28, 32].
- Decreased ability to catabolize cytotoxic drugs and repair the cellular damage of these drugs. This mechanism may be operative in the majority of older tissues and has already been described in circulating monocytes and intestinal mucosas [27, 28].
- Critical reduction in functional tissue, so that the loss of additional tissue may lead to organ failure. This

**Figure 2. Stem cell reserve and toxicity of chemotherapy.** Each figure consists of four compartments: a circle representing the total stem cell population that is arbitrarily established at 100; a square with dotted margin, representing the number of stem cells lost to commitment and differentiation; a small square representing the proliferative pool of the stem cells, and a large square representing the stem cells that re-enter the general pool after replication. In condition of homeostasis for every five stem cells lost to commitment and differentiation, five stem cells enter the proliferative pool and regenerate the initial pool of stem cells. This occurs both when the stem cell reserve is intact and when it is moderately depleted. In conditions of stress, however, the demand for commitment and differentiation may overcome the ability of a reduced stem cell reserve to replicate itself, and marrow failure may ensue.
mechanism may be responsible for the increase in the incidence of cardiomyopathy [33] and neurotoxicity [5, 34, 35].

Table 1 lists the complications of cytotoxic chemotherapy that become more common in older individuals.

Some controversy exists over whether the risk of myelotoxicity increases with the age of the patient. At least five retrospective studies compared the incidence and severity of myelodepression in younger and older patients, and failed to demonstrate increased incidence, severity, or duration of myelodepression [17, 36-39]. The study of Gelman and Taylor [17], previously described, showed that the toxicity of CMF was not increased in patients over 65 receiving CMF for metastatic breast cancer, when the doses of cyclophosphamide and methotrexate were adjusted to the patient’s GFR. Christman et al. [36] compared women aged under 55, 55-70 and over 70, with metastatic breast cancer, treated according to the protocols of the Piedmont Oncology Group. Ibrahim et al. [37] also compared women aged 70 and older and younger women, treated according to the M.D. Anderson protocols during a 15-year period. Beggs and Carbone [38] reviewed the cases of patients treated according to 10 solid tumor protocols within the Eastern Cooperative Oncology Group (http://ecog.dfci.harvard.edu), and compared the risk and severity of myelodepression in patients aged 70 and older and younger patients. In a number of phase II studies involving different tumors, Giovannazzi-Bannon et al. showed the risk and severity of myelodepression did not increase with the age of the patients [39]. These studies clearly demonstrate that age itself is not necessarily a risk factor for myelotoxicity. However, all of these studies have the limitations typical of retrospective analysis:

- Older persons were underrepresented. Persons over 70 made up only 10%-15% of the total patient population, while 40% of all malignancies occur in this age group.
- The oldest old (i.e., patients aged 80 and older) were virtually absent.
- Patients were highly selected in terms of performance status and comorbidity, as they all had been treated according to cooperative groups or major cancer center protocols.
- The dose intensities of most chemotherapy regimens were lower than those of current regimens.

A quite different picture emerges from the exam of a number of clinical trials of large-cell lymphoma, that were directed specifically to older patients (Table 2) [40-47]. With the exception of the study of Armitage [47], all studies were prospective and involved treatment regimens with a dose intensity comparable to CHOP. In three cases [41, 43, 44], randomized controlled studies compared the benefits of CHOP (or CTVP, the French version of CHOP) with a treatment regimen of lower toxicity, and demonstrated that CHOP produced the best outcome in terms of response rate and overall survival.

Table 1. Complications of cytotoxic chemotherapy more common in older individuals

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodepression</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td>Oropharyngo-esophagitis</td>
<td></td>
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<tr>
<td>Enterocolitis</td>
<td></td>
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<tr>
<td>Cardiodepression</td>
<td></td>
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<tr>
<td>Peripheral neuropathy</td>
<td></td>
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<tr>
<td>Central neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Cognitive decline</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
</tr>
<tr>
<td>Cerebellar dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Incidence of neutropenia, neutropenic fever, and treatment-related death among older individuals with non-Hodgkin’s lymphoma receiving CHOP and CHOP-like chemotherapy

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Patient n</th>
<th>Regimen</th>
<th>Age</th>
<th>Neutropenia</th>
<th>Neutropenic Fever</th>
<th>Treatment-related Deaths</th>
<th>Growth Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinzani [40]</td>
<td>350</td>
<td>VNCOP-B</td>
<td>60+</td>
<td>17%</td>
<td>8%</td>
<td>–</td>
<td>G-CSF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60+</td>
<td>44%</td>
<td>32%</td>
<td>1.3%</td>
<td>–</td>
</tr>
<tr>
<td>Sonneveld [41]</td>
<td>148</td>
<td>CHOP</td>
<td>60+</td>
<td>NR</td>
<td>NR</td>
<td>14%</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNOP</td>
<td>60+</td>
<td>NR</td>
<td>NR</td>
<td>13%</td>
<td>–</td>
</tr>
<tr>
<td>Gomez [42]</td>
<td>26</td>
<td>CHOP</td>
<td>60+</td>
<td>24%</td>
<td>8%</td>
<td>0</td>
<td>GM-CSF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70+</td>
<td>73%</td>
<td>42%</td>
<td>20%</td>
<td>GM-CSF</td>
</tr>
<tr>
<td>Tirelli [43]</td>
<td>119</td>
<td>VMP</td>
<td>70+</td>
<td>50%</td>
<td>21%</td>
<td>7%</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHOP</td>
<td>70+</td>
<td>48%</td>
<td>21%</td>
<td>5%</td>
<td>–</td>
</tr>
<tr>
<td>Bastion [44]</td>
<td>444</td>
<td>CVP</td>
<td>70+</td>
<td>9%</td>
<td>7%</td>
<td>12%</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTVP</td>
<td>70+</td>
<td>29%</td>
<td>13%</td>
<td>15%</td>
<td>–</td>
</tr>
<tr>
<td>Bertini [45]</td>
<td>98</td>
<td>P-VEBEC</td>
<td>65+</td>
<td>22%</td>
<td>4%</td>
<td>0</td>
<td>G-CSF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65+</td>
<td>46%</td>
<td>9%</td>
<td>2%</td>
<td>–</td>
</tr>
<tr>
<td>O’Reilly [46]</td>
<td>63</td>
<td>POCE</td>
<td>65+</td>
<td>50%</td>
<td>20%</td>
<td>8%</td>
<td>–</td>
</tr>
<tr>
<td>Armitage [47]</td>
<td>20</td>
<td>CHOP</td>
<td>70+</td>
<td>NR</td>
<td>NR</td>
<td>30%</td>
<td>–</td>
</tr>
</tbody>
</table>
The exam of Table 2 clearly shows that CHOP, or regimens of similar dose-intensity, were associated with a risk of grade III-IV neutropenia in older individuals higher than 50%, and with a risk of treatment-related death varying between 5%-30%. Gomez et al. [43] showed that myelodepression was particularly common among patients aged over 70.

The risk of grade III-IV thrombocytopenia was around 20% in the majority of studies. Two randomized and controlled studies [40, 45], demonstrated that G-CSF reduced the risk of severe neutropenia and neutropenic infections in older individuals by more than 50%. Zinzani et al. [40] reported life-threatening neutropenia in 18 of 77 (23%) patients who had received G-CSF and 40/72 (55.5%) patients treated without G-CSF (p = 0.00005). The rate of severe infection was 4/77 (5%) and 21/72 (21%), respectively (p = 0.004). Similar results were reported by Bertini et al. [45] among 100 patients aged over 65 treated with etoposide, epirubicin, cyclophosphamide, vincristine and prednisone.

A number of studies of patients with AML aged 60 and older also showed that the risk of life-threatening myelodepression was increased during induction and consolidation treatment [48, 49]. In the case of AML, the disease itself may cause a depletion of the reserve of normal hemopoietic stem cells [29]. The benefits of growth factors in the older patients with AML are controversial. The Eastern Cooperative Oncology Group reported decreased risk of neutropenic infections and infectious death and more prolonged survival for patients aged 65 and older treated with GM-CSF after induction treatment [48]. A number of studies summarized by Schiffer [49] showed that use of growth factors during consolidation treatment decreased the duration of hospital admissions.

Examination of these data indicates:

- The risk of neutropenic complications and death from neutropenic infections is increased for older individuals receiving moderately toxic chemotherapy.
- This risk is more pronounced after age 70.
- Hemopoietic growth factors are effective in preventing life-threatening neutropenia and neutropenic infections.

Until recently, scarce attention has been paid to the risk of anemia in patients receiving cytotoxic chemotherapy. In older individuals anemia may have a number of serious consequences, including:

- Enhanced toxicity of cytotoxic chemotherapy [5-9].
- Increased risk of fatigue that in older individuals may lead to functional dependence [50, 51].
- Increased risk of complications from medications or infections [52].

These findings support correction of anemia in older individuals undergoing cytotoxic chemotherapy.

The risk of mucositis increases with age. This issue was reviewed by Stein [28] who showed that mucositis may lead to lethal fluid depletion in individuals aged 66 and older. Decreased concentration of mucosal stem cells, increased destruction of rapidly proliferating mucosal cells, and decreased intracellular catabolism of fluoropyrimidine may contribute to the risk of mucositis in the elderly. Of interest, the risk and severity of mucositis was increased for women aged 65 and over, even in the study of Gelmann and Taylor [17] despite dose adjustment. This finding indicates that the mucosas of older individuals are more vulnerable by cytotoxic chemotherapy.

The risk of anthracycline cardiomyopathy increases with the age of the patient [33], but this risk is largely limited to elevated total doses of the drugs (equivalent to doses of doxorubicin ≥450 mg/m² of body surface area). In the absence of other risk factors, it does not appear reasonable to use special measures to prevent cardiotoxicity in patients receiving lower doses of the medications. Continuous slow infusion of anthracyclines may lead to enhanced risk of mucositis [53], whereas dexrazoxane may enhance myelosuppression and attenuate the antineoplastic activity of doxorubicin [54].

Adjuvant chemotherapy was found to compromise the cognitive function of young women with breast cancer [55]; therefore, the possibility that chemotherapy may precipitate dementia in older individuals is a reasonable concern.

Cerebellar toxicity is typical of high doses of cytara-bine. In addition to age, a decline in GFR is a risk factor for this complication [35]. Cerebellar toxicity appears to be due to the accumulation of arauridine in the cerebellum [56]. Arauridine is a product of the catabolism of cytarabine, and is excreted from the kidneys. When the GFR is reduced, arauridine accumulates in the plasma and tissues.

Surprisingly, the nephrotoxicity of cytotoxic chemotherapy does not appear enhanced in the aged [3].

Prevention and Amelioration of Chemotherapy-Related Toxicity in Older Individuals

A better understanding of PK and pharmacodynamics of antineoplastic agents, and the development of a number of antidotes to drug toxicity, may make the treatment of older individuals safer and more effective. Table 3 summarizes a number of recommendations that were recently presented to the National Cancer Center Network (NCCN) (http://www.nccn.org) [57]. As one can see, the only guidelines that are specific for older patients involve the administration of hemopoietic growth factors and erythropoietin, and the adjustment of the doses of chemotherapy to the GFR of patients at particular risk for toxicity. Given the
significant risk of neutropenic infections and death, it was felt that the use of G-CSF or GM-CSF should be recommended in all patients over 70 receiving chemotherapy with a dose intensity comparable to CHOP.

A hemoglobin level of 12 mg/dl is recommended because the control of fatigue appears optimal at that level [40, 41], since anemia may enhance the risk of chemotherapy-related toxicity [5-9], and anemia has other serious implications in the older person [32].

The dose adjustment to a patient’s individual GFR (Table 4) is recommended for patients deemed at increased risk of complication based on a comprehensive geriatric assessment (CGA). This assessment is important to account for the diversity of the geriatric population that underlies individual benefits and risk of cancer treatment. In the next section we illustrate how a CGA may guide the management of older individuals with cancer.

**Assessment of the Older Cancer Patients and Decision-Making Implications**

In the previous discussion aging was defined as a progressive loss in the functional reserve of multiple organ systems and consequent reduction in the tolerance of stress, including cytotoxic chemotherapy. Also, aging is associated with reduced life expectancy. Seemingly, the benefits of antineoplastic treatment are reduced, and the risks enhanced in the older person. The management of the older person with cancer, aimed to maximize the benefits and minimize the risk of treatment in individual situations, is based on two types of clinical decisions:

A. Recognition of those patients who may benefit most from standard treatment, and those for whom the therapeutic risks overwhelm the potential benefits.

B. Institution of medical, psychological and social interventions that may improve the tolerance of chemotherapy by individual patients.

Chronologic age and laboratory tests are of limited assistance in these decisions. As a general rule, two age landmarks may be established: age 70 and age 85. The adoption

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### Table 3. Provisions that may reduce complications of cytotoxic chemotherapy in older cancer patients

<table>
<thead>
<tr>
<th>A. Antidotes</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidote</strong></td>
<td><strong>G-CSF; GM-CSF</strong></td>
</tr>
<tr>
<td><strong>Erythropoietin</strong></td>
<td>Patients aged 70 and older to maintain hemoglobin levels ≥12 gm/dl</td>
</tr>
<tr>
<td><strong>IL-11</strong></td>
<td>Patients with solid tumors who have needed platelet transfusions</td>
</tr>
<tr>
<td><strong>Amifostine</strong></td>
<td>To prevent nephrotoxicity from high doses of cisplatin</td>
</tr>
<tr>
<td><strong>Desrazoxane</strong></td>
<td>To prevent salivary toxicity in patients with head and neck cancer receiving radiation therapy</td>
</tr>
</tbody>
</table>

### Table 4. Suggested dose adjustment for common antineoplastic agents to the GFR

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min</th>
<th>≤60</th>
<th>≤45</th>
<th>≤30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>0.7</td>
<td>0.6</td>
<td>NR</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Calvert’s formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carmustine</td>
<td>0.8</td>
<td>0.75</td>
<td>NR</td>
</tr>
<tr>
<td>Cisplatinum</td>
<td>0.75</td>
<td>0.50</td>
<td>NR</td>
</tr>
<tr>
<td>Cytarabine (high doses)</td>
<td>0.6</td>
<td>0.5</td>
<td>NR</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>0.8</td>
<td>0.75</td>
<td>0.70</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>0.8</td>
<td>0.75</td>
<td>0.65</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.8</td>
<td>0.75</td>
<td>0.7</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>0.8</td>
<td>0.75</td>
<td>0.7</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.85</td>
<td>0.75</td>
<td>0.7</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.65</td>
<td>0.5</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not recommended.
of age 70 as the lower limit of clinical senescence is suggested by the fact that the prevalence of age-related changes is represented by an almost flat line up to age 70, but increases sharply between age 70 and 75 [58]. Approximately 90% of the persons with clinical signs of aging are over 70. After age 85, the prevalence of clinical frailty (see following discussion) increases sharply [59-63]. Persons aged 85 and older are referred to as “oldest old” in geriatric circles; a more rapid decline in visual and hearing function makes these patients more susceptible to environmental injury and more prone to functional dependence [60]. These landmarks are useful to identify groups of persons that need special attention, because they may be old or frail, but chronologic age is otherwise inadequate to reflect individual functional reserve and life expectancy. This information is not provided by any laboratory test at present. Though GFR declines with aging [4, 64], this decline is quite variable from individual to individual, and may be influenced by a host of comorbid conditions. The circulating levels of interleukin 6 (IL-6) may be increased in the presence of dementia, osteoporosis, or other geriatric syndromes [65], but this elevation appears confined to a group of frail patients, whose functional reserve is practically exhausted [59]. Recently, German investigators reported that aging may be reflected by the ratio of cystein/thiolic groups in the circulation [66]. This index is also influenced by malnutrition and needs clinical validation.

Currently, the best estimates of individual functional reserve and life expectancy may be provided by a CGA, accounting for the multidimensional nature of aging (Table 5) [67].

Aging involves changes in the functional, emotional, socio-economic and cognitive domains [68-70]. In addition, age is associated with increased incidence of chronic diseases (comorbidity) [71-74] and a number of syndromes typical of the older persons, the so-called “geriatric syndromes” [43, 75-78], that imply shortened survival and enhanced vulnerability to even minimal stress.

In randomized and controlled studies, the CGA was found extremely helpful in the management of a number of geriatric problems, including prevention of institutionalization and maintenance of independence [79], prevention of delirium for hospitalized patients [77], falls [76], and hospital readmission [79-81]. In addition, the CGA was found to detect new and unsuspected problems in 76% of elderly persons living at home [80-82]. When the CGA was repeated yearly, the incidence of new problems was approximately 30%.

In the management of the older person with cancer, the value of the CGA includes:

- Assessment of comorbidity that may render older individuals more susceptible to the complications of chemotherapy. Many comorbid conditions may be reversed or ameliorated, and chemotherapy may be safer under these circumstances.
- Assessment of socioeconomic conditions that may prevent compliance with chemotherapy or enhance the risk of complications. This includes the inadequacy of transportation and home caregiving, as well as the inability to achieve timely help in case of serious complications.
- Assessment of functional dependence that may affect the tolerance of complications from cytotoxic agents.
- Recognition of frailty, a condition in which most functional reserve is exhausted, and the aim of treatment is palliation.
- Assessment of emotional and cognitive conditions, such as depression and memory disorders, that may interfere with comprehension and acceptance of treatment plans.
- Some gross estimate of life expectancy, based on functional status, comorbidity, cognition, presence or absence of geriatric syndromes. In general, this estimate is critical before instituting treatments whose benefits may be seen only years later, such as adjuvant treatment for breast cancer or colorectal cancer, primary treatment of prostate cancer, or the use of chemotherapy in myelodysplasia.
Application of a common language to the evaluation of the older patient. This common language is essential to compare the outcome of treatment in different practice and for quality assurance.

Although the CGA has not been standardized, the consensus is that it should include the elements summarized in Table 6.

The assessment of function needs to include Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs) in addition to performance status. ADLs include transferring, grooming, continence, using the toilet, dressing, and feeding. IADLs include use of transportation, money management, shopping, taking medications, and being able to provide one’s own meals. This assessment is important for the following reasons:

- Functional dependence is associated with shortened survival [80, 83, 84]. Average life expectancy for a person dependent in one or more ADLs is shorter than three years [83].
- Dependence in some IADLs, such as shopping, use of transportation and telephone, and money management predicts clinical dementia in the following two years [85] and is associated with reduced tolerance of cytotoxic chemotherapy [86].
- Dependence in one or more ADLs is a sign of frailty, a condition in which functional reserve is severely reduced and tolerance of even small stress is compromised [59].
- ADL and IADLs bear a poor correlation with performance status [87].

The assessment of comorbidity is important for the following reasons:

- Comorbidity is associated with decreased life expectancy [73] and is an independent prognostic factor for cancer outcome [88].
- Comorbidity may compromise the tolerance of cancer chemotherapy [1, 88].

### Table 6. Proposed screening tests

<table>
<thead>
<tr>
<th>Realm</th>
<th>Screening</th>
<th>Confirmatory test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental status</td>
<td>Serial three: tell patient: “I am going to name three objects (pencil, truck, book, and I am going to ask you to repeat them now and a few minutes from now.”</td>
<td>Folstein minimental status. If score &lt;24 institute work-up for dementia.</td>
</tr>
<tr>
<td>Emotional status/depression</td>
<td>Ask patient: “Do you feel often depressed or sad?”</td>
<td>GDS. If positive (score &gt;10), work up for depression.</td>
</tr>
<tr>
<td>ADL</td>
<td>Can you dress yourself?</td>
<td>Formal Katz ADL scale</td>
</tr>
<tr>
<td>IADL</td>
<td>Do you drive? Are you able to use public transportation?</td>
<td>Formal IADL scale</td>
</tr>
<tr>
<td>Home environment</td>
<td>Do you have trouble with stairs inside and outside the house?</td>
<td></td>
</tr>
<tr>
<td>Social support</td>
<td>Who would be able to help you in case of emergency?</td>
<td>If no caregiver, try to arrange for a caregiver. If the caregiver is a spouse, a sibling or a friend of the same age of the patient, assess independence of the caregiver.</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Evaluate the presence of following conditions from ROS: congestive heart failure, coronary artery disease, valvular heart disease, chronic lung disease (obstructive or restrictive), cerebrovascular disease, peripheral neuropathy, chronic renal insufficiency, hypertension, diabetes, coexisting malignancies, collagen vascular diseases, incapacitating arthritis.</td>
<td>Confirm the presence of the condition and grade the seriousness.</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Weigh patient, measure height, inquire about weight loss.</td>
<td>Mininutritional assessment (MNA)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Review number and type of medications.</td>
<td>If more than three medications look for duplications, interactions, and compliance.</td>
</tr>
</tbody>
</table>
The prevalence of comorbidity increases with age [72]. Ideally, comorbidity should be assessed as a comorbidity index, a number expressing the risk of death and therapeutic complications [70, 71]. Several comorbidity indices are used in geriatrics. Of these, the Charlson’s scale [89], and the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) [90], are the most popular. Ongoing studies assess the value of the CIRS-G and the Charlson’s scale in older cancer patients. Currently, the assessment of comorbidity includes the number of conditions that may compromise survival [73], including coronary artery diseases, congestive heart failure, chronic obstructive pulmonary diseases, renal insufficiency, cerebrovascular diseases, neurovascular complications of diabetes mellitus, arthritis that restricts mobility, and anemia [71-73].

Cognition becomes progressively more compromised with age; after age 85 approximately 50% of the population presents some degree of dementia [61]. A number of tests are available for the rating of dementia, and of these, the Folstein Minimental status is used most commonly because of its simplicity [78]. Dementia has been associated with decreased survival [91, 92]. Also, dementia may be worsened by cytotoxic chemotherapy [55] and associated with decreased tolerance of antineoplastic treatment [86].

Screening for depression is also important because depression may reduce the motivation to receive treatment [93]. The geriatric depression scale is a simple 15-item instrument that may be self-administered and proved very accurate for screening purposes [93]. Depression has been associated with decreased survival in older individuals [94, 95], and depression may be reversible by pharmacologic treatment. Severe depression, associated with weight loss and failure to thrive, is considered a geriatric syndrome [59]. The assessment of nutrition by the mini-nutritional assessment [96] allows recognition of patients who are malnourished and at risk of developing malnutrition. Some degree of protein/calorie malnutrition is present in approximately 20% of persons aged 70 and older [97]. In the presence of cancer, the prevalence and risk of malnutrition are higher [98]. Malnutrition in the aged has multiple causes, including decreased threshold for bitter taste, increased threshold for sweet taste, decreased gastric secretion, depression, forgetfulness, limited mobility, decreased ability to feed oneself from arthritis, and poverty [96]. Thus, older individuals are more vulnerable to nutritional complications of cancer and cancer treatment. Malnutrition is associated with a number of complications, including enhanced toxicity of cytotoxic chemotherapy [97]. With timely intervention malnutrition may be prevented or reversed in older cancer patients [98].

Polypharmacy is a common problem in the elderly and may be associated with a number of complications including cognitive deterioration, delirium, emotional instability, and drug interactions [23]. Elimination of unnecessary drugs may reduce the risk of both complications and treatment expenses. Adequate social support is essential for several aspects of treatment including transportation, timely management of fever, bleeding and other emergencies during chemotherapy, and emotional and physical assistance to the patient during treatment. Pivotal to the social management of the patient is an effective home caregiver [99] whose functions include:

- To coordinate the patient’s treatment;
- To recognize treatment complications in a timely manner;
- To arrange for transportation to the clinic and hospital on short notice;
- To bridge possible communication gaps among patient, family, and practitioner, and
- To facilitate the communication among family members, promoting the solution of conflicts and incomprehension.

The outcome of the treatment of the older cancer patient may be predicated upon the identification and selection of the family caregiver. Common problems related to the caregiver include the fact that caregiving is sometimes provided by an elderly spouse with health problems of his/her own, or by a married daughter who must take care of her own family at the same time, and caregiver burn-out. The practitioner needs to be sensitive to these problems and provide proper counseling to maintain an effective caregiver.

Whereas the general benefits of a CGA are easily recognized, it is not clear whether the CGA may fulfill the main need of geriatric oncology—an accurate estimate of risks and benefits of treatment. This estimate is desirable from both a practical and a research standpoint. From a practical standpoint it would provide valuable guidelines for the treatment of older individuals; from a research standpoint, it would allow stratification of older patients undergoing clinical trials according to the risk of treatment complications.

According to the CGA it is possible to recognize at least three groups of older cancer patients, with different life expectancies and risks of therapeutic complications (Fig. 3). Group 1 patients are functionally independent and without serious comorbidity; group 2 patients may be dependent in one or more IADLs and/or may present one or two comorbid conditions; group 3 patients represent the frail patients. As expected the prevalence of group 1 patients
declines and that of group 3 patients increases with age, whereas the prevalence of group 2 patients increases until age 85 and declines thereafter. Of these groups, the frail patients are the best defined [59, 62, 63].

Frailty involves limited life expectancy and near-to-exhausted functional reserve [59]. In the management of frail patients, symptom palliation and quality-of-life preservation are paramount. Whereas the frail patients may still benefit from chemotherapy with drugs with low complication rates such as gemcitabine, navelbine, or weekly taxanes [100], they are not candidates for more toxic treatment. General agreement exists on the definition of frailty [59, 100], that includes dependence in one or more ADLs, three or more comorbid conditions, and one or more geriatric syndromes. An area of controversy is whether there are chronologic boundaries of frailty. It appears reasonable to screen persons aged 85 and older for frailty very thoroughly, as the incidence of geriatric syndromes and functional dependence increases after this age [59, 100, 101].

The previous classification of aging into three groups of individuals of different functional reserve and comorbidity may be used as the basis for an algorithm for the treatment of cancer in older patients (Fig. 4). Classification and algorithm are meant as models for future studies, not as definitive constructs. As our understanding of aging evolves, new populations of patients may be defined that better reflect life expectancy and tolerance of stress [62, 63].

After exploring the benefits of a CGA, a number of practical questions need to be addressed: How are patients selected for whom the CGA is indicated? Who should perform the CGA? What kind of time investment is involved?

As the prevalence of age-related changes increases sharply between age 70 and 75 [58], it is reasonable to recommend that all cancer patients aged 70 and older receive some form of geriatric evaluation, just as a complete review of system and physical exam are obtained in all patients who come to a clinic for the first time. In addition, CGA may be indicated in those persons younger than 70 with clear signs of aging (functional dependence, memory disorders, history of falls, etc). The experience of the Senior Adult Oncology Program at the H. Lee Moffitt Cancer Center and Research Institute in Tampa (http://www.moffitt.usf.edu) supports this recommendation [87]. Among the first 200 patients aged 70 and older processed by this program, 18% were dependent in one or more ADLs; 72% in one or more IADLs; 36% had significant comorbidity according to the Charlson scale and 94% according to the CIRS-G scale; 22% had memory disorders, 19% malnutrition, and 41% polypharmacy. Many of these problems would have been missed in the absence of a CGA.

The CGA can be performed by any trained health professional. Whereas the ideal setting for a CGA is primary care, a large number of older individuals may reach an oncologist without any form of geriatric evaluation.

The time commitment for the CGA is a serious problem, given the current trend to process patients in shorter and
shorter time. Whereas the information related to function, living condition, depression, polypharmacy and comorbidity may be obtained from questionnaires completed by the patient or family member, the record and interpretation of the information is time-consuming. Furthermore, the minimental status needs to be administered by a professional and takes approximately 15 minutes. The average oncology practice cannot afford this time investment until the CGA is properly compensated by third-party payers. A reasonable compromise, endorsed by the NCCN task force for the management of cancer in the older person, involves the use of a short screening instrument (Table 6) to unearth potential problems in the various domains of the CGA and perform a complete assessment of that particular domain only for patients who screen positive. This screening instrument is an adaptation to cancer patients of the instruments proposed by Lachs et al. for the general geriatric population [102].

CONCLUSIONS AND PERSPECTIVES
This review has highlighted two aspects of aging:

• Aging is associated with a progressive reduction in the functional reserve of multiple organ systems and reduced tolerance of physical, emotional, and social stress.

• Aging is multidimensional and individualized. The physiologic, medical, social, emotional, and cognitive changes of aging are poorly reflected in chronologic age and can be best appreciated with a multidimensional assessment of the older person.

This finding suggests two special provisions in the management of the older cancer patient:

• Prevention of chemotherapy-related toxicity in patients aged 70 and over with prophylactic use of hemopoietic growth factors, prevention and management of anemia, and proper adjustment of drug dosages to individual GFR.

• A comprehensive assessment of the older person to unearth and address individual problems that may compromise the safety and effectiveness of treatment and to assess the risk/benefit balance in individual situations.

These recommendations represent the first attempt to address the management of cancer in the older person, and should not be considered final. These recommendations are the foundation upon which new recommendations may be built as our understanding of aging and the relationship between aging and cancer evolves.

Areas of active research that may produce new and more specific recommendations include:

• Laboratory assessment of aging.

• More precise assessment of the impact of comorbidity on life expectancy and treatment tolerance, with the use of comorbidity indices.

• Prediction of PK of antineoplastic drugs in the individual patient, with the assessment of GFR, hepatic blood flow and metabolism, lean body weight, and hemoglobin.

• Estimate of cancer prognosis based on the tumor-host condition, in addition to the aging of cancer, by unraveling the network of cytokines that promote tumor growth.

• Development of noncytotoxic agents for cancer treatment.

• Improved quality of information, based on uniform evaluation of the older patient.

A recent report from the Southwest Oncology Group (SWOG) (http://www.SWOG.org) highlighted the underrepresentation of older individuals in clinical trials of cancer treatment [103]. It would be critical to know whether these patients were excluded from the trials because of personal biases of the investigators or their conditions prevented safe administration of treatment [104]. The adoption of a common language in the assessment of older individuals may answer this question and allows us to formulate proper strategies for the management of cancer in older individuals.

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