Management of Cancer in the Elderly

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With the aging of the Western population, cancer in the older person is becoming increasingly common. After considering the relatively brief history of geriatric oncology, this article explores the causes and clinical implications of the association between cancer and aging. Age is a risk factor for cancer due to the duration of carcinogenesis, the vulnerability of aging tissues to environmental carcinogens, and other bodily changes that favor the development and the growth of cancer. Age may also influence cancer biology: Some tumors become more aggressive (ovarian cancer) and others, more indolent (breast cancer) with aging. Aging implies a reduced life expectancy and limited tolerance to stress. A comprehensive geriatric assessment (CGA) indicates which patients are more likely to benefit from cytotoxic treatment. Some physiologic changes (including reduced glomerular filtration rate, increased susceptibility to myelotoxicity, mucositis, and cardiac and neurotoxicity) are common in persons aged 65 years and older. The administration of chemotherapy to older cancer patients involves adjustment of the dose to renal function, prophylactic use of myelopoietic growth factors, maintenance of hemoglobin levels around 12 g/dL, and proper drug selection. Age is not a contraindication to cancer treatment: With appropriate caution, older individuals may benefit from cytotoxic chemotherapy to the same extent as the youngest patients.

Medicine is the crossroad between social and clinical sciences. The evolving social landscape indicates the goals of clinical research; the achievements of clinical research, in turn, influence social evolution. For example, improved medical and hygienic conditions have decreased mortality, resulting in the aging of the population, which has led to an explosion of chronic diseases including cancer.[1,2] The development of geriatric oncology represents one of the earliest and most consistent medical responses to the aging of the population, perhaps because cancer is largely a disease of aging.[1,3]

From Bedside to Bench: The History of Geriatric Oncology
In retrospect, one may wonder why a special interest in cancer and aging had emerged only in the past 2 decades, given that the average life expectancy of the population had been progressively increasing since World War II. Two factors likely delayed the development of geriatric oncology: The first is the absence of effective treatment or prevention of most advanced cancers, irrespective of a person's age, until 30 years ago. The second involves the difficulty of defining the boundaries of adulthood and aging, and the reluctance of clinical scientists to engage in the exploration of these unknown territories.

Undoubtedly, the foundation of geriatric oncology was laid at a National Institute of Aging conference held in 1981. Convened by Drs. Rosemary Yancik and Jerome W Yates, the conference addressed the topic of cancer and aging, serving a twofold purpose: It highlighted the extent of the problem and it provided a common forum for geriatricians, gerontologists, and oncologists. This encounter catalyzed the clinical developments that justified the existence of geriatric oncology—the application of geriatric principles to the assessment of older cancer patients. For the first time, clinical scientists studying cancer treatment were able to formulate specific questions about cancer and aging: Is the patient going to live long enough to die of and suffer from cancer? Can the patient tolerate the complications of cancer treatment? In the principles of geriatric assessments, clinicians were provided the means to address these questions.

After the conference, several reviews of the literature indicated that older individuals were underrepresented in clinical trials, which led to the elimination of upper age limits as discriminatory in studies sponsored by the National Cancer Institute (NCI). At the same time, numerous clinical trials focusing on older individuals were conducted, especially in large cell lymphoma. These trials established that older individuals may benefit from chemotherapy to the same extent as younger individuals (as long as the chemotherapy is administered in an adequate dose intensity) and that older individuals were more vulnerable to the complications of cytotoxic chemotherapy, especially myelotoxicity, mucositis, and cardiotoxicity.[4-10] It also became clear that the prognosis for some
neoplasms—including acute myelogenous leukemia (AML),[11] lymphoma,[12] breast cancer,[13] and ovarian cancer[1,3]—changes with aging, and the mechanisms of these changes were in part clarified.

Ensuing Conferences, Task Forces, and Initiatives

The need to organize the wealth of emerging information led to a number of international conferences with the combined sponsorship of the H. Lee Moffitt Cancer Center and Research Institute of Tampa, the Florida Exchange Center of Gerontology in Tampa, and the Istituto Nazionale Tumori of Genova, Italy. The attendees of these conferences became the original nucleus of the International Society of Geriatric Oncology (SIOG), founded in 2000 in New York and led by first president Dr. Paul Calabresi, a pioneer of medical oncology and one of the founders of the American Society of Clinical Oncology (ASCO). At almost the same time, a number of US clinicians and clinical scientists congregated as the Geriatric Oncology Consortium (GOC), the first cooperative group fully dedicated to the study of older cancer patients.[14]

Perhaps two initiatives have been the most consequential in promoting geriatric oncology: a retreat in Puerto Rico organized by the Hartford Foundation in 1997, which led to the financing of 10 training programs in geriatrics and oncology, and a combined conference of the NCI and National Institute on Aging (NIA) in 2002, attended by all the directors of the NCI-designated comprehensive cancer centers in the country, which led to the funding of eight multidisciplinary research programs in geriatric oncology and finally provided a legitimacy to this new discipline.

During the same period, the major cancer and geriatric organizations (American Association of Cancer Research, ASCO, American Geriatric Society) established task forces, special interest groups, and educational tracks in geriatric oncology, and the major cooperative oncology groups instituted subcommittees on cancer and aging.

One should not forget to mention simultaneous international initiatives. The European Organization for Research and Treatment of Cancer (EORTC) established a committee on cancer and aging; two cooperative groups in Italy (GROG and SIGERO) and one in France (Gerico) focused their activity on the study of older individuals, and most major European countries now have a representative group of geriatric oncologists.

Key Accomplishments

The notable achievements of these activities include the following:

- Determination of age as a risk factor for carcinogenesis.
- Determination of biologic differences in some malignancies occurring both in younger and older patients.
- Fine-tuning of life expectancy and treatment tolerance estimates based on function and comorbidity. Appreciation of the social issues (caregiver, transportation, nutritional, and emotional support) involved in the treatment of older persons with cancer.
- Feasibility and value of cancer prevention and early detection in older individuals.
- Feasibility of clinical trials accommodating the diversity of the older population.

The past 2 decades have established beyond doubt that age is a risk factor for cancer and that there are age-specific issues related to the prevention and management of cancer. These findings provide the basis for accommodating recent advances in both the biology of aging and the management of cancer, exemplified by the discovery that inflammatory cytokines represent biologic markers of aging,[15] the use of simple clinical tests such as those involved in the Cardiovascular Health Study (CHS),[16] the production of antidotes to chemotherapy-related toxicity, and most of all, the development of targeted antineoplastic therapy.

Managing Cancer in Older Patients

In the United States, 60% of all cancers and 80% of all cancer-related deaths affect the 12% of individuals aged 65 and older.[17] By the year 2030, 70% of all malignancies and 85% of all cancer-related deaths are expected to occur in this population. In the near future, older persons will likely represent the prototype of cancer patient. The remainder of this article will explore the differences between managing cancer in older and younger individuals and will provide a framework of reference for medical decisions in older people with cancer. We’ll address the following questions:
Why does cancer become more common with aging?
Are tumors different in older and younger patients?
Who is the older patient?
Is chemotherapy effective in older individuals?

Why Does Cancer Become More Common With Aging?

The association between cancer and aging may be accounted for by three non-mutually exclusive explanations.

First, carcinogenesis is a time-consuming process whose final product cancer is more likely to become apparent late in life.

Second, aging cells show a number of molecular changes that mimic late-stage carcinogenesis and prime the cell to the action of late-stage carcinogens.[3,18] In other words, older individuals are more prone than younger individuals to develop cancer when exposed to the same dose of carcinogens.

Third, environmental bodily changes associated with aging may favor the development and the growth of cancer. These include immune senescence[19] and proliferative senescence.[20] Immune senescence may favor the growth of highly immunogenic tumors.[21] The loss of self-replicating ability by the stromal cells is associated with the production of tumor growth factors and metalloproteinase, which disrupt the tumor stroma and favor metastases.

The clinical implications of these findings include the possibility of targeting the molecular changes of aging as a form of cancer chemoprevention.

Are Tumors Different in Older and Younger Patients?

If one thinks of neoplastic growth as the growth of a plant, one can expect this to be influenced by the nature of the seed (the tumor cell) and of the ground (the tumor host). The importance of the tumor host was well documented in experimental animals: When the same dose of Lewis lung carcinoma or B16 melanoma resulted in shorter survival in younger animals, these subjects also developed more numerous metastases than did older animals.[21]

Table 1 summarizes examples of human tumors whose biology changes with age. In the case of AML, a seed effect has been well demonstrated. Multidrug resistance, stem cell leukemia, and unfavorable chromosomal changes increase after age 60,[22] because the majority of AML cases in older individuals develop from preexistent myelodysplastic syndromes (MDS). MDS includes a number of conditions that become more common after age 60 and may be related to qualitative changes of hemopoiesis occurring with age. Age 60 and older is a poor prognostic factor for both large cell diffuse and follicular lymphomas.[12,23] It is reasonable to see in this relationship the effects of interleukin (IL)-6, whose concentration increases in the circulation with age[24]—an independent
poor prognostic factor for patients with non-Hodgkin's lymphoma.[25]
Both breast cancer and lung cancer are more indolent in the elderly than in the young.[13,26] It is reasonable to hypothesize that a form of natural selection (Figure 1) is responsible for an increased concentration of indolent tumors in older individuals; in addition (at least in the case of breast cancer), endocrine senescence may slow down tumor growth.
Two important clinical conclusions may be drawn from this brief discussion: (1) The biology of cancer may change with the age of the tumor host, and (2) contrary to what is commonly thought, cancer may become more aggressive with age. The interaction of cancer growth and the older tumor host is a promising area of future research, with important clinical implications, as it may help assess the risk of tumor recurrence and cancer-related deaths in individual patients.

Who Is the Older Patient?
Aging is associated with a progressive depletion of the functional reserve of multiple organs and systems, increased prevalence of comorbid conditions, and waning social and economic resources at a time when they are most needed. The combination of these factors leads to reduced life expectancy and tolerance of stress.[3,25] That said, the management of cancer in older cancer patients implies the following questions: Is the patient going to die of or with cancer? Is the patient going to suffer the consequences of cancer during his or her lifetime? Is the patient able to tolerate the treatment?

In some cases the answer is fairly simple: For example, most practitioners would agree that the benefits of adjuvant chemotherapy are negligible and the risks substantial for a 90-year-old woman with stage I breast cancer, but the same woman may obtain substantial benefits from chemotherapy if she has stage III or IV large cell lymphoma. In other cases the answer is not that clear-cut and requires a deeper analysis of the situation.
Aging is a highly individualized process, and chronologic age is inadequate for the estimate of individual life expectancy and functional reserve. The classification of the elderly into young old (age 65-75 years), old old (76-85), and oldest old (> 85) is useful for population studies, as the prevalence of comorbidity and functional dependence increase progressively with age but cannot inform individual patient management.
Comprehensive Geriatric Assessment—The comprehensive geriatric assessment (CGA) is a time-honored instrument that accounts for the diversity of the older population (Table 2).[27-29] Dependence in one or more activities of daily living (ADLs) is associated with a 2-year mortality rate of approximately 30% and the need for full-time caregiving.[30,31] Dependence in one or more of the instrumental activities of daily living (IADLs) is associated with a 2-year mortality of approximately 15%, the need for a part-time caregiver,[30,31] and approximately a 50% risk of dementia within 2 years.[32] Dependence in IADLs has also been associated with increased risk of chemotherapy-related myelotoxicity.[33]

Comorbidity, whose prevalence increases with age, may be associated with a reduction in both life expectancy and treatment tolerance.[34-38] Comorbidity may be assessed in terms of the number of comorbid conditions or as a comorbidity index reflecting the severity of each condition.[36] For population studies, the Charlson scale is preferred because of its simplicity; for the study of individual patients, the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) has proven more sensitive to mild and moderate comorbidity.[36]

Comorbidity may also influence cancer prognosis. Meyrhardt et al showed that the risk of colon cancer recurrence in patients with similar-stage disease was higher in the presence of metabolic syndrome and diabetes.[37] In addition, the medications used to treat comorbidity may influence the risk and course of cancer. For example, the statins used to control cholesterol are associated with a decreased risk of cancer of the breast, large bowel, and prostate.[38] Two common comorbid conditions, depression and anemia, are of special interest in older individuals as both are common and reversible.[39,40]

Geriatric syndromes include a number of conditions that are typical (although not exclusive) of advanced age and are associated with decreased survival and increased risk of functional dependence.[41,42] Moreover, geriatric syndromes may reduce the tolerance of cytotoxic chemotherapy.
The prevalence of polypharmacy increases with age, due to comorbidity, consultation with multiple health-care specialists, and the use of alternative medicine preparations.[43] Polypharmacy is a major cause of adverse drug reactions and interactions, as well as of out-of-pocket health-related costs.

Malnutrition is seen in approximately 20% of home-dwelling individuals aged 65 and over.[44] This condition is most often reversible but is an independent risk factor for chemotherapy-related toxicity. In general geriatrics, the CGA has helped preserve the functional independence of older individuals, reduced the risk of hospitalization and admission to adult living facilities,[27,28] and may also have reduced elderly mortality.[29] In geriatric oncology, the CGA has allowed the recognition of conditions that might have interfered with cancer treatment, as well as a more accurate estimate of life expectancy and treatment tolerance, and has provided a common language with which to describe older cancer patients.[45] Based on the CGA, one may plan cytotoxic chemotherapy in older cancer patients according to the algorithm in Figure 2. Special precautions may include reduction of the initial chemotherapy dose and provision of a caregiver able to assist the patient in the presence of an emergency.

• Other Forms of Assessment—Despite undeniable benefits, the CGA is time-consuming and may yield redundant information. In addition, the geriatric assessment may not help distinguish, among healthy elderly individuals, those who are more likely to be vulnerable to environmental stress. This is a major limitation, as healthy elderly individuals are more likely to receive adjuvant chemotherapy for curative purpose, and it is extremely important to recognize those for whom treatment is more likely to be harmful than beneficial.

For this reason, a number of studies have addressed the evaluation of healthy elderly patients with functional or laboratory tests. The Cardiovascular Health Study (CHS) validated a very simple form of assessment in approximately 8,500 home-dwelling individuals aged 65 and over, who were followed for an average of 11 years.[46] The authors established that five simple parameters (Table 3) identify three groups of older individuals with different risks of mortality and functional dependence. Ongoing clinical trials are aimed at establishing a correlation between the CHS classification and the risk of chemotherapy complications and cancer-unrelated death among patients receiving adjuvant chemotherapy for cancer of the breast, lung, or large bowel.
A group of investigators at Duke University School of Medicine established that the levels of IL-6 and D-dimer in the circulation of individuals 70 and older living at home predicted the risk of mortality and functional dependence during the following 24 months.[15] These findings support the hypothesis that aging is a chronic progressive inflammation and that the assessment of inflammation markers in the circulation provides an estimate of a person's physiologic age.

While the CGA remains the gold standard for the evaluation of older cancer patients, it is conceivable that in the near future, the CHS and the circulating values of inflammatory cytokines may be integrated in an index enabling the prediction of treatment risks and benefits in older individuals with cancer.

Aging and Cancer Chemotherapy
In the previous section, we provided criteria for identifying older individuals who are more likely to benefit from cancer treatment based on life expectancy, tolerance of stress, and social support. In this section, we analyze the interaction of physiologic changes of aging and cancer treatment, using cytotoxic chemotherapy as a paradigm of cancer treatment.
Older individuals may benefit from cancer chemotherapy to the same extent as younger individuals. In curable diseases such as large cell lymphoma, the response rates of younger and older individuals were similar when patients received the same doses of chemotherapy.[3,45] Likewise, it has been reported that the adjuvant chemotherapy of cancer of the large bowel produces comparable survival benefits in individuals older and younger than 70.[3] The question is not whether chemotherapy is effective in older individuals, but rather, how to ensure that they may receive adequate doses of treatment.

The pharmacology of cytotoxic chemotherapy may change with age, due to changes in pharmacokinetics and pharmacodynamics, and with increased vulnerability of normal tissues to treatment complications, due to more limited functional reserve.[47] Awareness of these changes allows the practitioner to deliver adequate doses of chemotherapy to the elderly by preventing dose-limiting toxicity.

- **Age-Related Pharmacokinetic Changes**—Pharmacokinetic changes of age are illustrated in Table 4.[47] Absorption of nutrients is progressively reduced with age,[46] but it is not clear whether the bioavailability of oral agents is reduced as well. This issue has gained new interest given the development of several oral cytotoxic agents as well as inhibitors of angiogenesis and of key tumor enzymes.[48] In light of this uncertainty, it would seem advisable to routinely conduct phase II studies of oral agents in persons aged 70 and older to establish whether the bioavailability and effectiveness of these compounds may be influenced by age.

The size of the liver decreases with age[49] due to a reduced number of hepatocytes and reduced hepatic blood flow. Also, P450 enzyme activity declines, especially in individuals who are functionally dependent. While it is reasonable to assume that both activation and deactivation of drugs metabolized by these enzymes is compromised, we have no conclusive data. This pharmacokinetic area deserves more research.

The volume of distribution (Vd) of hydrosoluble drugs declines with age, due to a reduction in total body water and albumin concentration as well as to a higher prevalence of anemia.[40,47] The majority of these agents are bound to albumin and red blood cells, which accounts in part for the Vd. A number of studies have shown that anemia is a risk factor for chemotherapy-related toxicity and have confirmed the relationship between red blood cells and Vd.[50] A reduction in Vd is responsible
for a change in the drug AUC (area under the concentration-time curve), with increased peak concentrations and risk of toxicity.[48] As anemia is the most easily modifiable component of Vd, it would appear reasonable to try maintaining hemoglobin levels at around 12 g/dL (using erythropoietic growth factors) in patients receiving chemotherapy.[45]

The GFR declines almost universally with age.[47,48] Consequently, the elimination of many drugs may be delayed. This includes drugs whose parent compounds are excreted by the kidneys (methotrexate, carboplatin, oxaliplatin [Eloxatin], bleomycin) and drugs that give origin to active (idarubicin, daunorubicin) or toxic (cytarabine) metabolites excreted from the kidneys. The importance of the decline in GFR in enhancing the toxicity of chemotherapy was documented in an important study performed by Gelman and Taylor more than 20 years ago.[51] The authors demonstrated that by adjusting the doses of methotrexate and cyclophosphamide to the GFR of women aged 65 and older with metastatic breast cancer, they reduced the risk of toxicity without compromising treatment effectiveness. Based on these results, it appears reasonable to recommend that the initial doses of chemotherapy in older individuals be adjusted to the GFR, provided that successive doses are escalated—if no toxicity is observed—to prevent undertreatment. An accurate estimate of GFR may be obtained with the formulas developed by Cockroft-Gault or Jolliffe,[52] based on age, weight, and serum creatinine.

The decline in GFR may also be responsible for more prolonged activity and more severe toxicity of opioids in the aged,[53] as the glucuronated metabolites of morphine and other opioids are more active than the parent compounds and are excreted by the kidneys.

**Age-Related Pharmacodynamic Changes**—These changes may alter both the effectiveness and toxicity of chemotherapy. The increased prevalence of multidrug resistance in the myeloblasts of older patients with acute myelogenous leukemia is the best documented change apt to reduce the effects of chemotherapy. In normal tissues, the ability to repair DNA damage[54] and more general oxidative damage[55] declines with age, which may explain why some forms of chemotherapy-related toxicity are more common and more severe in the elderly.

**Increased Susceptibility to Chemotherapy Complications**—The risk and severity of myelosuppression, mucositis, cardiotoxicity, and possibly neurotoxicity increases with age. Several studies[40,52,56] have demonstrated that an age of at least 65 years is an independent risk factor for incidence of and mortality from neutropenic infections. Fortunately, granulocyte colony-stimulating factor (filgrastim, Neupogen) and pegfilgrastim (Neulasta) reduce the incidence of neutropenic infections by approximately 50% in individuals 65 and over treated with CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) and CHOP-like regimens.[14,40] It would appear prudent to use these compounds prophylactically in older individuals receiving moderately toxic chemotherapy, beginning with the first course of treatment.

While it is not established whether chemotherapy-related anemia is more common in the elderly, it is clear that it should be aggressively treated. Not only is anemia associated with increased risk of chemotherapy-related toxicity, but it may also lead to fatigue and functional dependence that mandates expensive caregiving and may delay the administration of antineoplastic treatment. Older individuals are more subject to mucositis, especially following treatment with fluorinated pyrimidines.[57] The only effective antidote is a synthetic keratinocyte growth factor that reduces the risk and severity of mucositis in patients undergoing allogeneic bone marrow transplant.[58] In addition to being very expensive, this compound requires intravenous administration for several days and has never been studied in older individuals. Prevention of mucositis may involve substitution of intravenous fluorinated pyrimidines with capecitabine (Xeloda), a prodrug of fluorouracil that largely spares normal tissues, as it is activated in the tumor. Timely fluid resuscitation may prevent severe complications and even death of older individuals with mucositis. Age is an independent risk factor for anthracycline-related cardiomyopathy.[59] Of the various stratagems used to prevent this complication, the substitution of pegylated liposomal doxorubicin (Doxil) for conventional doxorubicin appears to be the most practical, albeit very expensive.[60] This is an almost ideal agent for older individuals, given the low risk of cardiomyopathy, myelosuppression, alopecia, and fatigue.

Peripheral neuropathy from paclitaxel, cisplatin, vincristine, and other neurotoxic drugs is particularly troubling for elderly patients, as it may impede fine movements and precipitate functional dependence. Unfortunately, short of close monitoring, there are no other ways of preventing this complication. Cerebellar toxicity from high doses of cytarabine is more common in older individuals, at least in part because the neurotoxic metabolite of cytarabine, ara-uridine, is excreted from the kidneys. This form of treatment is best avoided in the elderly.
Clearly, older individuals benefit from cytotoxic chemotherapy comparably to younger persons, as long as one takes care in selecting patients appropriately and in preventing common treatment complications. The National Comprehensive Cancer Network guidelines (Table 5)[45] are based on the evidence reviewed in this article and represent the first attempt to formalize an approach to treating the older cancer patient.

Conclusions

The most frequent type of cancer patient is already an individual aged 65 or older, and in the near future, cancer in the older person will become increasingly common. At least in part, this is the result of the aging of the population, as age is a risk factor for most common neoplasms. Older individuals benefit from cytotoxic chemotherapy to the same extent as younger individuals, as long as:

- Patients are selected on the basis of life expectancy and functional reserve, estimated by some form of geriatric assessment;
- Treatment is dosed according to individual kidney function;
- Myelopoietic growth factors are used to prevent neutropenic infections in patients receiving moderately toxic chemotherapy;
- Hemoglobin is maintained at around 12 g/dL.

Disclosures:
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