



Frank Colson. *Encore*. Fiber art, 40" × 60".

The cost effectiveness of treating elderly cancer patients may improve with appropriate patient selection and with the development of alternative treatment approaches.

Hemopoietic Reserve in the Older Cancer Patient: Clinical and Economic Considerations

Lodovico Balducci, MD, Cheryl L. Hardy, PhD, and Gary H. Lyman, MD, MPH

Background: *Older individuals are at increased risk for myelosuppression, the most common complication of cytotoxic chemotherapy. Causes include reduction in hemopoietic stem cell reserve, increased prevalence of chronic diseases, and increased prevalence of anemia. Anemia is an independent risk factor for myelotoxicity, in part because it decreases the volume of distribution of anthracyclines, epipodophyllotoxins, and taxanes and increases the circulating concentration of free drugs.*

Methods: *The authors review the effects of aging on the hemopoietic system and the consequences of reduced hemopoietic reserve on the safety and cost of chemotherapy.*

Results: *While it is unclear whether the responsiveness of hemopoietic progenitors to physiologic amounts of growth factors is preserved in older individuals, pharmacological doses of these factors stimulate hemopoiesis and mitigate myelosuppression. It is recommended that patients aged 70 and older receiving combination chemotherapy of dose-intensity comparable to CHOP be routinely treated with myelopoietic growth factor. The hemoglobin levels of these patients should be maintained at approximately 12 g/dL with erythropoietin. This treatment may prevent costly complications such as neutropenic infections and functional dependence.*

Conclusions: *Alternative approaches to the prevention of hemopoietic complications may include more conservative use of growth factors (later initiation of treatment and earlier termination), prophylactic antibiotics in patients at risk for prolonged neutropenia, and biological treatment. Dose-reduction of chemotherapy may lead to inferior outcomes and is not recommended for patients with good functional status.*

From the Senior Adult Oncology Program at the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, Tampa, Fla (LB), Department of Medicine, Division of Hematology at the University of Mississippi Medical Center, Jackson, Miss (CLH), and the Division of Hematology/Oncology at the Albany Medical College, Albany, NY (GHL).

Address reprint requests to Lodovico Balducci, MD, Senior Adult Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612.

Dr Balducci and Dr Lyman are members of the speakers' bureau for Amgen, Inc, and Ortho Biotech, Inc. Dr Hardy has no significant relationship with the companies/organizations whose products or services are referenced in this article.

Introduction

Aging is associated with a progressive decline in the functional reserve of multiple organ systems.¹ This functional restriction may enhance the susceptibility of normal tissues to cytotoxic chemotherapy in older patients.^{2,3} In this article, we explore the aging of the hemopoietic system and the consequences of reduced hemopoietic reserve on the safety and cost of cancer chemotherapy.

Aging and Hemopoiesis

The safety of cytotoxic chemotherapy is predicated on a full and prompt recovery from hemopoietic stress.² This recovery may be compromised in the elderly. Following a review of the fundamental elements of hemopoiesis, we examine the experimental and clinical evidence suggesting age-related hemopoietic alterations.

In the homeostasis process, the concentration of circulating blood elements is maintained by a strict balance of production and destruction (Fig 1).⁴ Hemopoiesis involves the commitment of pluripotent

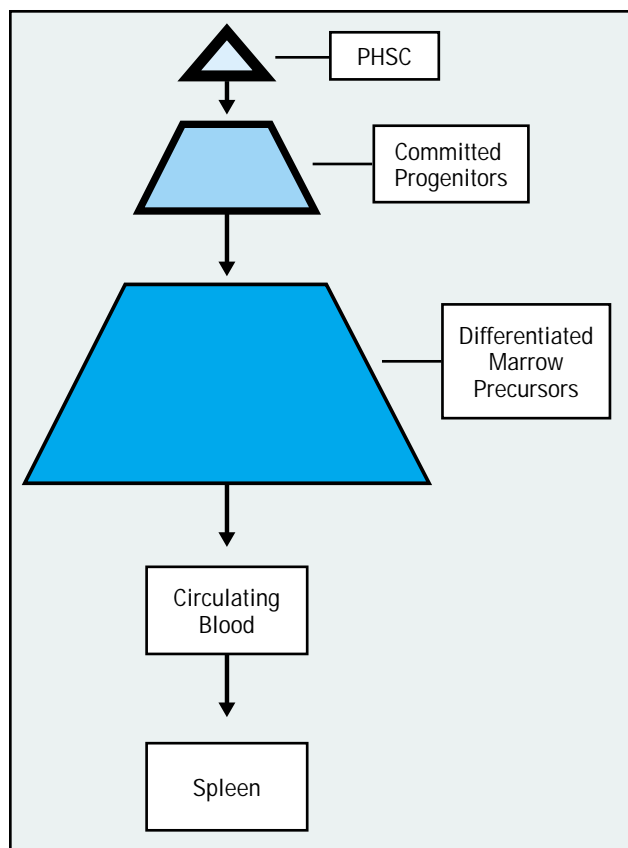


Fig 1. — Hemopoiesis. As PHSC enters commitment and differentiation, the population increases (darkness of the interior of the compartment), but the self-replicating ability (darkness of the margins) declines.

hemopoietic stem cells (PHSC) into hemopoietic progenitors and the differentiation of these progenitors into the marrow precursors from which the mature circulating blood elements are derived. The PHSCs are unique in their ability to enter different hemopoietic lineages, while the hemopoietic progenitors may differentiate only into one lineage. Commitment, differentiation, and maturation are modulated by a number of cytokines and require an intact hemopoietic microenvironment. The function of the microenvironment involves homing of PHSC and committed progenitors, as well as the production of some of the cytokines that modulate growth and differentiation. Thus, hemopoiesis can be disrupted by several factors, including a decline in PHSC reserve, an imbalance in the production of hemopoietic cytokines, a decreased sensitivity of PHSC and hemopoietic progenitors to the cytokines that modulate hemopoiesis, and hemopoietic microenvironment alterations that prevent homing. Fig 2 illustrates the consequences of a critical reduction in PHSC reserve on the tolerance of cytotoxic chemotherapy. PHSC and, to some extent, the committed progenitors are sheltered from destruction by cycle-active agents due to a low proliferative rate.^{4,5} Also, PHSC expresses the multi-drug resistance-1 (MDR-1) gene that encodes the P-glycoprotein, the main effector of multidrug resistance. The differentiated hemopoietic precursors of the bone marrow are the main target of cycle-active drugs.^{2,3} The increased destruction of these elements by chemotherapy induces increased differentiation of committed progenitors and enhanced commitment of PHSC. If the PHSC population is reduced to a level

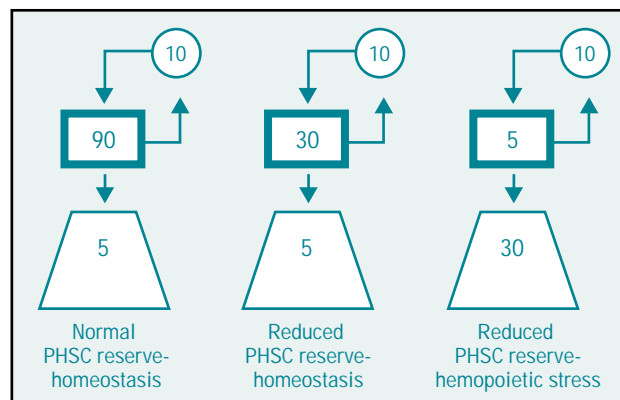


Fig 2. — Stem cell reserve and toxicity of chemotherapy. Each figure consists of three compartments: a square that represents the total stem cell population that is arbitrarily established at 100, a trapezoid that represents the number of stem cells lost to commitment and differentiation, and a circle that represents the proliferative pool of the stem cells. In condition of homeostasis, for every 5 stem cells lost to commitment and differentiation, 5 stem cells enter the proliferative pools and regenerate the initial pool of stem cells. This occurs when the stem cell reserve is intact as well as 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.

barely sufficient to repopulate itself, hemopoietic failure will result from enhanced commitment of PHSC.

Aging and PHSC Reserve

Several studies suggest the concentration of PHSC reduces with age. The ability to produce splenic colony-forming units (CFU-S) that reflect the concentration of PHSC was found to be decreased in older rodents.^{5,7} During conditions of stress, such as isolation, the marrow concentration of CFU-S declined in older mice but not in younger mice.⁸ In the presence of sublethal doses of *Escherichia coli*, older animals experienced a progressive reduction in PHSC concentration that did not occur in younger animals.⁹

Likewise, the concentration of committed hemopoietic progenitors and PHSC was reduced in the marrow of persons aged 65 and older with anemia but not in younger persons.⁷ Also, the response of circulating PHSC following an injection of granulocyte-macrophage colony-stimulating factor (GM-CSF) was reduced in individuals over 65 years of age compared with younger individuals.¹⁰ A number of clinical findings, including rising incidence and prevalence of anemia with age,^{7,11} reduced reticulocyte response in older anemic patients,¹² increased mortality from infection in the aged,¹³ and reduced concentration of hemopoietic tissue with age¹⁴ indicate a decline in PHSC reserve.

Aging and Production of Hemopoietic Cytokines

Not surprisingly, information relating to the production of hemopoietic cytokines with age is inconclusive.⁷ The network of these cytokines has been only partially clarified, and many of the stimuli that regulate the production of these factors are still unknown. A 1984 French study suggested that the production of GM-CSF from the circulating monocytes was reduced after age 65.¹⁵ These results have not been reproduced, and the study techniques may be obsolete. In some cases of otherwise unexplained anemia in older individuals, inadequate circulating levels of erythropoietin were found.¹¹ The possibility of kidney insufficiency was not excluded, however, and in the majority of older individuals, the production of erythropoietin appeared adequate. Several studies have shown that the production of interleukin 6 (IL-6)^{7,16} and tumor necrosis factor (TNF)⁷ increased with age, both in experimental animals and in humans. These cytokines inhibit hemopoiesis and may be partly responsible for inadequate recovery from hemopoietic stress. It is not clear whether the increased concentration of these substances is a physiological consequence of aging or a manifestation of common diseases associated with aging.

Aging and Sensitivity to Hemopoietic Cytokines

The information related to this issue is limited and circumstantial. The studies demonstrating decreased tolerance of hemopoietic stress by older rodents and older humans may also implicate reduced responsiveness of hemopoietic progenitors or PHSC to hemopoietic cytokines.⁷⁻¹⁴

Some authors reported decreased erythropoietic enhancement in vitro in older individuals following indomethacin therapy, while others reported that the same reticulocytic response was associated with higher circulating levels of erythropoietin in older anemic individuals compared with their younger counterparts.¹¹ These data are far from conclusive as the studies involved limited numbers of patients and were not confirmed by other investigators.

Of clinical interest, the response to pharmacological doses of G-CSF, GM-CSF¹⁷ and erythropoietin¹⁸ appears well maintained in older individuals.

Aging and Hemopoietic Microenvironment

One may infer that the ability of the hemopoietic progenitors to home to the hemopoietic microenvironment and PHSC declines with age from the result of bone marrow transplantation.¹⁹ The risk of graft failure in patients undergoing allogeneic bone marrow transplantation increases with the age of the patient. No other information is available to assess the influence of age on the hemopoietic microenvironment.

In conclusion, the ability to tolerate hemopoietic stress declines with age. This decline is highly individualized and may be due to comorbid conditions whose prevalence increases with age. The mechanism of this decline may involve reduced PHSC reserve and an imbalance in the levels of circulating cytokines.

Aging and Chemotherapy-Induced Myelotoxicity

The myelotoxicity of chemotherapy in older individuals has been explored in several studies. In at least five of these studies,²⁰⁻²⁴ no significant difference was found in the incidence and severity of myelotoxicity between patients over 65 or 70 years of age and younger patients. Of special interest is the study of Gelman and Taylor,²¹ which showed the influence of declining renal function on pharmacokinetics of cytotoxic drugs. These authors studied the effectiveness and toxicity of the cyclophosphamide, methotrexate, and fluorouracil regimen in women aged 65 and older

compared with younger women. In the older patients, the doses of methotrexate and cyclophosphamide were adjusted to the patient's glomerular filtration rate. With this provision, the effectiveness of chemotherapy was fully maintained, but the risk and severity of myelo-suppression were lower among older women.

These studies are important because they demonstrate that age between 70 and 80 years is not by itself a contraindication to cytotoxic chemotherapy. It is inappropriate to draw more general conclusions from these studies, however, for at least four reasons: (1) the elderly patient population was highly selected, (2) patients over 70 years of age represented only 10% of the study population; if the participation of older individuals had reflected the real prevalence of cancer in this age group, individuals over age 70 should have accounted for 30%-40% of the population, (3) the studies were conducted by cooperative oncology groups or major cancer centers and had exacting eligibility criteria, and (4) the number of persons aged 80 and older was too small to draw any meaningful conclusions for the oldest old. Many of the treatment regimens had a lower risk of toxicity than current chemotherapy regimens.

Several studies explored the treatment of non-Hodgkin's lymphoma in older individuals (Table 1).²⁵⁻³² These studies demonstrated that the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen and CHOP-like regimens were associated with life-threatening neutropenia in more than 50% of patients, and the mortality related to therapeutic complications varied between 5% and 30%. The risk of neutropenia and neutropenic deaths was more pronounced after 70 years of age.^{27,28}

Of special interest is the study of Zinzani et al²⁵ showing that a shortened course of chemotherapy may be as effective as traditional CHOP in elderly patients, but the risk of mortality was reduced. This study also showed that the use of G-CSF reduced the risk of life-threatening neutropenia by 50% and the risk of neutropenic infections by 75%.

In a smaller number of patients, the efficacy of G-CSF has also been demonstrated by Bertini and associates.³⁰ The lymphoma studies that were targeted to the older population appear to be more representative of the diversity of this population and reveal that age is

Table 1. — Incidence of Neutropenia, Neutropenic Fever, and Treatment-Related Death Among Older Individuals With Non-Hodgkin's Lymphoma Receiving CHOP and CHOP-like Chemotherapy

Authors	Number of Patients	Regimen	Age	Neutropenia	Neutropenic Fever	Treatment-Related Deaths	Growth Factor
Zinzani et al ²⁵	350	VNCOP-B	60+	17%	8%	-	G-CSF
			60+	44%	32%	1.3%	-
Sonneveld et al ²⁶	148	CHOP CNOP	60+	NR	NR	14%	-
			60+	NR	NR	13%	-
Gomez et al ²⁷	26	CHOP	60+	24%	8%	0	GM-CSF
			70+	73%	42%	20%	GM-CSF
Bastion et al ²⁸	444	CVP CTVP	70+	9%	7%	12%	-
			70+	29%	13%	15%	-
Tirelli et al ²⁹	119	VMP CHOP	70+	50%	21%	7%	-
			70+	48%	21%	5%	-
Bertini et al ³⁰	98	P-VEBEC	65+	22%	4%	0	G-CSF
			65+	46%	9%	2%	-
O'Reilly et al ³¹	63	P/DOCE	65+	50%	20%	8%	-
Armitage and Potter ³²	20	CHOP	70+	NR	NR	30%	-

VNCOP-B = cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, prednisone
 CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
 CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone
 CVP = cyclophosphamide, teniposide, prednisone
 CTVP = cyclophosphamide, teniposide, prednisone, pirarubicin
 VMP = etoposide, mitoxantrone, prednimustine
 P-VEBEC = epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin, prednisone
 P/DOCE = epirubicin or doxorubicin, vincristine, cyclophosphamide, etoposide, prednisone
 G-CSF = granulocyte colony-stimulating factor
 GM-CSF = granulocyte-macrophage colony-stimulating factor
 NR = not reported

associated with an increased risk of myelosuppression by moderately toxic forms of chemotherapy. The combination of cyclophosphamide and doxorubicin or cyclophosphamide and epirubicin — commonly used in breast cancer — has a dose intensity comparable to that of CHOP. It is reasonable to expect severe neutropenia in the majority of older women treated with these regimens.

Similar findings of the benefits of hemopoietic growth factors and of prolonged and more severe myelosuppression have been reported for older patients with acute myelogenous leukemia.³³⁻³⁷ However, the disease itself might have compromised the hemopoietic reserve of the patient. The involvement of PHSC by the leukemic process is common in patients over 60 years of age.³⁷

The lymphoma studies showed that the risk of severe thrombocytopenia increases with age but not to the same extent as the risk of neutropenia.²⁶⁻³² Unfortunately, no information is available on the risk of anemia following chemotherapy. At the time that many of these studies were conducted, the affect of anemia on the quality of life of cancer patients was not yet considered.

The only guidelines relating to anemia required blood transfusions for hemoglobin levels of <8 g/dL in the absence of coronary artery disease and 10 g/dL in the presence of coronary artery disease to prevent myocardial ischemia. Today, however, anemia appears to be a more critical parameter. It is associated with a decline in quality of life and energy levels. The optimal levels of energy occur at hemoglobin levels between 11 and 13 g/dL.^{38,39} Adequate energy levels may support the independence of older individuals. Loss of independence may result in deterioration of quality of life, inability to receive further treatment, and expensive home care or institutionalization. Also, anemia may be associated with enhanced toxicity of cytotoxic chemotherapy because many agents are tightly bound to red blood cells. In the presence of anemia, the concentration of free drug in the circulation and the toxicity may increase.⁴⁰⁻⁴² In addition, anemia may cause a number of complications in the care of the older persons, including postoperative delirium.⁴³

Based on these findings, the National Cancer Center Network (NCCN) panel for the development of guidelines on management of cancer in the older person has proposed a series of recommendations to ameliorate the toxicity of chemotherapy in the older-aged person (Table 2).⁴⁴

The prophylactic use of growth factors is recommended in view of the early mortality observed in

Table 2. — Proposed National Cancer Center Network (NCCN) Guidelines to Ameliorate the Risk of Myelosuppression From Cytotoxic Chemotherapy in Older Persons With Cancer

Use hemopoietic growth factors (G-CSF or GM-CSF) in patients aged 70+ who receive combination chemotherapy of dose/intensity equivalent to CHOP.
Maintain hemoglobin levels at ≥ 12 g/dL with erythropoietin.
Consider adjusting the dose of renally excreted drugs according to the predicted glomerular filtration rate.

older individuals who are treated with CHOP or CHOP-like regimens. Maintaining hemoglobin levels at approximately 12 g/dL is suggested to prevent the complications of anemia and life-threatening neutropenia. Dose adjustment of renally excreted drugs is recommended for those patients who are at risk for chemotherapy-related toxicity due to factors other than age. These include patients who are dependent on assistance in one or more instrumental activities of daily living (using transportation and the telephone, providing one's meals, managing money, shopping, taking medications), those with severe comorbid medical conditions, and the oldest of the elderly (85 years of age and older).^{2,44,45}

Due to increased risk of complications and heightened need of supportive care, the cost of using cytotoxic chemotherapy appears to be higher for the older cancer patient than for the younger cancer patient. The increased total cost of treatment, combined with a decline in life-expectancy and therapeutic response, may render cytotoxic chemotherapy less cost-effective in the older person. Whereas it is generally considered unethical to deny life-saving treatment to a person because of age, it is legitimate to explore strategies that minimize the treatment costs without compromising effectiveness.

Cost Implications of Declining Hemopoietic Reserve in the Older Cancer Patient

Any study of cost-related issues must acknowledge the limitations in assessing cost. These include the inability to dissect cost and price of a substance or service and the lack of a precise frame of reference to assess cost.

Inability to Dissect Cost and Price

Price is the amount of money charged to customers for goods or services and includes the profit of one or more intermediaries. The price of a drug often

reflects serial price increases, such as gross price and retail price. The cost is the amount of money necessary to produce, distribute, and administer a certain drug or service. Price is negotiable according to the law of the market down to the point of zero profit. Cost is not negotiable, unless a provider is willing to take a loss.

Cost has at least three components: direct, indirect, and intangible. *Direct* costs are the costs of specific products or services. For patients receiving chemotherapy for cancer, direct costs involve not only the cost of the drug, but also the cost of administering the drug and managing treatment complications. *Indirect* costs are those costs incurred by the patient and the patient's family in order to obtain the chemotherapy treatments, including the cost of employment missed due to the disease and the treatment, the cost of transportation to and from the treating center, the cost to the patient's or caregiver's employer, and the cost of child care or home care necessitated by the patient treatment. *Intangible* cost includes more far-reaching consequences of the disease, such as the costs of psychiatric help or marital counseling for a family member caring for an older person.

The assessment of direct cost is far from precise. For example, the cost of research and development and production of a medication may be estimated, but the cost of the training of scientists, technicians, and marketing professionals involved in the production is impossible to estimate with precision. Estimating indirect and intangible costs is even more problematic.

Lack of a Precise Frame of Reference to Assess Cost

The perspective of a health maintenance organization (HMO) may differ from the patient's perspective. For example, corporate profits may be enhanced and personal finances devastated by limiting the hospitalization time of a dependent patient.

For the purpose of this discussion, we will assume that cost is an absolute entity, ie, that the care of each patient has objective minimum cost below which optimal care cannot be provided. Our goal is to establish which treatment strategy is more effective in minimizing this total cost, not to establish whether the strategy will reduce the burden of a specific payor (eg, patient, private insurance, HMO).

To estimate different costs, we referred to current charges in a given area, on the unproven assumption that the margin of profit is the same for each substance and service. We examined two practical situations based on the NCCN guidelines: the prophylactic use of

hemopoietic growth factors and the maintenance of hemoglobin levels close to 12 g/dL.

Prophylactic Use of Hemopoietic Growth Factors

This recommendation was based on the evaluation of the lymphoma data (Table 1) indicating that neutropenia may be fatal for a number of patients aged 70 years or more. While life-saving considerations should supersede cost considerations, it is important to determine if this treatment strategy involves a substantial increment in cost. Our opinion is that it does not. The current guidelines of the American Society of Clinical Oncology (ASCO)⁴⁶ recommend that hemopoietic growth factors be used prophylactically in patients who have a risk of 40% or higher of neutropenic infections. These recommendations are based, in part, on the study of Lyman et al⁴⁷ showing that hemopoietic growth factors reduced total costs above the threshold risk of hospitalization. This study was derived from the experience of patients with limited-disease small-cell lung cancer treated with the combination of cyclophosphamide, doxorubicin, and vincristine. Thus, according to the guidelines, the use of hemopoietic growth factors would increase the cost of managing older patients with cancer. This conclusion should be tempered by the following considerations:

- The cost assessment by Lyman and colleagues⁴⁷ considered only direct hospital costs at that time, and an average length of hospitalization which may be unrealistically low for older individuals.

- In the original study of Lyman et al,⁴⁷ the direct cost of hospitalization utilized was \$1,000 per day. Updated hospitalization cost information including indirect institutional costs indicates that actual costs for hospitalization are at least 75% greater than those originally estimated, although the cost of hemopoietic growth factors has not changed.⁴⁸

- A number of older individuals die as a consequence of neutropenic infections. A recent study of risk factors for medical complications including death during episodes of febrile neutropenia indicates that increased age is a significant independent risk factor for such complications.⁴⁹

When current hospitalization costs are taken into account, the threshold for neutropenic fever at which the prophylactic use of growth factors becomes cost effective is approximately 30%, which is in the range of neutropenic fever for patients aged 70 years or more who are treated with CHOP-like combinations of chemotherapy.⁴⁸

Maintenance of Hemoglobin Levels

Using erythropoietin to maintain hemoglobin levels ≥ 12 g/dL is an expensive strategy. However, not using erythropoietin may have even more expensive consequences including:

- Increased use of red blood cell transfusions. Administering red blood cells for hemoglobin levels of ≤ 8 g/dL in patients without coronary artery disease and ≤ 10 g/dL in those with coronary artery disease is approximately half the cost of using erythropoietin to maintain the same hemoglobin levels.⁵⁰ This is a conservative estimate, however, that does not consider the cost of short- and long-term complications of blood transfusions.

- Increased risk of neutropenic fever and related costs. In the study by Pierelli et al,⁴⁰ patients receiving high-dose chemotherapy treated with a combination of G-CSF and erythropoietin had a 4% incidence rate of grade 4 neutropenia compared with a 47% incidence rate for those treated with G-CSF alone. In addition, anemia was found to be an independent risk factor for chemotherapy-induced myelosuppression.^{41,42}

- Increased risk of functional dependence. In a population of general oncology patients, most of whom were younger than age 65, the Fatigue Coalition reported that fatigue was the most common chronic complaint among patients after receiving cytotoxic chemotherapy.⁵¹ Fatigue led to the retirement of approximately one fourth of the patients and a reduction of working capacity in approximately half. Fatigue also generated a severe burden for caregivers; approximately 40% undertook a less demanding job, and 15% quit working. It is reasonable to infer that fatigue may be even more devastating in older individuals, whose functional reserve is reduced. In many cases, fatigue may precipitate functional dependence, mandating around-the-clock home care or even institutionalization.

From these considerations, it is reasonable to propose that the cost of erythropoietin be compared with the cost of anemia in older cancer patients.

Cost Management

Faced with a mounting epidemic of cancer in the older population, it is necessary to plan strategies that consider the cost of managing these patients. Our professional and societal ethics do not allow restriction of care to older individuals as a form of cost management. The question, then, is how to provide the best care at a reduced cost. A number of alternative

approaches to the current use of growth factors may be reasonably tested:

Shorter duration of cytotoxic chemotherapy — In 390 patients aged 65 or older, Zinzani and colleagues²⁵ reported that 6 weeks of treatment with cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisone (VNCOP-B) produced results comparable to 18 weeks of CHOP in patients with large-cell lymphoma. A reduction in dose intensity does not appear to be advisable because it has been associated with poorer results in large-cell lymphoma.^{26,28,29}

Late initiation of the treatment with hemopoietic growth factors — Currently, treatment with hemopoietic growth factors is frequently instituted the day after chemotherapy and lasts until the absolute neutrophil count is approximately 10,000/ μ L. Since the nadir of neutrophils occurs at 7-10 days after chemotherapy treatment, it may be reasonable to delay the initiation of hemopoietic growth factors by 3 or 4 days. Also, since the neutrophil count drops by approximately 60% when growth factors are discontinued, it may be reasonable to stop the treatment for a neutrophil count at approximately 3,500/ μ L. This approach could be compared to the current practice of initiating treatment with growth factors on the day after termination of chemotherapy and continuing the treatment until the neutrophil count is higher than 10,000/ μ L.

The use of prophylactic antibiotics such as trimethoprim/sulfamethoxazole or quinolones — These agents may prevent infections from intestinal Gram-negative organisms and should be compared with the use of hemopoietic growth factors in terms of effectiveness and cost.¹³

New developments in cancer treatment — These approaches (eg, monoclonal antibodies, antiangiogenesis factors, farnesyl-transferase inhibitors) may reduce the risk of myelosuppression and the need for hemopoietic growth factors and erythropoietin.

Development of slow-release preparation of growth factors, including the pegylated form of G-CSF, currently undergoing clinical trials — These preparations reduce the cost of administration and travel to the clinic.

Proper selection of patients as candidates for cytotoxic treatment — A comprehensive geriatric assessment⁴⁵ may be helpful to identify different categories of patients for whom different therapeutic approaches are indicated.⁵² These categories include

independent patients without serious comorbidity for whom treatment with full-dose chemotherapy is indicated, frail patients who have exhausted their functional reserve and generally are not candidates for any form of cytotoxic treatment,⁵³ and those who fall between these extremes, representing the majority of patients over 80 years of age. This population includes patients with some severe comorbidities as well as those who are dependent in some instrumental activities of daily living (eg, using transportation, managing money, and taking medications). They are still candidates for cytotoxic chemotherapy but are at increased risk of complications. Also, a number of laboratory data may be used to predict the risk of myelotoxicity, including hemoglobin levels⁴³ and urine nitrogen.⁵⁴ The applicability of these parameters to older individuals needs further study.

Conclusions

The decline in hemopoietic reserve in older individuals increases their susceptibility to hemopoietic stress, including cytotoxic chemotherapy. The use of colony-stimulating factors and erythropoietin may reduce the mortality and morbidity of myelosuppression in older patients who receive chemotherapy.

The cost of treating older persons with cancer appears to be higher than the cost of treating younger individuals, but the use of hemopoietic growth factors does not appear to substantially increase the cost of treatment. The cost effectiveness of managing older persons with cancer may improve with proper patient selection and with exploration of alternative treatment strategies.

References

- Duthie E. Physiology of aging: relevance to symptom perceptions and treatment tolerance. In: Balducci L, Lyman GH, Ershler WB. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands: Harwood Academic Publishers; 1998:247-262.
- Balducci L, Corcoran MB. Antineoplastic chemotherapy of the older cancer patient. *Hematol Oncol Clin North Am*. 2000;14:193-212. Review.
- Cova D, Beretta G, Balducci L. Cancer chemotherapy in the older patient. In: Balducci L, Lyman GH, Ershler WB. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands: Harwood Academic Publishers; 1998:429-442.
- Moscinski L. Hemopoiesis and aging. In: Balducci L, Lyman GH, Ershler WB. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands: Harwood Academic Publishers; 1998:399-412.
- Hardy CL, Balducci L. Hemopoietic alterations of cancer. *Am J Med Sci*. 1985;290:196-205. Review.
- Albright JW, Makinodan T. Decline in the growth potential of spleen-colonizing bone marrow stem cells of long-lived aging mice. *J Exp Med*. 1976;144:1204-1213.
- Baraldi-Junkins CA, Beck AC, Rothstein G. Hematopoiesis and cytokines. Relevance to cancer and aging. *Hematol Oncol Clin North Am*. 2000;14:45-61.
- Lipschitz DA. Age-related declines in hematopoietic reserve capacity. *Semin Oncol*. 1995;22(suppl 1):3-5.
- Rothstein G, Christensen RD, Nielsen BR. Kinetic evaluation of the pool sizes and proliferative response of neutrophils in bacterially challenged aging mice. *Blood*. 1987;70:1836-1841.
- Chatta GS, Price TH, Allen RC, et al. Effects of in vivo recombinant methionyl human granulocyte colony-stimulating factor on the neutrophil response and peripheral blood colony-forming cells in healthy young and elderly adult volunteers. *Blood*. 1994;84:2923-2929.
- Balducci L, Hardy CL. Anemia of aging: a model of erythropoiesis in cancer patients. *Cancer Control*. 1998;5(2 suppl 1):17-21.
- Boggs DR, Patrene KD. Hematopoiesis and aging III: anemia and a blunted erythropoietic response to hemorrhage in aged mice. *Am J Hematol*. 1985;19:327-338.
- Greene J. Infections in the older cancer patient. In: Balducci L, Lyman GH, Ershler WB. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands: Harwood Academic Publishers; 1998.
- Moscinski L. The aging bone marrow. In: Balducci L, Lyman GH, Ershler WB. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands: Harwood Academic Publishers; 1998:414-423.
- Lighthart GJ, Corberand JX, Fournier C, et al. Admission criteria for immunogerontological studies in man: the SENIEUR protocol. *Mech Ageing Dev*. 1984;28:47-55.
- Ershler WB, Sun WH, Binkley N, et al. Interleukin-6 and aging: blood levels and mononuclear cell production increase with advancing age and in vitro production is modifiable by dietary restriction. *Lymphokine Cytokine Res*. 1993;12:225-230.
- Shank WA Jr, Balducci L. Recombinant hemopoietic growth factors: comparative hemopoietic response in younger and older subjects. *J Am Geriatr Soc*. 1992;40:151-154.
- Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol*. 1998;16:3412-3425.
- Elfenbein G, Fields K. Bone marrow transplant in the older person. In: Balducci L, Lyman GH, Ershler WB. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands: Harwood Academic Publishers; 1998.
- Christman K, Muss HB, Case LD, et al. Chemotherapy of metastatic breast cancer in the elderly: the Piedmont Oncology Association experience. *JAMA*. 1992;268:57-62.
- Gelman RS, Taylor SG IV. Cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: the elimination of age trend in toxicity by using doses based on creatinine clearance. *J Clin Oncol*. 1984;2:1404-1413.
- Ibrahim N, Buzdar A, Frye D, et al. Should age be a determinant factor in treating breast cancer patients with combination chemotherapy? *Proc Annu Meet Am Soc Clin Oncol*. 1993;12:A68.
- Newcomb PA, Carbone PP. Cancer treatment and age: patient perspectives. *J Natl Cancer Inst*. 1993;85:1580-1584.
- Giovanazzi-Bannon S, Rademaker A, Lai G, et al. Treatment tolerance of elderly cancer patients entered onto phase II clinical trials: an Illinois Cancer Center Study. *J Clin Oncol*. 1994;12:2447-2452.
- Zinzani PL, Storti S, Zaccaria A, et al. Elderly aggressive-histology non-Hodgkin's lymphoma: first-line VNCOP-B regimen. Experience on 350 patients. *Blood*. 1999;94:33-38.
- Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. *J Clin Oncol*. 1995;13:2530-2539.
- Gomez H, Mas L, Casanova L, et al. Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: identification of two age subgroups with differing hematologic toxicity. *J Clin Oncol*. 1998;16:2352-2358.
- Bastion Y, Blay JY, Divine M, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment and survival. A Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. *J Clin Oncol*. 1997;15:2945-2953.
- Tirelli U, Errante D, Van Glabbeke M, et al. CHOP is the standard regimen in patients > or = 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of a random-

ized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group. *J Clin Oncol*. 1998;16:27-34.

30. Bertini M, Freilone R, Vitolo U, et al. The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: feasibility and efficacy of an intensive multidrug regimen. *Leuk Lymphoma*. 1996;22:483-493.

31. O'Reilly SE, Connors JM, Howdle S, et al. In search of an optimal regimen for elderly patients with advanced-stage diffuse large-cell lymphoma: results of a phase II study of P/DOCE chemotherapy. *J Clin Oncol*. 1993;11:2250-2257.

32. Armitage JO, Potter JF. Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly: increased complications with advancing age. *J Am Geriatr Soc*. 1984;32:269-273.

33. Rowe JM, Andersen J, Mazza JJ, et al. A randomized placebo-controlled study on granulocyte macrophage colony-stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). *Blood*. 1995;86:257-263.

34. Schiffer CA. Hematopoietic growth factors as adjuncts to the treatment of acute myelogenous leukemia. *Blood*. 1996;88:3675-3685.

35. Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. *N Engl J Med*. 1995;332:1671-1677.

36. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients-with-previously untreated acute myelogenous leukemia: a Southwest Oncology Group study (9031). *Blood*. 1998;91:3607-3615.

37. Lancet JE, Willman CL, Bennett JM. Acute myelogenous leukemia and aging. Clinical interactions. *Hematol Oncol Clin North Am*. 2000;16:251-267. Review.

38. Cleeland CS, Demetri GD, Glaspy J, et al. Identifying hemoglobin level for optimal quality of life: results of an incremental analysis. *Proc Annu Meet Am Soc Clin Oncol*. 1999;18:A2215.

39. Gabrilove JL, Einhorn LH, Livingston RB, et al. Once-weekly dosing of epoetin alfa is similar to three-times-weekly dosing in increasing hemoglobin and quality of life. *Proc Annu Meet Am Soc Clin Oncol*. 1999;A2216.

40. Pierelli L, Perillo A, Gregg S, et al. Erythropoietin addition to granulocyte colony-stimulating factor abrogates life-threatening neutropenia and increases peripheral-blood progenitor-cell mobilization after epirubicin, paclitaxel and cisplatin combination chemotherapy: results of a randomized comparison. *J Clin Oncol*. 1999;17:1288.

41. Ratain MJ, Schilsky RL, Choi KE, et al. Adaptive control of etoposide administration: impact of interpatient pharmacodynamic variability. *Clin Pharmacol Ther*. 1989;45:226-233.

42. Silber JH, Fridman M, DiPaola RS, et al. First-cycle blood counts and subsequent neutropenia, dose reduction, or delay in early-stage breast cancer therapy. *J Clin Oncol*. 1998;16:2392-2400.

43. Marcantonio ER, Goldman L, Orav EJ, et al. The association of intraoperative factors with the development of postoperative delirium. *Am J Med*. 1998;105:380-384.

44. Balducci L, Yates G. Report of the panel on clinical guidelines for the management of the older cancer patients. *Oncology*. In press.

45. Extermann M, Aapro M. Assessment of the older cancer patient. *Hematol Oncol Clin North Am*. 2000;14:63-77. Review.

46. American Society of Clinical Oncology. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. *J Clin Oncol*. 1996;14:671-679.

47. Lyman GH, Lyman C, Sanderson R, et al. Decision analysis of hematopoietic growth factor use in patients receiving cancer chemotherapy. *J Natl Cancer Inst*. 1993;85:488-493.

48. Lyman GH, Kuderer N, Green J, et al. The economics of febrile neutropenia: implications for the use of colony stimulating factors. *Eur J Cancer*. 1998;34:1857-1864.

49. Kim YJ, Rubenstein EB, Rolston KVI, et al. Colony stimulating factors (CSFs) may reduce complications and death in solid tumor patients (pts) with fever and neutropenia. *Proc Annu Meet Am Soc Clin Oncol*. 2000;19:A2411.

50. Griggs JJ, Mushlin AI. Economic analysis of expensive technologies: the case of erythropoietin. *Cancer*. 1998;83:2427-2429.

51. Curt GA, Breitbart W, Cella DF, et al. Impact of cancer-related fatigue on the lives of patients. *Proc Annu Meet Am Soc Clin Oncol*. 1999;A2214.

52. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist*. 2000;5:224-237.

53. Balducci L, Stanta G. Cancer in the frail patient. A coming epidemic. *Hematol Oncol Clin North Am*. 2000;14:235-250. Review.

54. Aslani A, Smith RC, Allen BJ. The predictive value of body protein for chemotherapy-induced toxicity. *Cancer*. 2000;88:796-803.