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

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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.

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

Aging is associated with a progressive decline in the functional reserve of multiple organ systems. This functional restriction may enhance the susceptibility of normal tissues to cytotoxic chemotherapy in older patients. 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. 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). Hemopoiesis involves the commitment of pluripotent 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. 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. 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...
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. During conditions of stress, such as isolation, the marrow concentration of CFU-S declined in older mice but not in younger mice. In the presence of sublethal doses of \textit{Escherichia coli}, older animals experienced a progressive reduction in PHSC concentration that did not occur in younger animals.

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. 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. A number of clinical findings, including rising incidence and prevalence of anemia with age, reduced reticulocyte response in older anemic patients, increased mortality from infection in the aged, and reduced concentration of hemopoietic tissue with age 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. 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. 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. 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) and tumor necrosis factor (TNF) 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.

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. 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-CSF and erythropoietin 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. 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, 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, 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 myelosuppression 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 al 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>
<thead>
<tr>
<th>Authors</th>
<th>Number of Patients</th>
<th>Regimen</th>
<th>Age</th>
<th>Neutropenia</th>
<th>Neutropenic Fever</th>
<th>Treatment-Related Deaths</th>
<th>Growth Factor</th>
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<tr>
<td>Zinzani et al25</td>
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<td>G-CSF</td>
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<tr>
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<td>20</td>
<td>CHOP</td>
<td>70+</td>
<td>NR</td>
<td>NR</td>
<td>30%</td>
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</tbody>
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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/DIGE = 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. 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.

The lymphoma studies showed that the risk of severe thrombocytopenia increases with age but not to the same extent as the risk of neutropenia. Unfortunately, no information is available on the risk of anemia following chemotherapy. At the time that many of these studies were conducted, the effect 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. 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. In addition, anemia may cause a number of complications in the care of the older persons, including postoperative delirium.

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).

<table>
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<tr>
<th>Table 2. — Proposed National Cancer Center Network (NCCN) Guidelines to Ameliorate the Risk of Myelosuppression From Cytotoxic Chemotherapy in Older Persons With Cancer</th>
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<tbody>
<tr>
<td>Use hemopoietic growth factors (G-CSF or GM-CSF) in patients aged 70+ who receive combination chemotherapy of dose/intensity equivalent to CHOP.</td>
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<tr>
<td>Maintain hemoglobin levels at ≥12 g/dL with erythropoietin.</td>
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<tr>
<td>Consider adjusting the dose of renally excreted drugs according to the predicted glomerular filtration rate.</td>
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</table>

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) 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 al 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 colleagues 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, 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.

• 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.

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.
Maintenance of Hemoglobin Levels

Using erythropoietin to maintain hemoglobin levels $\geq 12$ 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 $\leq 8$ g/dL in patients without coronary artery disease and $\leq 10$ g/dL in those with coronary artery disease is approximately half the cost of using erythropoietin to maintain the same hemoglobin levels.\textsuperscript{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.,\textsuperscript{40} patients receiving high-dose chemotherapy 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.\textsuperscript{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.\textsuperscript{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 colleagues\textsuperscript{25} 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.\textsuperscript{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/$\mu$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/$\mu$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/$\mu$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.\textsuperscript{13}

New developments in cancer treatment — These approaches (eg, monoclonal antibodies, angiogenesis 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 assessment\textsuperscript{k45} may be helpful to identify different categories of patients for whom different therapeutic approaches are indicated.\textsuperscript{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, 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 levels and urine nitrogen. The applicability of these parameters to older individuals needs further study.

Conclusions

The decline in hematopoietic reserve in older individuals increases their susceptibility to hematopoietic 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 hematopoietic 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

29. 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 lymphomas: results of a random-


