



EVIDENCE-BASED MANAGEMENT OF CANCER IN THE ELDERLY

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Introduction

A discussion of evidence-based management of cancer in the elderly assumes an evidence-based position that senescence is a distinct stage of human development that affects the biology of cancer as well as the goals, efficacy, and tolerance of cancer treatment. This article explores the levels of evidence supporting this assumption in three areas: (1) clinical assessment of age, (2) age-related changes in tumor biology, and (3) age-specific issues related to cancer treatment. The levels of evidence are defined in Table 1.

Evidence Relating to Assessment of Age

Age differences are apparent in a series of pictures of the same person over a year or in a family

portrait that includes members of different generations. Yet, determining the onset of senescence or defining a person's physiologic age in objective terms remains controversial. The aging process is composed of several stages¹ that, from a clinical standpoint, do not accurately differentiate young from old. This differentiation is needed, however, to provide optimal care.

To address these issues from an evidence-based standpoint, we will examine the implications of aging on which wide consensus exists. These implications include a progressive reduction in the life expectancy² and deterioration of the functional reserve of different organs and systems.³ Also, aging generally is associated with increasing prevalence of comorbid conditions,^{2,4} disability,⁴ and a group of disorders defined as "geriatric syndromes"⁵ (Table 2). The

Table 1. — Definition of Levels of Evidence

| Level of Evidence | Definition |
|-------------------|---|
| I | Supported by one or more randomized controlled trials |
| II | Supported by one or more retrospective studies or by one or more cohort studies |
| III | Supported by clinical experience or review of case report |
| IV | Supported only by expert opinion |

Table 2. — Geriatric Syndromes

| |
|---|
| Dementia |
| Delirium (induced by drugs or by organ-confined infections not involving the central nervous system) |
| Depression |
| Falls (≥3 per month) |
| Fecal incontinence |
| Osteoporosis associated with spontaneous fractures |
| Failure to thrive |
| Presence of neglect and abuse |

Table 3. — Clinical Assessment of Functional Status, Comorbidity, and Geriatric Syndromes on Life Expectancy and Functional Reserve

| Parameter | Correlation With Life Expectancy | Correlation With Declining Functional Reserve | Level of Evidence | References |
|--|---|---|---|--|
| Functional Status | 2-year mortality doubles with dependence in IADLs and increases threefold with dependence in ADLs. | Mortality of elderly hospitalized patients increases with decline in functional status. | Life expectancy: II Functional reserve: II | Reuben et al ⁶ Manton ⁷ Inouye et al ⁸ |
| Comorbidity: - Number of comorbid conditions - Comorbidity index | Risk of non-cancer-related death increases in breast cancer patients with the number of comorbid conditions. Risk of cancer-related death may increase as well with the number of comorbid conditions. Risk of mortality is a function of a comorbidity index measuring the seriousness of comorbid conditions. | Patients with multiple comorbid conditions or with severe comorbidity have increased surgical mortality and are generally excluded from clinical trials and may receive reduced doses of chemotherapy in clinical practice. | Life expectancy: II Functional reserve: II-III | Satariano and Regland ⁹ Piccirillo et al ¹⁰ Newschaffer et al ¹¹ Extermann ¹² |
| Cognition | Risk of mortality increases with decline in minimal status. | Demented patients are generally excluded from chemotherapy trials. | Life expectancy: II Functional reserve: IV | Eagles et al ¹³ Flacker and Kiely ¹⁴ Winograd et al ¹⁵ |
| Depression | Depression is an independent prognostic factor for mortality in elderly patients. | | Life expectancy: II Functional reserve: IV | Covinsky et al ¹⁶ |
| Falls | Falls are harbingers of mortality. | Patients who fall frequently are considered frail | Life expectancy: II Functional reserve: IV | Tinetti and Williams ¹⁷ |
| Delirium | Short- and long-term mortality increases in patients experiencing delirium during hospitalization or as a result of medications and infections. | Patients with a history of delirium are considered frail and incapable of independent living. | Life expectancy: II Functional reserve: III-IV | Inouye et al ¹⁸ |
| Fecal Incontinence | Increased mortality is associated with fecal incontinence. | Patients have serious neurological or mental problems. | Life expectancy: II Functional reserve: IV | Rockwood et al ¹⁹ |
| Neglect and abuse | Mortality increases among elderly subjected to neglect and abuse. | Patient are incapable of independent living. | Life expectancy: II-III Functional reserve: IV | Mendonca ²⁰ |

next step is to investigate whether the clinical assessment of functional status, comorbidity, and geriatric syndromes may reflect decreases in life expectancy and functional reserve. This issue has been addressed by several authors over the last decade. Recent results are summarized in Table 3.⁶⁻²⁰

Prospective and retrospective studies have shown that functional status, comorbidity, geriatric syndromes, and mortality are all correlated. Less clear is the correlation between these parameters and functional reserve. Perhaps the major obstacle in establishing this correlation is the absence of "gold standards" for assessing functional reserve. While the functional reserve of individual organs such as the lung or kidney can be accurately assessed, a comprehensive measurement of functional reserve is lacking. Reduced functional reserve may be inferred from reduced ability of the body to cope with stress. For example, mortality from emergency surgery increases two- to three-fold after age 70, suggesting that the elderly are less equipped than younger individuals to withstand severe stress.²¹ Likewise, a lack of independence in the activities of daily living (ADLs) predicts increased immediate and 6-month mortality for hospitalized elderly patients.^{8,22} These data suggest a correlation between severe functional impairment and functional reserve. However, in the majority of cases, clinicians are more interested in detecting early limitations in functional reserve that do not compromise daily function but may lead to decreased

tolerance of cancer chemotherapy. For this purpose, the information is inadequate. It is possible that dependence in one or more instrumental activities of daily living (IADLs) may provide a clue to these lesser but clinically relevant restrictions in functional reserve.²²⁻²⁶ IADLs include shopping, use of transportation, medication management, meal preparation, money management, and housekeeping. Extermann et al⁴ reported that the prevalence of dependence in IADLs was higher than 70% in a population of cancer patients aged 70 and older who were studied at our institute over 2 years. These individuals tended to be relatively healthy as they were well enough to have been referred to a tertiary cancer care center. Barberger-Gateau et al²³ showed that dependence in using transportation, managing finances, and taking medications correlated with the onset of cognitive disorder. Monfardini et al²⁴ showed a correlation between dependence in some IADLs and the risk of complications from cytotoxic chemotherapy.

In recent years, a special component of older individuals has been described — those who are frail. The frail patient has a severely limited functional reserve and generally is not a good candidate for aggressive cancer treatment. Commonly accepted criteria for frailty are listed in Table 4.⁵ Age is the most controversial factor because many of the persons surviving in the 9th and 10th decade of life are healthy with decreased prevalence of oxidative stress and arteriosclerosis.^{25,26} The population

Table 4. — Clinical Diagnostic Criteria of Frailty

| |
|---|
| Age ≥ 85 |
| Dependence in 1 or more activities of daily living (ADLs) |
| Presence of 3 or more comorbid conditions |
| Presence of 1 or more geriatric syndromes |

of the oldest old seems to be composed of at least two groups: (1) those who are frail but have survived due to advances in medical treatment and (2) those who have survived because of inherited resistance to environmental insults; these may or may not be frail. Thus, in terms of treatment options, age should be considered as one piece of evidence rather than as a diagnostic criterion of frailty.

The claim that frailty is a distinct clinical condition is based on level II evidence (dependence in ADLs and comorbidity) and level III evidence (all other criteria).^{8,22} Despite the limitations on the level of evidence, the definition of frailty serves an important clinical function in geriatric oncology: preventing harm from chemotherapy to a particularly vulnerable group of patients. For this population, it is reasonable to expect the risks of chemotherapy to outweigh its potential benefits for the following reasons:

- The shortened life expectancy of frail patients limits survival benefit from aggressive chemotherapy.
- Age is associated with increased risk of chemotherapy complications.²⁷ Frail patients appear to be the least fit of the aged and

thus are the most vulnerable to therapeutic complications.

- Performance status is a predictor of chemotherapy toxicity in younger patients. Frail patients almost by definition have a poor performance status.

There is the risk, however, that too broad a definition of frailty may prevent the treatment of patients who may benefit from chemotherapy. The definition of frailty needs clarification with hypothesis-driven research as follows:

- Substitute the number of comorbid conditions with comorbidity indices that reflect the severity of the conditions.

- Grade the severity of some geriatric syndromes (eg, dementia, depression, osteoporosis).

- Study the possibility that one or more components of frailty may be reversible. Of special concerns are situations in which an older patient becomes functionally dependent over a short period of time. In these situations, the tumor itself may be responsible for the rapid functional decline, and aggressive antineoplastic treatment may improve the patient's function.

- Establish reliable biochemical markers of aging. At present, there are no reliable biochemical markers of aging. Proposed markers include changes in creatinine clearance,⁵ in plasma osmolality,²⁸ in serum concentrations of interleukin 6,²⁹ and in the cysteine/thiol

ratio in the circulation.³⁰ All of these tests lack specificity and are not sensitive to early age-related changes. Likewise, clinical tests of physical function should be considered experimental and of limited clinical applicability.³¹

In conclusion, the evidence suggests that aging may be assessed by a number of clinical parameters. These parameters not only reflect the individual's life expectancy, but also may reflect the individual's functional reserve to some extent. A valid, well-substantiated definition of frailty will allow the identification of older patients whose functional reserve is particularly compromised. This definition may be adjusted with further research.

Age-Related Changes in Tumor Biology

Level II evidence shows that the prognosis of three malignancies — acute myelogenous leukemia,^{32,33} large-cell non-Hodgkin's lymphoma,³⁴ and celomic ovarian cancer³⁵ — worsens with advancing patient age. The mechanisms of these changes are only partly understood and may involve changes in the malignant cell (the seed), the tumor host (the soil), or both. In the case of acute myelogenous leukemia, the main determinant of poorer prognosis is the presence of a more chemoresistant disease in older patients. The prevalence of myeloblasts expressing MDR-1 gene and of unfavorable chromosomal abnormalities increases after age 60.³⁶ In the case of large-cell non-Hodgkin's lym-

phoma, patient-related changes may be responsible for a poorer prognosis. The concentration of circulating interleukin 6 (IL-6) increases with the age of the patient, and increased levels of IL-6 are a poor prognostic factor for large-cell lymphoma.³⁷ In the case of breast cancer, level II evidence suggests a more indolent disease³⁸ characterized by well-differentiated, hormone-receptor-rich tumors. However, it is not clear whether age affects the overall prognosis. Likewise, non-small cell lung cancer is more likely to present at an early stage in older individuals, but whether age affects the overall prognosis is unclear.³⁹

In conclusion, level II evidence shows that the behavior and the prognosis of some malignancies may change with the age of the patient. Age itself, however, is a poor predictor of the course of a particular neoplasm in a particular patient. Research should include identifying tumor markers of prognostic value (eg, the MDR-1 product or abnormalities of p53) and patient markers (eg, circulating levels of IL-6 and other cytokines) in older individuals.

Cytotoxic Chemotherapy in the Older Cancer Patient

It is reasonable to expect that older persons may be more susceptible than younger persons to the toxicity of cytotoxic chemotherapy, given the reduced functional reserve of many organ systems and the possible alterations in the phar-

macokinetics of drugs.^{3,27} This section examines the evidence related to the following questions: Do the complications of cytotoxic chemotherapy become more common and more severe in the older patient? Are there effective methods to ameliorate the toxicity of chemotherapy in the elderly?

Five retrospective studies of chemotherapy-induced toxicity⁴⁰⁻⁴⁴ failed to demonstrate a clear correlation between patient age and the incidence and severity of therapeutic complications. Newcomb and Carbone⁴⁰ reviewed the 10-year experience of the Eastern Cooperative Oncology Group (ECOG). Christman et al⁴¹ reviewed the experience of the Piedmont Oncology Group studies of metastatic breast cancer. Ibrahim and colleagues⁴² reported on the 20-year experience of the University of Texas-M.D. Anderson Cancer Center in the management of metastatic breast cancer. Giovanazzi-Bannon et al⁴³ reviewed

the toxicity of patients involved in phase II studies at the Illinois Cancer Center, and Gelman and Taylor⁴⁴ reported on the incidence of myelotoxicity in breast cancer patients treated with combination chemotherapy for those 65 years of age and older compared with those under 65 years of age.

While these studies are important because they indicate that age over 70 years does not inevitably involve more serious complications of chemotherapy, they can hardly be considered representative of the older population at large for several reasons: (1) There was a clear selection bias. In the ECOG study,⁴⁰ only 11% of patients were over 70 years of age, while the incidence of various cancers treated suggests that 40% of the patients should have been 70 years of age or older. (2) Only a small minority of patients were 75 years of age or older, so the data are skewed toward the so-called "young old." (3) The toxicity of

treatment protocols in use at the time of these studies may not be comparable with the toxicity of more recent treatment protocols.

Based on a review of older patients with large-cell non-Hodgkin's lymphoma⁴⁵ (Table 5) and with gastrointestinal malignancies treated by the Gastrointestinal Tumor Study Group,⁴⁶ level II evidence suggests that the incidence and severity of myelotoxicity and mucositis increase with age. A close examination of the lymphoma studies indicates that in persons over age 70, the incidence of neutropenia was consistently higher than 50%⁴⁴⁻⁴⁹ and the incidence of treatment-related mortality in patients over 70 ranges between 5%^{47,48} and 30%.³⁶ Most of the treatment-related mortality occurred during the first course of chemotherapy. This incidence of toxicity and mortality is higher than that seen in younger individuals undergoing the same form of treatment.

Table 5. — Risk of Myelotoxicity in Older Individuals With Large-Cell Non-Hodgkin's Lymphoma Treated With CHOP-Like Combination Chemotherapy

| Author(s) | Regimen | Age | Grade III and IV Neutropenia | Treatment-Related Mortality |
|-----------------------------------|------------|-------|------------------------------|-----------------------------|
| Zinzani et al ⁴⁷ | VNCOP-B | 65+ | 55% | - |
| Gomez et al ⁴⁸ | CHOP | 60-69 | 42% | 0% |
| | | >69 | 100% | 7% |
| Armitage and Potter ⁴⁹ | CHOP | 70+ | - | 30% |
| Bastion et al ⁵³ | CTVP | 70+ | 55% | 15% |
| Sonneveld et al ⁵⁴ | CHOP, CNOP | 60+ | - | 5% |
| Tirelli et al ⁵⁵ | CHOP, VMP | 70+ | 55% | 5% |

VNCOP-B = cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, prednisone
 CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
 CTVP = cyclophosphamide, teniposide, prednisone, pirarubicin
 CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone
 VMP = etoposide, mitoxantrone, prednimustine

Table 6. — Current Recommendations to Ameliorate
Chemotherapy-Related Toxicity in Older Persons With Cancer

- Base patient selection on comprehensive geriatric assessment, with exclusion of frail patients from aggressive forms of treatment and interventions aimed to restore nutrition and social support and to control underlying diseases and disabilities.
- Adjust dose of the first dose of chemotherapy to the patient's creatinine clearance.
- Maintain hemoglobin levels ≥ 12 g/dL with erythropoietin.
- Use hemopoietic growth factors prophylactically in patients aged ≥ 70 receiving moderately toxic chemotherapy (eg, CHOP, cyclophosphamide/doxorubicin, carboplatin/paclitaxel).
- Institute timely and aggressive fluid resuscitation for mucositis.

Several recommendations have been made to ameliorate the toxicity of chemotherapy in older cancer patients (Table 6).⁵⁰ The decline in glomerular filtration rate (GFR) is one of the most common and consistent changes in aging.³ In a retrospective analysis, Gelman and Taylor⁴⁴ compared the toxicity and effectiveness of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in women aged 65 and older and in younger women. In the older group, the doses of methotrexate and cyclophosphamide were adjusted to the patient's creatinine clearance. The authors reported that the therapeutic response was similar in the two age-groups, but the incidence of myelodepression was lower for the older women. This study represents level II evidence of the benefits of dose adjustment for CMF in older patients. Can this conclusion be extended to other treatment regimens and to drugs with complex pharmacology (eg, idarubicin, which is metabolized to idarubicinol, an active alcohol excreted through the kidneys)?⁵⁰ Which formula should be used for dose adjustment and for calculating the

GFR? The answers to these questions cannot be based on either level I or level II evidence. A further complication is the fact that the pharmacokinetics of many drugs is unpredictable.^{51,52} For example, Borkowski et al⁵² showed that the renal clearance of dichloromethotrexate declines with the age of the patient, but the total clearance of the drug declines to a much lesser extent, thereby suggesting the existence of other pathways of elimination. Thus, the recommendation to adjust the first dose of treatment to the measured GFR and the subsequent doses according to the degree of toxicity appears reasonable. However, one could argue for starting with the full dose, ignoring the GFR, and making further adjustments according to the toxicity observed.

Supportive Care

The benefits of granulocyte colony-stimulating factor (G-CSF) were demonstrated by Zinzani et al⁴⁷ in a randomized, prospective study. These authors found that the prophylactic addition of G-CSF to a

regimen of cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisone (VNCOP-B) in patients 65 years of age and older with large-cell non-Hodgkin's lymphoma decreased the risk of grade III and IV neutropenia by 60% and the risk of neutropenic infections by 75%. However, the survival rate of patients in the two groups was the same. Whether the indiscriminate use of growth factors is cost effective when the risk of neutropenic fever is lower than 40% is debatable. A strong argument in favor of prophylactic growth factors is the high treatment-related mortality rate reported by others^{48,49,53-55} during the first course of treatment.

Anemia was found to be an independent risk factor for myelotoxicity,^{56,57} because a number of agents are bound to the red blood cells.⁵⁰ When anemia is present, the concentration of circulating free drugs appears to increase. A recent randomized, controlled study of patients younger than age 65 who underwent high-dose chemotherapy showed that erythropoietin in combination with G-CSF is more effective than G-CSF alone in preventing life-threatening neutropenia.⁵⁸ This study provides level I evidence to support the use of erythropoietin in combination with G-CSF in anemic older individuals. Another advantage of erythropoietin is the prevention of fatigue, as reported in three cohort studies (level II evidence).⁵⁹⁻⁶¹ It is reasonable to expect that fatigue may precipitate functional dependence in the older cancer patient.

The recommendation to utilize aggressive fluid resuscitation in older individuals experiencing grade III or IV mucositis or diarrhea is based on level IV evidence (ie, common sense). As the mucositis-related mortality approached 10% in the original studies of 5-fluorouracil and high doses of leucovorin in persons aged 65 and older⁴⁶ and since an effective antidote to mucositis is not yet available, it appears reasonable to provide fluid replacement as soon as toxicity becomes evident.

A comprehensive geriatric assessment (CGA) proved effective in randomized, controlled studies of the general geriatric population (level I evidence) in preventing dependence,⁶² falls,⁶³ and delirium.¹⁸ A CGA also may be beneficial for older patients with cancer as a tool to recognize the frail patient, manage coexistent conditions, provide adequate social support, and predict quality of life and functional reserve. Ongoing trials may provide adequate evidence of these benefits.

In addition to special provisions for the administration of chemotherapy, other age-specific problems warrant prospective study in older patients with cancer. These issues include alternative forms of adjuvant chemotherapy for colorectal cancer, the value of adjuvant chemotherapy in breast cancer patients aged 70 and older, the role of amifostine in the prevention of peripheral neuropathy, and the value of methylphenidate (Ritalin) in preventing cognitive complications of chemotherapy.

Conclusions

The study of cancer and aging provides an excellent model to study the interaction of evidence-based medicine and common sense intervention.

Level II evidence supports (1) estimate of life expectancy based on function, comorbidity, cognition, and emotional status, (2) staging of functional age based on function and comorbidity into three stages, from totally independent to frail, (3) age-related difference in the behavior of certain neoplasms, such as acute myeloid leukemia, large-cell non-Hodgkin's lymphoma, ovarian cancer, and breast cancer, and (4) increased risk and severity of myelodepression and mucositis in older individuals.

Based on these findings, a number of reasonable recommendations are proposed. Careful perspective study of the implementation of these recommendations may provide level II evidence of their value. In some cases, randomized, controlled studies should be planned, while in other cases, such as the relatively routine use of growth factors in patients aged 70 and older, ethical and practical considerations may prevent the conduct of a randomized trial.

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