Feature Article

Use of Colony-Stimulating Factors in the Elderly Cancer Patient

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ABSTRACT

Cancer is, in large part, a disease of aging. The progressive decline with age in the functional reserve of specific organs including bone marrow may limit the ability of elderly cancer patients to tolerate treatment. Myelosuppression with neutropenia remains the major dose-limiting toxicity of cancer chemotherapy, especially in the elderly. The hematopoietic growth factors have been shown to reduce the severity and duration of myelosuppression and its complications, including febrile neutropenia and reduced chemotherapy dose intensity. To illustrate the impact of aging, a systematic review was conducted of neutropenic complications and the efficacy of the colony-stimulating factors (CSFs) in elderly patients with non-Hodgkin's lymphoma receiving cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or CHOP-like regimens. The risk of febrile neutropenia in this population averages between 25% and 40%, while the use of prophylactic CSF is associated with approximately a 50% reduction in the risk of febrile neutropenia. We also present a systematic review of the use of CSFs in elderly patients with acute myelogenous leukemia. Although there is no consistently observed effect on complete remission rates, there is a significant increase in the proportion of patients alive at 2 years. An economic analysis demonstrates cost savings with the use of CSFs in elderly patients receiving chemotherapy with a dose intensity equivalent to CHOP. Clinical practice guidelines that are consistent with these observations are presented. Further data are needed on the impact of CSFs on quality of life as well as their ability to sustain dose intensity in responsive and potentially curable malignancies in the elderly.

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INTRODUCTION

Approximately 80% of all cancers occur in individuals over age 60 and nearly 25% of cancers occur in those over 80.[1] Cancer in the elderly raises numerous important issues that must be considered in clinical decision-making and healthcare policy formulation.[2,3] Aging is associated with a progressive decline in the functional reserve of the bone marrow as well as other organ systems.[4] Myelosuppression is the most common dose-limiting toxicity associated with systemic cancer chemotherapy. Hematopoietic growth factors including granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony-stimulating factors (GM-CSFs) have been shown to reduce the severity and duration of neutropenia and associated infectious complications, including febrile neutropenia (FN).[5] A recent meta-analysis of randomized controlled trials of prophylactic G-CSF use in patients receiving cancer chemotherapy has confirmed its effectiveness across disease entities and treatment regimens.[6] This article summarizes the use of hematopoietic growth factors in older cancer patients receiving systemic chemotherapy. We will pay particular attention to the limited hematopoietic reserve in elderly cancer patients and the impact of comorbidities on the risk, severity, and duration of FN and on the effectiveness and cost-effectiveness of CSFs.

DEFINING AND CHARACTERIZING THE ELDERLY

Aging is associated with a progressive restriction in functional, medical, cognitive, emotional, nutritional, and socioeconomic domains due to loss in the functional reserve of multiple organ systems, increased prevalence of

EDUCATIONAL OBJECTIVE

Obtain a systematic overview of the impact of cancer chemotherapy on the elderly patient with cancer, including chemotherapy toxicity and the impact of the colony-stimulating factors on the risk of neutropenic complications.

TALKING POINTS	Physicians	Pharmacy	Formulary	Cancer Nurses
Aging is associated with a progressive decline in the functional reserve of many organs including bone marrow.				
The hematopoietic growth factors have been shown to reduce the severity and duration of neutropenia and its complications, including febrile neutropenia				
Use of colony-stimulating growth factors in elderly patients receiving cancer chemotherapy equivalent to CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) is associated with a net cost savings.				
Colony-stimulating factors have been shown to improve quality of life and allow full dose intensity chemotherapy on time.				

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comorbidities and polypharmacy, more limited social support, reduced ability to process new information and to adapt to environmental changes, and reduced income. Actual chronological age as opposed to physiologic age correlates poorly with life expectancy and to level stress. Nevertheless, the prevalence of age-related changes, including functional dependence, comorbidity, and risk of chemotherapy-related toxicity, increases more rapidly after age 70. Age 85 often heralds the onset of frailty, and more than 50% of persons aged 85 and older have some degree of functional dependence.[7] The most accurate determination of aging is provided by a comprehensive geriatric assessment, including functional, medical, socioeconomic, and cognitive domains. Dependence in one or more activities of daily living is associated with a more than threefold increase in short-term mortality and is considered a sign of frailty. Comorbidities may be assessed as the number of selected comorbid conditions, or it can be scored according to a comorbidity index that reflects the seriousness of these conditions.[8] Comorbidities may be associated with reduced life expectancy as well as with reduced tolerance to a particular treatment.

AGE AND HEMATOPOIESIS

Hematopoiesis involves the commitment of pluripotent hematopoietic stem cells into progenitors and the subsequent differentiation of these progenitors into marrow precursors, from which the mature circulating blood elements are derived. Commitment, differentiation, and maturation are modulated by a number of cytokines, and require an intact hematopoietic microenvironment. A number of clinical and experimental observations suggest an age-related reduction in hematopoietic stem cells, including a progressive restriction in hematopoietic tissue, increased mortality from infection, and more limited response to CSFs.[9] There is also evidence for a decline in hematopoietic reserve with age, but this becomes clinically relevant only under conditions of stress. An increased incidence of neutropenia, FN, and thrombocytopenia following systemic chemotherapy has been reported and good responses to pharmacologic doses of G-CSF, GM-CSF, and erythropoietin may be observed regardless of age. While the risk of engraftment failure for allogeneic bone marrow transplantation increases with the recipient's age, it is important to note that autologous stem cell rescue has been found effective even in persons aged 70 and older after high-dose chemotherapy.

"A number of clinical and experimental observations suggest an age-related reduction in hematopoietic stem cells, including a progressive restriction in hematopoietic tissue, increased mortality from infection, and more limited response to CSFs."

TABLE 1. NEUTROPENIA, FEBRILE NEUTROPENIA (FN), AND TREATMENT-RELATED DEATHS IN INDIVIDUALS WITH NON-HODGKIN'S LYMPHOMA TREATED WITH CHOP-LIKE REGIMENS

Author (Year)	Patients (N)	Regimen	Age	Neutropenia (%)	FN (%)	Treatment-Related Deaths (%)
Zinzani (1997)[10]	72	VNCOP-B	60+	55.5	6.9	1
Gomez* (1998)[11]	15	CHOP	60–69	24	8	0
	11		70–84	73	42	18
Tirelli (1998)[12]	60	VMP	70+	51	3.3	3
	60	CHOP	70+	47	5.1	2
Bastion (1997)[13]	218	CVP	70+	3.7†	NR	12
	226	CTVP	70+	15†	NR	15
O'Reilly (1993)[14]	63	P/DOCE	65+	50	20	8
Bjorkholm (1999)[15]	206	CHOP/CNOP	60+	91	47	NR
Bertini (1996)[16]	54	P-VEBEC	65+	46	18	2
Armitage (1984)[17]	20	CHOP	70+	NR	NR	30
TOTAL	541	All	60+	66	25	10

*All patients received GM-CSF prophylactically.
†First cycle results only.

CHOP=cyclophosphamide/doxorubicin/vincristine/prednisone; FN=febrile neutropenia; VNCOP-B=VP16/mitoxantrone/cyclophosphamide/vincristine/prednisone-bleomycin; VMP=VP16/mitoxantrone/prednimustine; CVP=cyclophosphamide/vincristine/prednisone; CTVP=cyclophosphamide/tiazorubicin/vincristine/prednisone; P=prednisone; DOCE=dexamethazone/vincristine/cyclophosphamide/epirubicin; CNOP=cyclophosphamide/mitoxantrone/doxorubicin/prednisone; P-VEBEC=prednisone/vinblastine/etoposide/bleomycin/epirubicin/cyclophosphamide; NR=not reported; GM-CSF=granulocyte-macrophage colony-stimulating factor.

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"…the risk, duration, and severity of neutropenia have been shown to increase with age, particularly after age 70."

AGE AND CHEMOTHERAPY TOXICITY

Do age-related limitations in hematopoiesis result in more severe and prolonged myelosuppression following systemic cancer chemotherapy? Several early clinical studies failed to demonstrate an increased risk and severity of myelosuppression in patients over 65 or 70 vs younger patients, suggesting that age by itself is not a contraindication to systemic chemotherapy. Unfortunately, these studies were all retrospective and fraught with the limitations of such studies, including missing data. Few patients were over 75 and virtually no patients were over 80. In addition, the dose intensity of the older treatment regimens was frequently compromised vs more modern regimens and schedules. On the other hand, the risk, duration, and severity of neutropenia have been shown to increase with age, particularly after age 70. The risk of severe neutropenia in studies of elderly patients with non-Hodgkin's lymphoma treated with modern chemotherapy regimens has ranged from 24% to 91% and averages 66% across all studies (Table 1).[10-17] The risk of FN ranges from 3.3% to 47% and averages 25% across all studies. The risk of treatment-related mortality ranges from 0% to 30% and averages 10% across all studies.

In a recent study of 1,243 community practices, risk factors for FN were assessed in 20,799 women receiving various adjuvant breast cancer chemotherapy regimens.[18] The risk of FN for various chemotherapy regimens among women aged 65 and over ranged from 5% to 23%. Recent studies have also demonstrated that the risk of serious medical complications including death is greater among elderly cancer patients receiving chemotherapy than among younger patients, even after adjustment for severe burden of illness, complexity of infection, uncontrolled cancer, or neutrophil counts on admission.[19]

There are a variety of strategies available to clinicians treating elderly cancer patients who are at risk for such chemotherapy-related toxicities as neutropenia and FN. These include reducing the dose and/or delaying treatment, proceeding with full-dose chemotherapy, and using concurrent prophylactic agents, eg, antibiotics, antifungals, and CSFs, to reduce the risk of neutropenia or neutropenic complications. Excessive dose reduction in otherwise healthy elderly patients without comorbidities, and particularly reduction of doses of agents eliminated by other routes may lead to unnecessary reduction in dose intensity and treatment effectiveness.

AGE AND EFFECTIVENESS OF HEMATOPOIETIC GROWTH FACTORS

Although the sensitivity of hematopoietic progenitors to physiologic levels of cytokines may be compromised in the elderly,

TABLE 2. EFFICACY OF COLONY-STIMULATING FACTORS IN OLDER PATIENTS WITH LARGE CELL NON-HODGKIN'S LYMPHOMA RECEIVING COMBINATION CHEMOTHERAPY

Study (Year)	Randomized	Chemotherapy	G-CSF	Patients (N)	Grade IV Neutropenia (%)	FN (%)
Zinzani (1997)[10]	Yes	VNCOP	Yes	77	23	5
			No	72	55.5	21
Zagonel (1994)[20]*	No	CHOP	Yes	12	4.8	4.8
			No	11	27.7	15.6
Bertini (1996)[16]	No	P-VEBEC	Yes	46	22	2
			No	54	44	9
Bjorkholm (1999)[15]	Yes	CHOP/CNOP	Yes	211	62	32
			No	206	91	47
Muhonen (1996)[21]	Yes	MMM	Yes	16	25	NA
			No	15	80	
All (except Zagonel)			Yes	350	47	22
			No	347	76	35
All RCTs			Yes	304	50	25
			No	293	82	40

G-CSF=granulocyte colony-stimulating factor; FN=febrile neutropenia; VNCOP=etoposide/mitoxantrone/cyclophosphamide/vincristine/prednisone; CHOP=cyclophosphamide/doxorubicin/vincristine/prednisone; P-VEBEC=prednisone/vinblastine/etoposide/bleomycin/epirubicin/cyclophosphamide; CNOP=cyclophosphamide/mitoxantrone/doxorubicin/prednisone; MMM=mitomycin-C/mitoxantrone/methotrexate; NA=not assessed; RCTs=randomized controlled trials.

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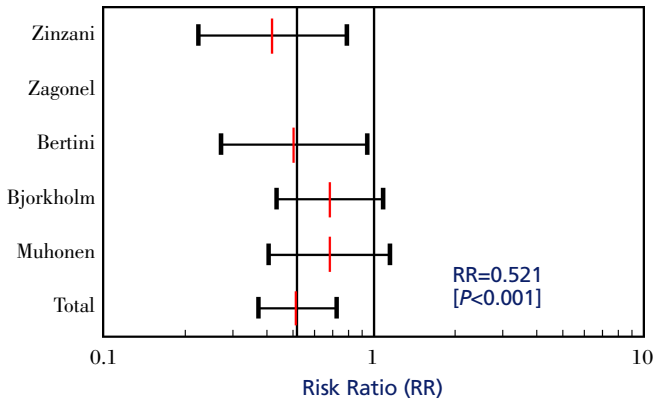
sensitivity to pharmacologic doses of these compounds appears well maintained. The effectiveness of G-CSFs and GM-CSFs in older patients has been well established in a number of studies. Our systematic review of controlled clinical trials totaling nearly 700 patients with non-Hodgkin's lymphoma demonstrates that the use of G-CSF in older patients is associated with decreased risk of grade IV neutropenia and FN (Table 2). Across the comparative trials summarized, the risk of severe neutropenia was 47% in those receiving CSFs vs 76% in control subjects.[10,15,16,20,21]

In a formal meta-analysis based on a random effects model, the summary relative risk estimate of grade IV neutropenia among those receiving growth factor was 0.52 (0.37, 0.73 ±95% confidence limits, $P<.001$) (Fig. 1). As also shown in Table 2, the risk of FN was 22% among those receiving CSF vs 35% in control subjects. The accompanying Forrest plot shown in Figure 2 reveals that the summary relative risk estimate ±95% confidence limits of FN among those receiving growth factor was 0.425 (0.191, 0.945) ($P=.036$). A recent Italian trial demonstrated that the combined use of G-CSF and erythropoietin was associated with a significantly lower risk of FN than G-CSF alone.[22]

Several studies have also investigated the potential role of either G-CSF or GM-CSF in elderly patients with newly diagnosed acute myelogenous leukemia (AML). These studies have generally demonstrated the safety of these agents in patients recovering from induction therapy. The Eastern Cooperative

FIGURE 1. GRADE IV NEUTROPENIA, NHL
Relative Risk (95%CL)*



*Random effects model.

NHL=non-Hodgkin's lymphoma; CL=confidence limits.

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TABLE 3. RANDOMIZED CONTROLLED TRIALS OF THE COLONY-STIMULATING FACTORS IN ACUTE MYELOID LEUKEMIA

Author (Year)	Age	Treatment	Patients (N)	CR (%)	Treatment-related Deaths (%)	Median Recovery (Days)	2-year DFS (%)
Rowe (1995)[23]	55–70	GM-CSF	62	60	6	13	30
		No CSF	62	44	15	17	17
Heil (1995)[24]	>50	G-CSF	19	79	-	24	NS
		No CSF	18	83	-	50	NS
Lowenberg (1997)[25]	61+	GM-CSF	157	56	14	23	22
		No CSF	161	55	10	25	22
Witz (1998)[26]	55–75	GM-CSF	114	63	9	24	48
		No CSF	126	60.5	10	29	21
Stone (1994)[27]	60+	GM-CSF	193	51	7	15	-
		No CSF	195	54	7	17	-
Godwin (1995)[28]	55+	G-CSF	105	41	20	24	23
		No CSF	106	50	19	27	17
Maslak (1996)[29]	60+	G-CSF	No random	41	58	13	18
		No CSF	historic controls	50	-	17	8
Dombret (1995)[30]	>65	Glyc-G-CSF	88	70	23	21	10
		No CSF	85	47	27	27	8
TOTAL		CSF	738	56	13	-	27
		No CSF	753	54	13	-	18

CR=complete remission; DFS=disease-free survival; GM-CSF=granulocyte-macrophage colony-stimulating factor; CSF=colony-stimulating factor.

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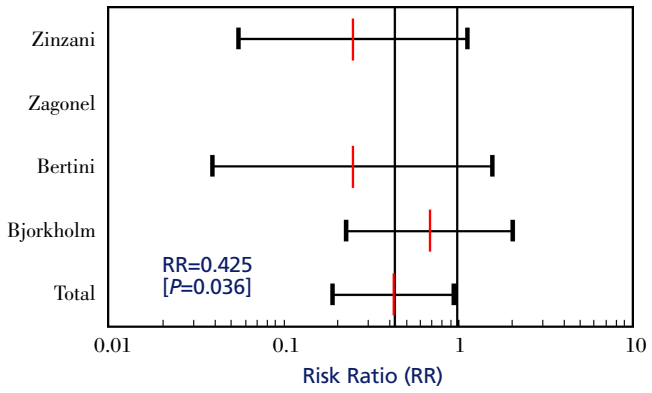
Oncology Group study administering GM-CSF after demonstrating marrow aplasia reported a doubling of median survival and a 30% increase in complete response among patients aged 55 and above.[20] However, in a study by the Cancer and Leukemia Group B, in which all patients received growth factor support, a comparable benefit was not found.[27]

A systematic review of the available literature revealed eight controlled clinical trials of CSFs in elderly patients with AML.[23-30]

FIGURE 2. FEBRILE NEUTROPENIA, NHL
Relative Risk (95%CL)*



*Random effects model.

NHL=non-Hodgkin's lymphoma.

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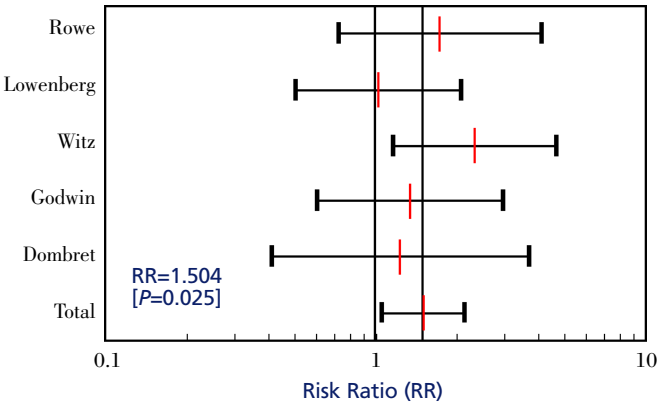
FIGURE 3. 2-YEAR DISEASE-FREE SURVIVAL, AML
Relative Risk (95%CL)*



*Random effects model.

AML=acute myelogenous leukemia.

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These studies, summarized in Table 3, show a cumulative complete remission rate of 56% among those receiving growth factor and 54% among controls (*P*=not significant). There was also no difference in the proportion of treatment-related deaths reported for CSF-treated patients vs controls. The effect on survival and complete remission rate, although inconclusive, reveals that 27% of CSF-treated patients survived disease free for 2 years vs 18% of controls. As shown in Figure 3, the relative risk for disease-free survival at 2 years with use of the CSFs was 1.5 (1.05, 2.15) (*P*=.025).

The most commonly reported side effect associated with the administration of CSFs is transient and treatable bone pain. This may be prevented or alleviated by regular administration of acetaminophen and should not prevent use of CSFs. GM-CSF may also be associated with a flulike syndrome, fluid retention, and rash. Other concerns about the hematopoietic growth factors have been largely hypothetical and, although of particular concern in elderly individuals with limited hematopoietic reserve, not confirmed clinically. These include hematopoietic exhaustion due to excessive drainage of pluripotent stem cells through commitment and proliferation, and stem cell competition due to excessive commitment and proliferation at the expense of other lines. Although leukemic myeloblasts often express receptors for G-CSF and GM-CSF, the concern that use of CSFs may lead to AML has also never been conclusively shown. Protein malnutrition, although very rare, may follow prolonged treatment.

ECONOMIC ANALYSIS

Management of older individuals with cancer is often more costly and less cost-effective than management of younger patients. Elderly people with cancer have an increased risk of therapeutic complications and a reduced potential for benefit due to limited life expectancy and less responsive malignancies.[2,3]

Healthcare costs consist of direct, indirect, and intangible components. Direct costs include the medical costs of delivering medical care, eg, hospitalization, and the nonmedical costs incurred while receiving care, eg, transportation or childcare. Indirect costs include those associated with treatment morbidity, eg, days lost from work, or mortality associated with premature death from disease. While difficult to measure, intangible costs such as pain and suffering

and loss of companionship should also be considered.

Economic analyses must consider the clinical outcome as well as the economic outcome or cost, and are of greatest value when the clinical outcome is the same or better but the cost is greatly increased. Economic analyses are also of value when the cost is the same or less but the clinical outcome is not as good. The most efficient programs will be those with the lowest cost per unit of benefit or the greatest benefit per unit cost. When clinical outcomes are not considered substantially different, the focus of the economic analysis is directed at cost minimization or choosing the approach associated with the least cost. When clinical outcomes differ, the most commonly utilized approach is that of cost-effectiveness, generally expressed as the cost per life saved or life-year gained. A cost-utility analysis can be conducted in the same fashion by utilizing a quality-adjusted outcome measure such as quality-adjusted life years as the clinical outcome of interest.

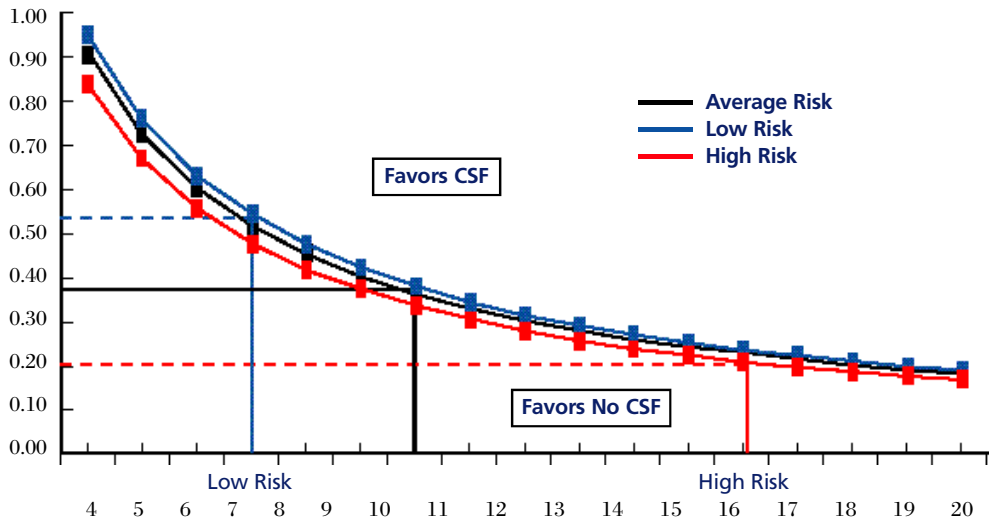
Lyman et al previously reported that when only direct medical costs of hospitalization are considered, the use of G-CSF is associated with an overall cost savings when the risk of FN is 40% or higher.[31,32] In a more recent analysis including both direct and indirect institutional costs, threshold risks in the range of 20–25% were estimated.[33] This study also demonstrated that patients with FN are heterogeneous; low-risk patients experience relatively uncomplicated short-term admissions while high-risk patients are likely to have more complicated, prolonged hospitalizations that account for the majority of cost. The threshold risk of FN when managing high-risk patients based on the recent meta-analysis was found to be approximately 20%.[6] Numerous supporting studies have confirmed the clinical efficacy and cost efficiency of the CSFs in patients receiving cancer chemotherapy.[34,35]

"…when only direct medical costs of hospitalization are considered, the use of G-CSF is associated with an overall cost savings when the risk of FN is 40% or higher."

RECOMMENDATIONS FOR HEMATOPOIETIC GROWTH FACTOR USE IN THE ELDERLY

We conclude from the above that older individuals receiving moderately toxic chemotherapy are at increased risk for severe myelosuppression, which may result in morbidity and mortality from overwhelming

FIGURE 4. THRESHOLD RISK OF HOSPITALIZATION FOR FN



FN=febrile neutropenia; CSF=colony-stimulating factor.

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infection. The morbidity and perhaps mortality associated with severe and prolonged neutropenia can be reduced by the use of hematopoietic growth factors. Recently updated guidelines from the American Society of Clinical Oncology for the use of hematopoietic growth factors only partially address issues related to the elderly cancer patient.[36,37] Specific recommendations for the use of hematopoietic growth factors in the elderly cancer patient have recently been developed for the National Comprehensive Cancer Network. These include:

- CSFs should be used prophylactically in cancer patients aged 70 and older receiving chemotherapy with the dose intensity of cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP).
- Hemoglobin should be maintained at levels >12 g/dL with recombinant erythropoietin.
- Renally excreted drugs should be adjusted to the patient's glomerular filtration rate.

"The use of CSFs in patients aged 70 and older treated with regimens of dose intensity comparable to that of CHOP should not be associated with increased cost, and may even lead to cost savings…."

The use of CSFs in patients aged 70 and older treated with regimens of dose intensity comparable to that of CHOP should not be associated with increased cost, and may even lead to cost saving for the following reasons:

- The risk of FN in these patients is >20% in most series;
- CSFs have been shown to reduce the risk of FN by at least 50% in these patients;
- The cost of hospitalization has continued to increase and the impact of indirect or out-of-pocket costs is only now being investigated;
- The duration of hospitalization for FN for older individuals is probably greater than for younger patients due to associated comorbidities;
- The consequences of hospitalization in older individuals may be devastating and may lead to functional dependence requiring prolonged and costly rehabilitation.

The validity of these conclusions might be challenged by strategies to treat low-risk patients with FN in the ambulatory setting. However, recent modeling of the cost impact of such an approach has demonstrated minimal impact on the risk thresholds previously defined.[38] In addition, the safety of such an approach in patients older than 70 is open to serious question. Alternatively, since the cost of caring for elderly cancer patients with comorbidities is considerably more expensive than it is for younger patients, the potential cost savings associated with reducing risks and duration of hospitalization with use of CSFs is substantial, partially or completely offsetting the cost of the agent. **OS**

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