



Paul Gauguin. *Bathing, Dieppe*, 1885. Oil on canvas.

Evidence supports the use of primary colony-stimulating factors in elderly patients receiving moderately intensive chemotherapy for potentially curable malignancies.

Evidence-Based Use of Colony-Stimulating Factors in Elderly Cancer Patients

Gary H. Lyman, MD, MPH, FRCP(Edin), Nicole Kuderer, MD, Olayemi Agboola, MS, and Lodovico Balducci, MD

Background: *Neutropenia and its complications represent the major dose-limiting toxicity of cancer chemotherapy, especially in the elderly. Hematopoietic growth factors have been shown to reduce the severity and duration of febrile neutropenia (FN) and to sustain chemotherapy dose intensity.*

Methods: *A systematic review was undertaken of studies of the relationship between age and the risk of neutropenia and its complications. Recent studies of the "Awareness of Neutropenia in Chemotherapy Study Group" related to the impact of age on neutropenic complications are also summarized.*

Results: *The risk of FN associated with standard regimens increases with age and appears to be greatest during the first cycle of chemotherapy. FN continues to have a considerable clinical, economic, and quality-of-life impact on affected individuals. The risk of mortality associated with hospitalization with FN also increases with age but is largely associated with the higher rate of comorbidities observed in the elderly population. Despite increasing evidence that elderly patients experience similar benefit from cancer chemotherapy, reductions in dose intensity often compromise response rates and long-term survival. The hematopoietic growth factors reduce the risk of neutropenic events and the need for reduced dose intensity in elderly cancer patients. Primary prophylaxis with colony-stimulating factors (CSFs) reduces the risk of FN and its complications in elderly patients receiving moderately intensive systemic chemotherapy for responsive malignancies. CSFs also appear to reduce cost and improve quality of life in selected elderly patients receiving chemotherapy.*

Conclusions: *Primary prophylaxis with CSFs should be considered in elderly patients with responsive and potentially curable malignancies who receive moderately intensive chemotherapy.*

From the Health Services and Outcomes Research Program, James P. Wilmot Cancer Center, University of Rochester Medical Center; Rochester, New York (GHL, NK, OA), and the Senior Adult Oncology Program, H. Lee Moffitt Cancer Center & Research Institute at University of South Florida, Tampa, Florida (LB).

Submitted April 7, 2003; accepted May 16, 2003.

Address reprint request to Gary H. Lyman, MD, MPH, FRCP (Edin), James P. Wilmot Cancer Center, 601 Elmwood Avenue, Rochester, NY 14642. E-mail: Gary_Lyman@urmc.rochester.edu

Dr Lyman is on the Speaker's Bureau of Amgen Inc and Ortho Biotech Products and receives grant support from Amgen and GlaxoSmithKline. Dr Balducci receives grant/research support from Eli Lilly and Co and Novartis Pharmaceuticals, and he receives honoraria from Amgen Inc, Novartis Pharmaceuticals, and Roche Pharmaceuticals. The other authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

Introduction

The risk of cancer rises progressively with increasing age, with approximately 80% of all cancers occurring in individuals over 60 years of age.¹ Cancer in the elderly raises numerous important issues that must be considered in clinical decision-making and healthcare policy formation.^{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 represents the most common dose-limiting toxicity associated with systemic cancer chemotherapy.

The hematopoietic growth factors including granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony-stimulating factors (GM-CSFs) reduce the severity and duration of neutropenia and associated infectious complications such as febrile neutropenia (FN).⁵ A recent meta-analysis of randomized, controlled trials of the use of prophylactic G-CSF in patients receiving cancer chemotherapy has confirmed its effectiveness across disease entities and treatment regimens.⁶ This article summarizes the evidence that severe and febrile neutropenia has major clinical, economic and quality of life effects on elderly cancer patients receiving systemic chemotherapy. In addition,

evidence supporting the efficacy and safety of the CSFs in elderly cancer patients receiving chemotherapy is reviewed and updated with recent studies conducted under the auspices of the Awareness of Neutropenia in Chemotherapy Study Group. Finally, evidence is provided based on clinical, economic and quality of life considerations for the use of G-CSF as primary prophylaxis of severe and febrile neutropenia in elderly cancer patients receiving moderately intensive systemic chemotherapy.

Age and the Risk of Severe and Febrile Neutropenia

Aging is associated with a progressive restriction in functional, medical, cognitive, emotional, nutritional, and socioeconomic domains due to a loss in the functional reserve of multiple organ systems, increased prevalence of comorbidities and polypharmacy, more limited social support, reduced ability to process new information and to adapt to environmental changes, and reduced income. The prevalence of age-related changes including functional dependence, comorbidity, and the risk of chemotherapy-related toxicity increase more rapidly after age 70.^{7,8} Comorbidities may be

Table 1. — Neutropenia, Febrile Neutropenia, and Treatment-Related Death in Older Patients With Non-Hodgkin's Lymphoma Treated With CHOP-like Regimens*

Author	No. of Patients	Regimen	Age	Neutropenia (%)	Febrile Neutropenia (%)	Treatment-Related Deaths (%)
Zinzani et al ¹⁰	72	VNCOP-B	60+	56	21	0
Tirelli et al ¹¹	60	VMP	70+	51	3	3
	60	CHOP	70+	47	5	2
Bastion et al ¹²	226	CTVP	70+	15**	NR	15
O'Reilly et al ¹³	63	P/DOCE	65+	50	20	8
Bertini et al ¹⁴	54	P-VEBEC	65+	46	9	2
Armitage and Potter ¹⁵	20	CHOP	70+	NR	NR	30
Osby et al ¹⁶	104	CHOP	60+	89	50	5
	100	CNOP	60+	86	50	1
Zagonel et al ¹⁷	11	CHVmP/VB	60-70	28	16	0
Total	770	All	60+	49.6	27.1	6.9

* All patients received GM-CSF prophylactically.
 ** First cycle results only.
 VNCOP-B = cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisone
 VMP = etoposide, mitoxantrone, and prednimustine
 CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone
 CTVP = cyclophosphamide, pirarubicin, vincristine, and prednisone
 P/DOCE = epirubicin or doxorubicin, vincristine, cyclophosphamide, etoposide, and prednisone
 P-VEBEC = epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin, and prednisone
 CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone
 CHVmP/VB = cyclophosphamide, doxorubicin, teniposide, prednisone, vincristine, and bleomycin
 NR = not reported

associated with reduced life expectancy as well as with reduced tolerance of particular treatments.

A number of clinical and experimental observations suggest an age-related reduction of hematopoietic stem cells in humans, including a progressive restriction in hematopoietic tissue with age that is associated with an increased mortality from infection.⁹ While there is evidence for a decline in hematopoietic reserve with age, this decline becomes clinically relevant only under conditions of stress. An increased incidence of neutropenia and FN as well as thrombocytopenia following systemic chemotherapy has also been reported.

The risk of neutropenia as well as its duration and severity has been shown to increase with the age, particularly after age 70. The risk of severe neutropenia in studies of elderly patients with non-Hodgkin's lymphoma (NHL) treated with modern chemotherapy regimens has ranged from 15% to 89%, averaging 50% across all studies (Table 1).¹⁰⁻¹⁷ The risk of FN ranged from 3% to 50%, averaging 27% across all studies. Finally, the risk of treatment-related mortality ranged from 0 to 30%, averaging 7% across all studies. Across these clinical trials, the response rate to moderately aggressive chemotherapy appeared comparable to that achieved in younger patients, with complete remission rates ranging from 46% to 67% and median survivals of 3 to 5 years. In a recent study, the addition of rituximab to CHOP chemotherapy increased complete remission rates and median disease-free survival in elderly patients with NHL.¹⁸ While not explicitly reporting on FN, fever and infection represented the major serious toxicities in patients with these regimens. The treatment protocol called for G-CSF support after episodes of severe or febrile neutropenia and was required in 37% by the fourth cycle and 43% by the eighth cycle.¹⁸

A number of efforts to identify risk factors for the occurrence of FN or its consequences in those with established FN have been reported. A systematic review of published studies of risk models for FN and its consequences has recently been published.¹⁹ Virtually every study of risk factors for neutropenic complications in patients receiving cancer chemotherapy has identified increasing age as a significant independent predictor of severe neutropenia or serious med-

ical consequences of FN, including death. 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.^{20,21} The risk of FN for various chemotherapy regimens among women aged 65 and over ranged from 5% to 23% (Fig 1). Increasing age was a significant independent predictor in multivariate model of risk of FN across a number of adjuvant breast cancer treatment regimens. Patients over 65 years of age experienced nearly twice the rate of reduced dose intensity in multivariate analyses after adjustment for the type of regimen that was utilized. In a recent prospective study of 729 women started on adjuvant chemotherapy for early-stage breast cancer, the decision to begin growth factor support was determined on the basis of the first-cycle absolute neutrophil count (ANC) nadir.²² If the first-cycle ANC was ≤ 500 cells/mm³, women were given prophylactic G-CSF for all subsequent cycles, whereas all other patients received growth factor support only if a neutropenic event actually occurred. In further analysis of these data, pretreatment factors predictive of first-cycle hematologic toxicity included age over 65, white race, use of an anthracycline-containing regimen, body surface area less than 2 M², and low baseline ANC.²³ Significant predictors of subsequent neutropenic complications including FN were age 65 years or greater and first-cycle events including ANC nadir, FN, and a drop in hemoglobin by 1 g/dL or more. While the risk of FN increases progressively as the number of risk factors increases, the presence of one or more risk factor is associated with a significantly higher cumulative risk over the course of treatment (Fig 2).

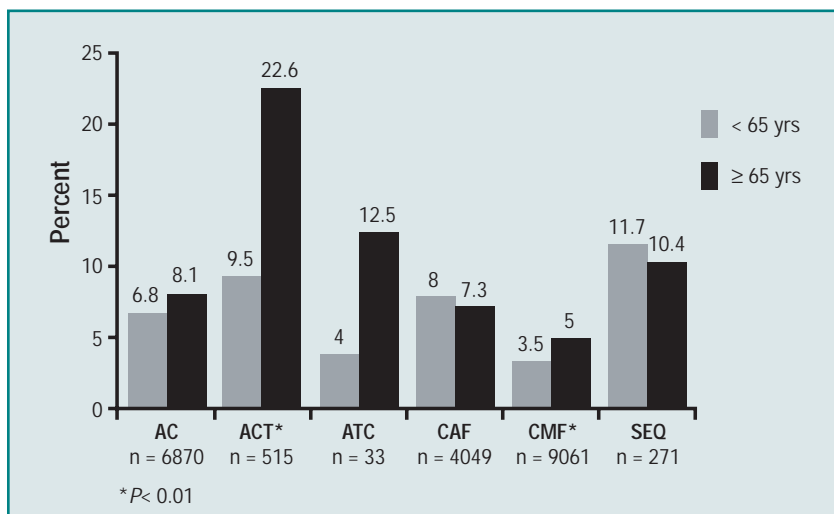


Fig 1. — Frequency of FN in approximately 20,000 women with breast cancer receiving various adjuvant chemotherapy regimens from a large practice-based survey.²⁰ The risk of FN was generally greater in older women (black bars) than in younger women (gray bars). AC = doxorubicin + cyclophosphamide, ACT = doxorubicin + cyclophosphamide followed by paclitaxel, ATC = doxorubicin + cyclophosphamide + docetaxel, CAF = cyclophosphamide + doxorubicin + 5-fluorouracil, CMF = cyclophosphamide + methotrexate + 5-fluorouracil, SEQ = sequential agents.

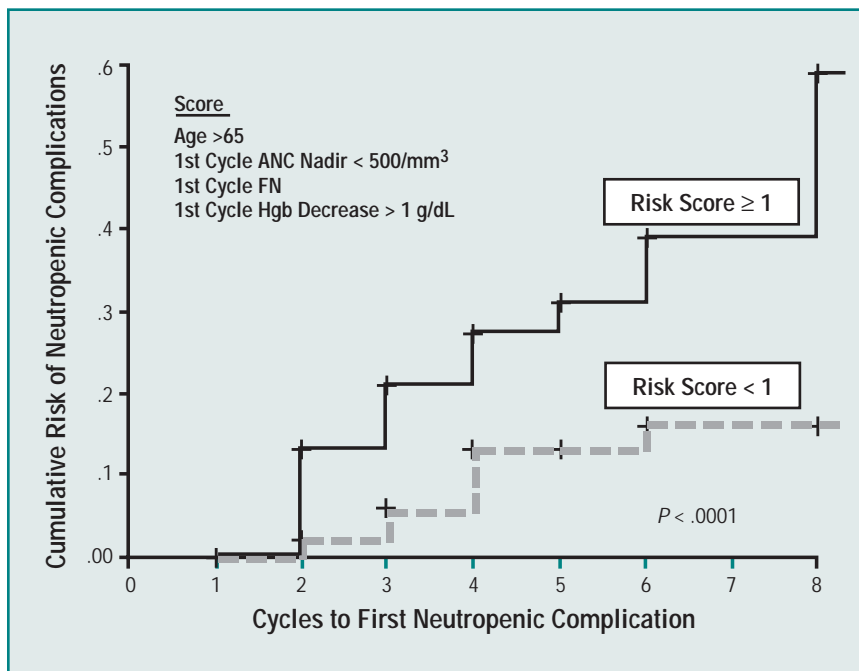


Fig 2. — Actuarial plot of the time to first subsequent neutropenic complication in women receiving adjuvant systemic chemotherapy for early-stage breast cancer. A risk score was generated based on four independently significant factors: age ≥ 65 years, first-cycle events including an FN episode, ANC $< 500/\text{mm}^3$, and a decrease in hemoglobin > 1 g/dL. Shown are the cumulative risk of subsequent neutropenic events in those with no risk factors and those with one or more risk factors ($P < .0001$).²³

Age and the Timing of Severe and Febrile Neutropenia

The risk of a neutropenic event including FN is not uniformly distributed across treatment courses. The risk of FN with each cycle depends on dose intensity, age, growth factor usage, and prior treatment. Thus, in patients continuing to receive full dose intensity, the risk may increase with each subsequent cycle, with the greatest risk for those who have experienced FN on a previous cycle. However, the risk of the initial FN event appears to be greatest during the first one or two cycles of chemotherapy. The risk of initial FN in 577 patients with NHL receiving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy demonstrated that 58% of patients destined to experience one or more episodes of FN do so during the first cycle of CHOP.^{24,25} Risk factors for early FN event included age, low hemoglobin, patients with heart or renal disease, planned dose intensity $> 80\%$, and the failure to provide primary G-CSF prophylaxis. We have recently reported a doubling of the risk of FN in patients receiving

CHOP therapy for NHL over the age of 65. The major difference in risk of the initial episode of FN in older patients is observed during the first cycle of CHOP chemotherapy (Fig 3).

Age and the Risk of Medical Complications of Febrile Neutropenia

Recent studies have demonstrated that the risk of serious medical complications including death is greater among elderly cancer patients receiving chemotherapy than in younger patients, even after adjustment for severe burden of illness, complexity of infection, uncontrolled cancer, or neutrophil counts on admission. Age was a significant predictor of serious medical complications, including death, among patients with FN evaluated by the Multinational Association for Supportive Care in Cancer scoring system.²⁶ In this multinational study of more than 1,100 episodes of FN from 15 countries, analysis of 339 episodes in patients with solid tumors, excluding marrow/stem cell transplants and patients receiving therapeutic CSF, demonstrated that age over 60 was a signifi-

cant predictor of serious medical complications, including death, among patients with FN evaluated by the Multinational Association for Supportive Care in Cancer scoring system.²⁶ In this multinational study of more than 1,100 episodes of FN from 15 countries, analysis of 339 episodes in patients with solid tumors, excluding marrow/stem cell transplants and patients receiving therapeutic CSF, demonstrated that age over 60 was a signifi-

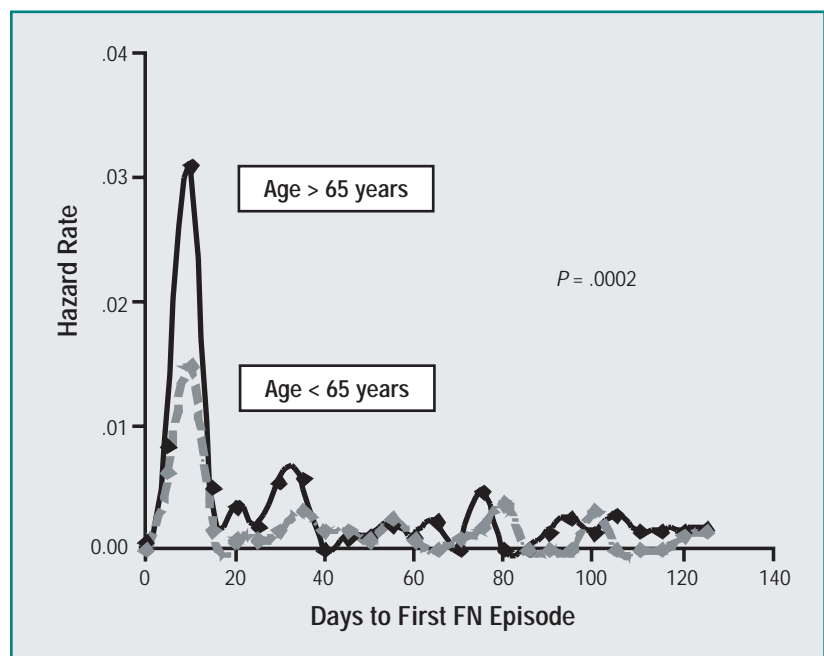


Fig 3. — Hazard plot of the time (in days) to the first episode of FN in 577 patients with non-Hodgkin's Lymphoma treated with CHOP chemotherapy stratified by age 65 and over vs under 65 years ($P = .0002$).²⁴

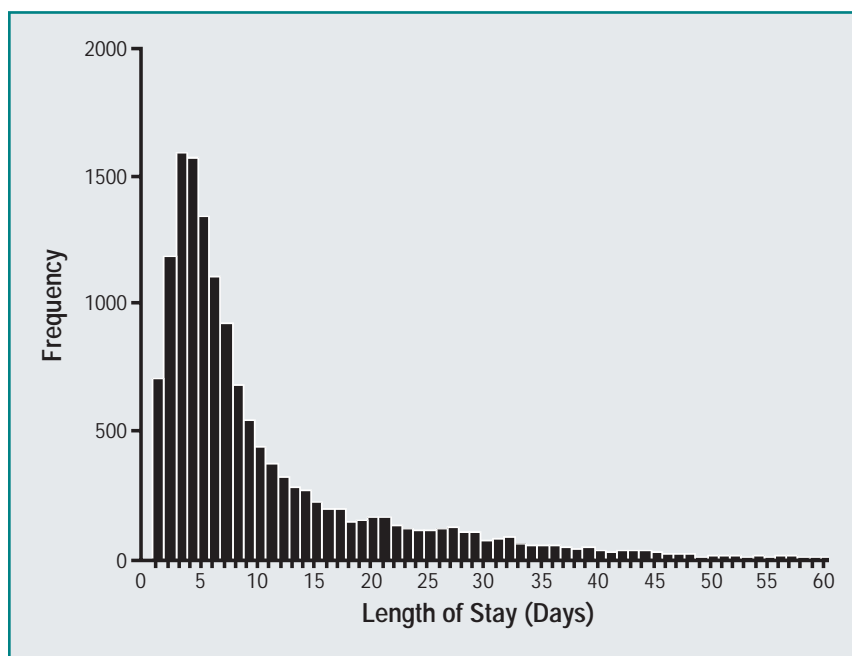


Fig 4. — Frequency distribution of the length of stay (in days) among adult cancer patients age 65 and over (excluding bone marrow transplantation patients) hospitalized for FN in institutions reporting to the University HealthSystem Consortium, 1995-2000.²⁷

icant risk factor for risk of serious medical complications in multivariate analysis (odds ratio [OR] = 4.36; $P < .004$).

In a recent study of more than 55,000 episodes of FN reported to the University HealthSystem Consortium over a 6-year period, associated mortality was significantly increased among those age 65 and older (OR = 1.55 [1.45, 1.65]; $P < .001$).²⁷ Thus, the consequences of severe and febrile neutropenia in older individuals may be devastating, leading to early death or serious illness associated with functional dependence requiring prolonged and costly rehabilitation.

Age and the Cost of Febrile Neutropenia

The major economic impact of neutropenic complications is the cost associated with hospitalization and the ensuing length of stay. Economic studies of FN in the multiple institutions reporting discharge data to the University HealthSystem Consortium including 115 academic medical centers have been reported.^{28,29} A total of 55,276 episodes of FN in 41,779 adult non-transplant patients have been reported over a 6-year period. The average age of the patients was 53.6 years, 73% were white, and 54% were women; 53%

had a solid tumor, 26% had lymphoma, and 21% had leukemia. As shown in Fig 4, the distribution of length of stay among the 14,741 patients over the age of 65 is skewed to the right, with a median length of stay of 6 days but a mean of 10.7 days in this population. Longer lengths of stay were associated with more frequent comorbidities, complications, and mortality. Hospital mortality increased progressively with increasing age (Fig 5). As shown for the population as a whole, the cost of caring for FN among patients age 65 and older increased over the 6 years of observation from \$1,275 (US) per day to over \$1,700 per day, with the total cost per episode of FN increasing approximately 25% over this time period (Fig 6).

Age and Reduced Chemotherapy Dose Intensity

In the community-based study of 20,799 women receiving various adjuvant breast cancer chemotherapy regimens discussed above, older women were also more likely to experience significant reductions in dose intensity relative to either target dose intensity or published reference standards with these regimens.^{20,21} The proportion of women receiving less than 85% of reference standard dose intensity was 53% for those less than 65 and 67% in those age 65 and over (Fig 7). In fact, nearly

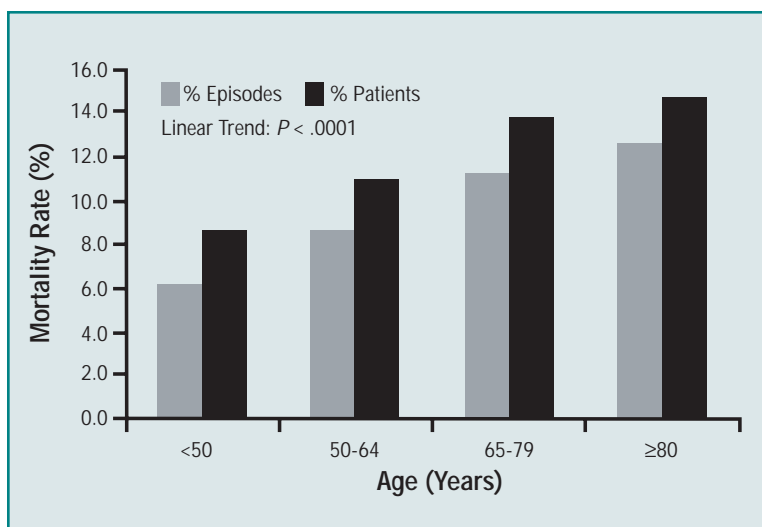


Fig 5. — Risk of mortality across age groups based on deaths as a proportion of patients (black bars) or deaths as a proportion of admissions (gray bars) among patients admitted for FN to institutions reporting to the University HealthSystem Consortium, 1995-2000.²⁷

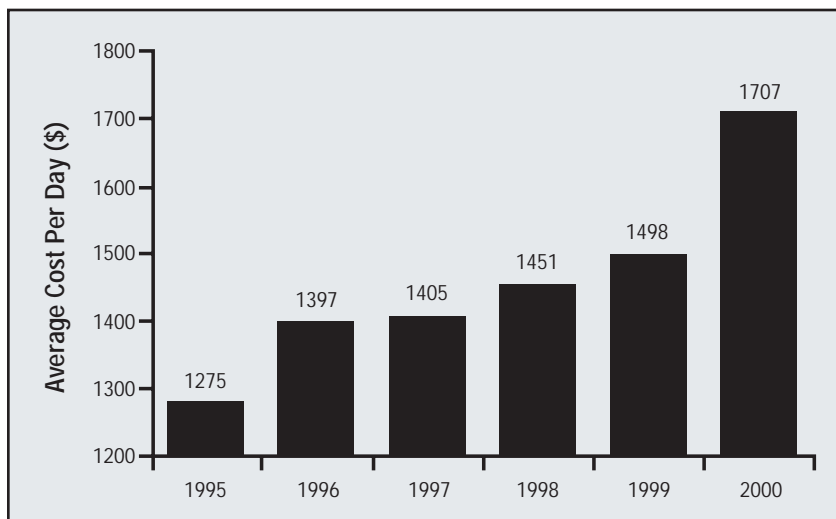


Fig 6. — Distribution of mean cost per day for patients age 65 and over admitted with FN to institutions reporting to the University HealthSystem Consortium from 1995 to 2000.²⁹

15% of women over age 65 received less than 50% of reference-standard dose intensity in this study. Multivariate analysis identified several significant independent predictors of reduced relative dose intensity, including increased age, positive axillary nodes, negative estrogen receptors, and high body surface area as well as CMF (cyclophosphamide, methotrexate, and fluorouracil) or CAF (cyclophosphamide, doxorubicin, and fluorouracil) chemotherapy regimen and 28-day schedules.

Age and the Effectiveness of Hematopoietic Growth Factors

Several studies of the efficacy of the CSFs on the prevention of neutropenic complications including infection risk associated with cancer chemotherapy in a variety of malignancies using different chemotherapy regimens have been reported.^{5,30-36} Controlled clinical trials conducted in both Europe and the United States have demonstrated the ability of recombinant human G-CSF (rHu-G-CSF, filgrastim) to reduce the risk of FN associated with systemic chemotherapy when administered prophylactically prior to the onset of fever or neutropenia. A systematic review with a formal meta-analysis of all randomized, controlled trials of prophylactically administered G-CSF in patients receiving cancer chemotherapy was recently reported.⁶ Summary estimates across the eight trials that were identified confirmed

a high level of efficacy and safety across a wide variety of disease entities and treatment regimens (OR = 0.38; $P < .001$). In addition, patients randomized to receive G-CSF experienced fewer episodes of documented infection (OR = 0.51; $P < .001$) as well as fewer dose reductions and treatment delays (OR = 0.32; $P < .001$). The OR ($\pm 95\%$ CLs) for mortality was 0.60 (0.30, 1.22), suggesting but not proving a 40% reduction in the odds of mortality ($P = .16$).

Although the sensitivity of hematopoietic progenitors to endogenous cytokines may be compromised in the elderly, sensitivity to therapeutic doses of recombinant G-

CSF appears well maintained. The effectiveness of G-CSF in older patients has been established in a number of studies.³⁷ A systematic review of controlled clinical trials totaling nearly 700 patients with NHL demonstrated that the use of G-CSF in older patients is associated with decreased risk of severe and febrile neutropenia³⁸ (Table 2). The risk of severe and febrile neutropenia was 72% and 36%, respectively, across all comparative trials for those not receiving CSF and 44% and 22%, respectively, among those receiving CSF support. Focusing only on the randomized, controlled trials, the risk of severe and febrile neutropenia was 79% and 42%, respectively, among those not receiving CSFs and 50% and 25%, respectively, among those receiving CSF

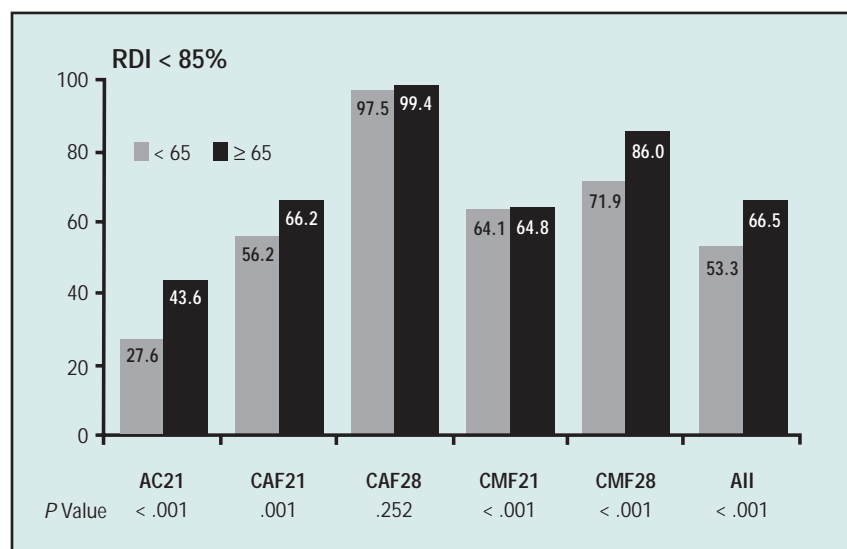


Fig 7. — Frequency of reduced relative dose intensity (RDI) <85% compared to published reference standards in approximately 20,000 women with breast cancer receiving various adjuvant chemotherapy regimens from a large practice-based survey.²¹ The risk of FN was generally greater in older women (black bars) than in younger women (gray bars). AC = doxorubicin + cyclophosphamide, CAF = cyclophosphamide + doxorubicin + 5-fluorouracil, CMF = cyclophosphamide + methotrexate + 5-fluorouracil.

support. In a formal meta-analysis, the summary OR estimates $\pm 95\%$ CIs for severe and febrile neutropenia among those receiving growth factor for all trials were 0.26 (0.19, 0.36; $P < .0001$) and 0.24 (.17, .35; $P < .0001$), respectively (Fig 8A). Likewise, the summary OR estimates for severe neutropenia and febrile neutropenia for the randomized, controlled trials were .44 (.31, .62; $P < .0001$) and .45 (.31, .64; $P < .0001$), respectively (Fig

8B). As also shown in Table 2, the risk of FN was 22% among those receiving CSF compared with 35% in controls. No significant difference in complete remission rates and disease-free survival was observed across all trials combined. However, in the recent study by Osby et al,¹⁶ elderly patients randomized to G-CSF support not only experienced fewer episodes of severe or febrile neutropenia, but also received a greater propor-

Table 2. — Efficacy of Colony-Stimulating Factors in Older Patients With Non-Hodgkin's Lymphoma Receiving CHOP-like Combination Chemotherapy

Study	Randomized	Chemotherapy	G-CSF	No. of Patients	Grade 4 Neutropenia (%)	Febrile Neutropenia (%)
Zinzani et al ¹⁰	Yes	VNCOP-B	Yes	77	23	5
			No	72	56	21
Zagonel et al ¹⁷ *	No	CHOP	Yes	12	5	5
			No	11	28	16
Bertini et al ¹⁴	No	P-VEBEC	Yes	46	22	2
			No	54	46	9
Osby et al ¹⁶	Yes	CHOP	Yes	101	55	34
			No	104	89	50
Osby et al ¹⁶	Yes	CNOP	Yes	103	64	32
			No	100	86	50
All Trials			Yes	339	44.5	21.5
			No	341	72.4	36.4
All Randomized Clinical Trials			Yes	281	49.8	25.2
			No	276	79.3	42.3

* Percent of chemotherapy courses (grade 3/4 neutropenia)
VNCOP-B = cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisone
CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone
P-VEBEC = epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin, and prednisone
CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone

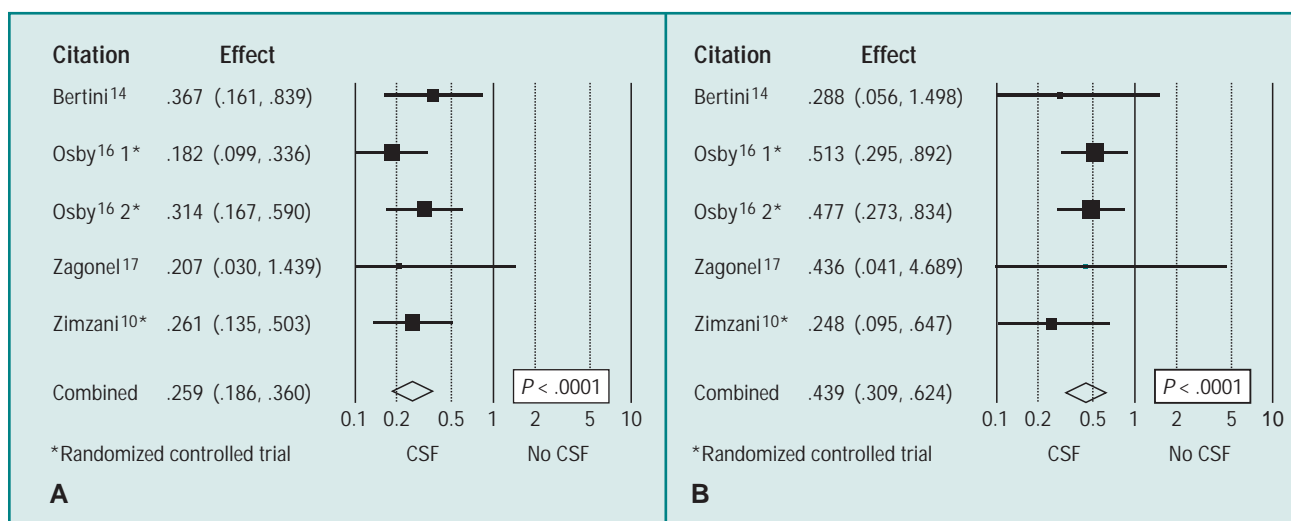


Fig 8. — Forrest plots of the Peto odds ratios among five controlled trials of prophylactic G-CSF vs control in elderly patients with non-Hodgkin's lymphoma along with a weighted summary measure across trials. The size of the point estimate rectangles are inversely proportional to the variance associated with each study. Also shown are the 95% confidence limits for each estimate. Results are shown for all controlled trials including randomized, controlled trials (*) for severe neutropenia (A) and febrile neutropenia (B). All studies demonstrate an effect estimate below 1.0 favoring G-CSF. The study by Osby et al¹⁶ included four arms: two with CNOP and two with CHOP, each with and without G-CSF support. Due to the large difference in outcome based on the type of chemotherapy, accompanying heterogeneity, and apparent interaction between chemotherapy regimen and growth factor support for the primary outcomes, these are displayed separately as Osby1 (CHOP) and Osby2 (CNOP), respectively.

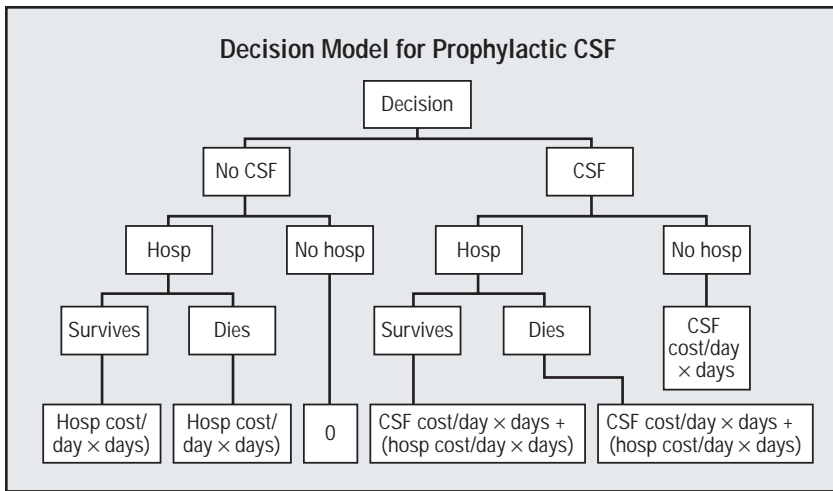


Fig 9. — Decision tree for a cost minimization model of the use of prophylactic CSF or no CSF in chemotherapy patients at risk for FN. The model assumes all patients with FN are hospitalized (Hosp), the risk of hospitalization for FN in those receiving prophylactic G-CSF is reduced by 50%, and equal duration of hospitalization and mortality among those hospitalized for FN in both groups. Cost considerations are limited to those related to hospitalization for FN (average length of stay × average cost/day (\$) and G-CSF (average duration of administration × average cost/day for drug and administration). Patients not hospitalized and not receiving G-CSF have no associated costs.⁴²

tion of planned chemotherapy dose intensity than patients not receiving G-CSF. While CNOP chemotherapy (doxorubicin replaced with mitoxantrone) was associated with worse time to failure and overall survival, CHOP-treated patients supported with G-CSF experienced significantly longer overall survival than those not receiving G-CSF ($P=.045$).

Economic Analysis of the Colony-Stimulating Factors in the Elderly

Economic Analyses

Management of older individuals with cancer is often more costly and less cost-effective than that of managing younger patients due to increased risk of therapeutic complications and the reduced potential for benefit due to limited life expectancy and less responsive malignancies than in younger patients.^{2,3} 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 increased. When clinical outcomes differ, the most commonly utilized approach is that of cost-effectiveness. 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. However, when clinical outcomes are not considered substantially different, the focus of the economic analysis is directed at minimizing cost or choosing the approach associated with the least cost. A variety of economic analyses of the hematopoietic growth factors have been presented over the last several years.³⁹⁻⁴¹

Cost-Minimization Models

A decade ago Lyman et al^{42,43} undertook a cost minimization analysis based on a decision analytic model incorporating the results of the pivotal randomized, controlled trial of G-CSF reported by Crawford and colleagues⁵ (Fig 9). This study concluded that when only itemized direct medical costs of hospitalization at a single institution are considered, the use of G-CSF is associated with an overall cost savings in situations when the risk of FN is 40% or higher. Above this threshold, a net cost savings is estimated, while below the threshold a net excess cost is projected, although their continues to be offsetting cost for CSF through the reduction in hos-

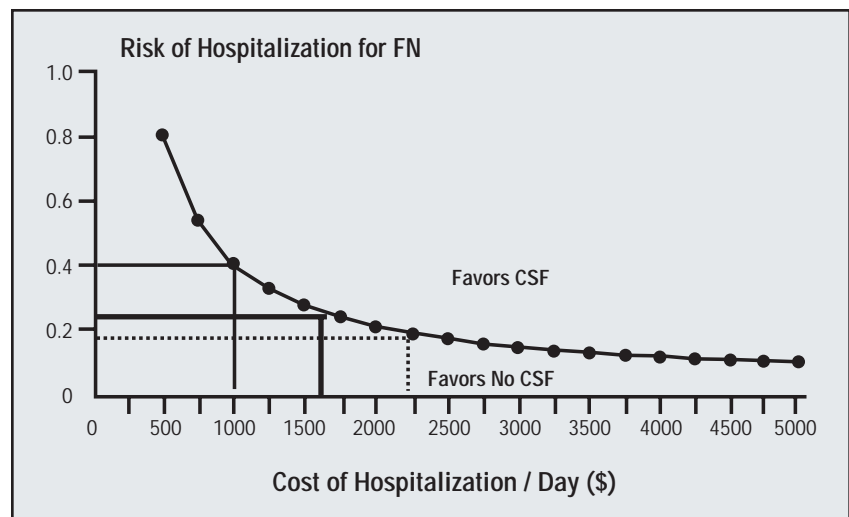


Fig 10. — Two-way sensitivity analysis of the threshold for cost associated with FN hospitalization and G-CSF use based on the decision model shown in Fig 9. The horizontal axis varies the cost/day (\$) for hospitalization and the vertical axis varies the risk of FN hospitalization. The threshold curve demonstrates lower thresholds for cost-saving use of G-CSF with increasing cost of hospitalization. Combinations of risk and cost above the threshold are associated with a reduction in cost with the use of prophylactic G-CSF, and those below the threshold curve are associated with greater cost with the use of G-CSF. Three sequential cost estimates and the accompanying risk threshold are shown: thin line = based on the original estimate of direct medical costs for hospitalization (threshold = 40%),⁴² thick line = based on revised cost estimates of total hospital costs (threshold = 23%),⁴⁴ and dotted line = based on full cost estimates including total hospital costs and indirect costs (threshold = 18%).⁴⁶

pitalization for FN. In a more recent analysis including the total direct institutional costs of treating FN, threshold risks in the range of 20% to 25% were estimated (Fig 10).⁴⁴ This study also demonstrated that patients with FN are heterogeneous, with low-risk patients experiencing relatively uncomplicated short-term admissions and high-risk patients being likely to have more complicated and prolonged hospitalizations that account for the majority of cost. Based on a recent meta-analysis,⁶ the threshold risk of FN when managing high-risk patients such as the elderly was found to be less than 20%. In sensitivity analysis, the cost-saving threshold decreases as the cost per day and length of stay for FN increase. These models have been further expanded and refined to consider indirect and out-of-pocket costs as well as quality of life, incorporation of an ambulatory treatment option for FN in selected low risk patients, and the use of predictive models permitting individualization of risk estimation and selection of high-risk patients for targeted G-CSF prophylaxis.

Incorporation of Indirect Costs

Estimated additional indirect and patient out-of-pocket costs have been incorporated into the cost-minimization model discussed above for the prophylactic use of the CSFs. These costs were added to the direct costs of hospitalization for FN as well as for those of the growth factor and its administration.^{45,46} The additional costs in the branches for patients treated with prophylactic CSF were adjusted based on an assumption of efficacy of a risk reduction of severe neutropenia of 50% with prophylactic CSF. A sensitivity analysis was then conducted across a range of potential indirect cost estimates from \$0 to \$5,000 per inpatient FN episode. As the estimates for indirect costs increase, the threshold favoring the use of CSF decreases from the baseline estimate. When the indirect and patient out-of-pocket costs attributable to severe neutropenia approach that estimated from the survey data of \$3,834 per episode, the risk threshold is reduced to 18% (Fig 10).

Incorporation of Quality of Life Considerations

Little investigation has been conducted on the impact of neutropenia and its complications on quality of life or on the impact of the CSFs. Preliminary efforts to study the impact of severe neutropenia on patient quality of life have been reported using various health profile measures. In a series of studies in a practice setting, changes in quality of life were measured weekly in patients scheduled to receive myelosuppressive chemotherapy without growth factor support using the Short-Form 36 (SF-36), the Hospital Anxiety and Depression Scale, and the Psychological Adjustment to

Illness Scale.^{47,48} Significant correlations were observed between changes in neutrophil counts and measures of physical functioning, general health, vitality, and mental health. The greatest decrease in quality of life was observed in patients with grade 4 neutropenia. An effort is currently underway to develop a more sensitive and specific measure for detected changes associated with severe or febrile neutropenia in patients undergoing cancer chemotherapy. This approach is modeled after the Functional Assessment of Cancer Therapy (FACT) health profile scales and is termed the FACTN. The current version of the tool consists of 19 questions generated from semistructured interviews and previous studies. The measure has been found to have good construct validity and internal consistency.⁴⁹

Additional early efforts have attempted to evaluate the impact of neutropenia and the hematopoietic growth factors on patient quality of life by eliciting patient preferences or utilities for anticipated health states. Using techniques such as a standard reference gamble and time trade-off, quality of life can be assessed more globally but without detailed information about the impact on the various dimensions of quality of life. Preliminary data assessed as willingness to pay to avoid FN corresponded to daily costs ranging from \$0 to \$500. The generated utilities may permit the conduct of useful cost-utility analyses even in the absence of proven effects on patient survival and will also extend previous work on the incorporation of quality of life measures into cost minimization risk threshold models.⁵⁰ The issue of quality of life assessment and the impact of G-CSF in patients with cancer and HIV has been recently reviewed.⁵¹

Incorporation of an Ambulatory Treatment Option

It is now possible to identify a population of patients at lower risk for serious medical complications and thus potential candidates for outpatient treatment of FN with antibiotics with or without G-CSF. The Multinational Association for Supportive Care in Cancer has developed a formal scoring system for evaluating cancer patients with FN for possible outpatient management.²⁶ It has been suggested that such an approach will reduce the costs associated with episodes of FN based on the reduced need for hospitalization of a proportion of these patients.^{52,53} The limitations of this approach have been extensively discussed including (1) the need for a nearly zero predictive value negative, (2) the need for a substantial (and costly) infrastructure and organization to manage patients with FN as outpatients, and (3) the large number of logistical and social issues that must be addressed (eg, proximity to the healthcare facility,

availability of a full-time caretaker, sufficient awareness and education concerning the seriousness of the condition). These issues are potentially problematic for the management of FN in the elderly cancer patient. Nevertheless, it has also been suggested that the reduction in cost that is likely with outpatient management of patients with FN will have a direct impact on raising cost-minimization thresholds that are largely driven by the costs of hospitalization for FN. However, such an approach will likely increase indirect and out-of-pocket expenses to the family and other caretakers. More fundamentally, patients with FN are a heterogeneous population with considerable variation in length of stay and in the potential risk for serious medical complications, including death. In fact, high-risk patients with long hospitalizations drive most of the associated cost, while low-risk patients generally have relatively short hospitalizations and contribute a relatively small proportion of the costs associated with FN. This association, combined with the cost of the required infrastructure to develop and maintain an ambulatory FN treatment program, questions the economic impact of such a strategy, particularly in the care of the elderly patient with FN. A recent analysis of an economic model for the use of the CSFs incorporating an ambulatory treatment strategy for low-risk FN patients demonstrated that such an approach has minimal impact on risk thresholds for CSF use due to the continued need for hospitalization of high-risk individuals who generate longer hospitalizations and greater cost.⁵⁴

Clinical Prediction (Risk) Models

The use of CSFs in all patients at risk for severe neutropenia or its complications has been considered cost prohibitive. Selecting patients for CSF use has generally been based on the previous occurrence of such complications, the intensity of the chemotherapy regimen selected, or the clinical perception of risk. Several investigators have attempted to complement such considerations in order to improve the ability to predict those at greatest risk of neutropenia.^{55,56} Virtually all of these efforts have led to the conclusion that increasing age is one of the strongest risk factors for the occurrence of FN or its serious medical consequences, including death. In addition, increasing age has been associated with considerable decreases in dose intensity in this population, potentially compromising long-term disease control. As we and others have shown, consideration of comorbidities as well as disease and treatment-related factors permits the more accurate discrimination of high- and low-risk patients, thus allowing the more effective and cost-effective application of the CSFs in those in greatest need and most likely to benefit. In malignancies that require moderately intensive

chemotherapy such as the NHLs, age appears to be associated with sufficient risk of FN and its complications within the first one or two cycles to provide compelling clinical and economic arguments for primary prophylaxis of all patients receiving such regimens with G-CSF.²⁴ Incorporation of a risk-model-targeted strategy for primary prophylaxis in NHL into an economic model discussed above demonstrates that in high-risk populations, eg, the elderly, primary prophylaxis of all patients represents the most cost-effective approach.

In other responsive malignancies that are often treated with less aggressive chemotherapy regimens, such risk models can enhance the cost-effective use of the CSFs. Silber and colleagues⁵⁷ described a clinical prediction model that was based on a population receiving adjuvant breast cancer chemotherapy and incorporated baseline and first-cycle hematologic data. The model was capable of discriminating high-risk women for future neutropenic complications, which might compromise dose intensity and long-term outcome. Based on the importance of sustained dose intensity on disease-free survival reported in patients with early-stage breast cancer, Silber et al⁵⁸ studied a strategy of targeted G-CSF support in the one-half of women at greatest risk in order to sustain dose intensity compared with a standard dose-reduction strategy in such patients. The estimated cost effectiveness for the G-CSF support strategy for high-risk patients of \$34,000 per life-year gained was reasonably robust across a range of baseline assumptions. The value of such a simple prediction tool for reducing the risk of neutropenic complications with targeted use of the CSFs has been validated prospectively.²² As discussed previously, women receiving adjuvant breast cancer chemotherapy who were assigned to G-CSF using a simple risk model consisting of the first-cycle ANC nadir experienced fewer episodes of hospitalization for FN ($P < .001$) and greater dose intensity ($P = .003$) than historical controls without such a strategy. It has also been shown in this same population that consideration of age and first-cycle events (eg, FN, a drop in hemoglobin >1 g/dL, ANC nadir $<500/\text{mm}^3$) permits more accurate risk prediction.²³ Patients age 65 and older who experience severe or febrile neutropenia and/or a drop in hemoglobin >1 g/dL during the first cycle of chemotherapy experience a subsequent risk of FN in the range of 10% to 20% and all neutropenic complications of 30% to 40%. These data thus provide compelling clinical and economic arguments for subsequent prophylaxis with G-CSF of all additional cycles in elderly patients experiencing significant first-cycle hematologic toxicity in order to reduce serious complications and sustain chemotherapy dose intensity.

Efforts are underway to develop more accurate risk models and to validate their use based on prospective-

ly collected data to assist clinicians in the selection of high-risk patients and the targeting of supportive care measures such as the CSFs.⁵⁹ The economic impact of incorporation of a risk or clinical prediction model into a treatment decision pathway for the management of patients at risk for FN depends on the risk of FN in the population and the test performance characteristics of the model. As more accurate risk models are developed that are independently validated in a variety of clinical settings, their value to clinicians in providing optimal care to the cancer chemotherapy patient as well as to society in terms of obtaining the most value with limited resources can be anticipated.

Conclusions and Recommendations for Colony-Stimulating Factor Use in the Elderly

We conclude that older individuals receiving myelosuppressive chemotherapy are at increased risk for severe and febrile neutropenia, which may result in mortality from overwhelming infection. The morbidity and perhaps mortality associated with severe or prolonged neutropenia can be reduced by the use of hematopoietic growth factors. Recently updated guidelines for the hematopoietic growth factors from the American Society of Clinical Oncology have only partially addressed issues related to the elderly cancer patient.³⁷ Specific recommendations for the use of the hematopoietic growth factors in the elderly cancer patient have recently been developed for the National Comprehensive Cancer Network (NCCN) including (1) using the CSFs prophylactically in cancer patients aged 70 and older receiving chemotherapy with the dose intensity of CHOP, (2) maintaining hemoglobin levels at ≥ 12 g/dL with erythropoietin, and (3) adjusting renally excreted drugs to the patient's glomerular filtration rate.⁴¹ Similar recommendations have recently been presented by the EORTC Cancer in the Elderly Task Force.⁶⁰

The studies reviewed here support primary prophylaxis with G-CSF in patients aged 70 and older treated with regimens of comparable dose intensity to that of CHOP. In addition, the data support the subsequent use of G-CSF in older patients experiencing severe or febrile neutropenia and anemia during the initial cycle of adjunctive chemotherapy for early-stage breast cancer. These recommendations are based primarily on clinical efforts to provide optimal efficacious chemotherapy, to reduce life-threatening toxicity, and to improve quality of life in the elderly population. However, with the continuing rise in healthcare costs associated with hospitalization for FN, the economic arguments supporting the use of prophylactic G-CSF in elderly cancer patients are increasingly strong. The introduction of a potentially

more effective and long-acting pegylated G-CSF provides additional opportunities for the optimally effective, safe, and convenient supportive care of elderly patients receiving cancer chemotherapy.

Note

Since this manuscript was accepted for publication, an additional randomized controlled trial of CHOP chemotherapy with and without G-CSF support in patients age 65 to 90 with aggressive non-Hodgkin's lymphoma (NHL) has been reported.⁶¹ Fewer infectious complications were observed with G-CSF during the first cycle when patients were receiving full-dose chemotherapy (20% vs 32%). There was no difference in overall mortality with 123 deaths in each study arm, most of which were due to NHL. Deaths due to infection were reduced in those receiving G-CSF (16 vs 11), but the difference did not reach statistical significance. The number of patients dying of unknown causes was also imbalanced favoring G-CSF (11 vs 4). If infectious and unknown deaths are combined, G-CSF treatment was associated with lower cause-specific mortality than non G-CSF ($P=.04$).

Note that this study utilized an unconventional fixed dose of G-CSF of 300 μ g daily regardless of patient weight. This may have led to a consistent under-dosing of G-CSF in approximately 85% of the patients in this study. In addition, the study was underpowered (50%) for the primary endpoints of disease-free and overall survival. It was completely underpowered for the quality of life and economic measures collected in small subgroups of patients, so no meaningful conclusions can be drawn from these results.

References

1. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. *CA Cancer J Clin*. 2003;53:5-26.
2. Lyman GH. Essentials of clinical decision analysis: a new way to think about cancer and age. In: Balducci L, Lyman GH, Erschler W, eds. *Comprehensive Geriatric Oncology*. London: Harwood Academic Publishers; 1998:7-17.
3. Lyman GH, Kuderer N, Balducci L. Cancer care in the elderly: cost and quality of life considerations. *Cancer Control*. 1998;5:347-354.
4. Chatta GS, Dale DC. Aging and haemopoiesis: implications for treatment with haemopoietic growth factors. *Drugs Aging*. 1996; 9:37-47.
5. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med*. 1991;325:164-170.
6. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. *Am J Med*. 2002;112:406-411.
7. Marley SB, Lewis JL, Davidson RJ, et al. Evidence for a continuous decline in haemopoietic cell function from birth: application to evaluating bone marrow failure in children. *Br J Haematol*. 1999; 106:162-166.
8. Extermann M, Overcash J, Lyman GH, et al. Co-morbidity and

functional status are independent in older cancer patients. *J Clin Oncol*. 1998;16:1582-1587.

9. Balducci L, Hardy CL, Lyman GH. Hemopoietic reserve in the older cancer patient: clinical and economic considerations. *Cancer Control*. 2000;7:539-547.

10. Zinzani PL, Pavone E, Storti S, et al. Randomized trial with or without granulocyte colony-stimulating factor as adjunct to induction VNCOP-B treatment of elderly high-grade non-Hodgkin's lymphoma. *Blood*. 1997;89:3974-3979.

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

12. 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.

13. 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.

14. 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.

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

16. Osby E, Hagberg H, Kvaloy S, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. *Blood*. 2003;101:3840-3848.

17. Zagonel V, Babare R, Merola MC, et al. Cost-benefit of granulocyte colony-stimulating factor administration in older patients with non-Hodgkin's lymphoma treated with combination chemotherapy. *Ann Oncol*. 1994;5(suppl 2):127-132.

18. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med*. 2002;346:235-242.

19. Lyman GH, Lyman C, Ogboola Y. Risk models for the prediction of chemotherapy-induced neutropenia. *Neutropenia Oncol*. 2001;1:2-7.

20. Lyman GH, Dale D, Crawford J. Incidence, practice patterns, and predictors of low dose intensity in adjuvant breast cancer chemotherapy: results of a nationwide survey of community oncology practices. *J Clin Oncol*. 2003;21. In press.

21. Paridaens R, Lyman GH, Leonard R, et al. Delivering optimal adjuvant chemotherapy in primary breast cancer: the role of rHuG-CSF. *Eur J Cancer*. 2003;1(suppl 9):1-12.

22. Rivera E, Erder MH, Moore TD, et al. Targeted filgrastim support in patients with early-stage breast carcinoma: toward the implementation of a risk model. *Cancer*. 2003;98:222-228.

23. Lyman GH. Risk assessment in oncology clinical practice: from risk factors to risk models. *Oncology*. 2003. In press.

24. Lyman GH, Morrison VA, Dale DC, et al, for the ANC Study Group. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. *Leuk Lymphoma*. 2003;44:2069-2076.

25. Lyman GH, Delgado D. Risk and timing of hospitalization for febrile neutropenia in patients receiving CHOP, CHOP-R, or CNOP chemotherapy for intermediate-grade non-Hodgkin's lymphoma. *Cancer*. 2003. In press.

26. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk-index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18:3038-3051.

27. Lyman GH, Kuderer NM. Cost effectiveness of myeloid growth factors in cancer chemotherapy. *Curr Hematol Rep*. 2003;2:471-479.

28. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. *Supp Cancer Ther*. 2003;1:1-13.

29. Lyman GH, Kuderer NM. Economics of hematopoietic growth factors. In: Morstyn G, Foote M, Lieschke GJ, eds. *Hematopoietic Growth Factors in Oncology: Basic Science and Clinical Therapeutics*. Totowa, NJ: Humana Press Inc; 2003:409-443.

30. Trillet-Lenoir V, Green JA, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer*. 1993;29A:319-324.

31. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood*. 1992;80:1430-1436.

32. Chevallier B, Chollet P, Merrouche Y, et al. Lenograstim prevents morbidity from intensive induction chemotherapy in the treatment of inflammatory breast cancer. *J Clin Oncol*. 1995;13:1564-1571.

33. Bui BN, Chevallier B, Chevreau C, et al. Efficacy of lenograstim on hematologic tolerance to MAID chemotherapy in patients with advanced soft tissue sarcoma and consequences on treatment dose-intensity. *J Clin Oncol*. 1995;13:2629-2636.

34. Zinzani PL, Pavone E, Storti S, et al. Randomized trial with or without granulocyte colony-stimulating factor as adjunct to induction VNCOP-B treatment of elderly high-grade non-Hodgkin's lymphoma. *Blood*. 1997;89:3974-3979.

35. Gisselbrecht C, Haioun C, Lepage E, et al. Placebo-controlled phase III study of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) in aggressive non-Hodgkin's lymphoma: factors influencing chemotherapy administration. Groupe d'Etude des Lymphomes de l'Adulte. *Leuk Lymphoma*. 1997;25:289-300.

36. Fossa SD, Kaye SB, Mead GM, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. *J Clin Oncol*. 1998;16:716-724.

37. Balducci L, Lyman GH. Patients aged > or = 70 are at high risk for neutropenic infection and should receive hemopoietic growth factors when treated with moderately toxic chemotherapy. *J Clin Oncol*. 2001;19:1583-1585.

38. Lyman GH, Balducci L, Agboola Y. Use of hematopoietic growth factors in the older cancer patient. *Oncol Spectrums*. 2001;2:414-421.

39. Lyman GH, Kuderer NM, Balducci L. Economic impact of granulopoiesis stimulating agents on the management of febrile neutropenia. *Curr Opin Oncol*. 1998;10:291-296.

40. Lyman GH, Balducci L. Update of the economic analyses of the use of the colony-stimulating factors. *Curr Opin Hematol*. 1999;6:145-151.

41. Lyman GH, Kuderer NM, Balducci L. Cost-benefit analysis of granulocyte colony-stimulating factor in the management of elderly cancer patients. *Curr Opin Hematol*. 2002;9:207-214.

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

43. Lyman GH, Balducci L. A cost analysis of hematopoietic colony-stimulating factors. *Oncology (Huntingt)*. 1995;9:85-91.

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

45. Calhoun EA, Chang CH, Welshman EE, et al. Evaluating the total costs of chemotherapy-induced toxicity: results from a pilot study with ovarian cancer patients. *Oncologist*. 2001;6:441-445.

46. Cosler L, Calhoun E, Agboola O, et al. Impact of indirect and patient out-of-pocket costs on the risk threshold for prophylaxis with colony-stimulating factors in patients at risk for neutropenic complications from cancer chemotherapy. *Pharmacotherapy*. 2003. In press.

47. Fortner BV, Stolshek B, Schwartzberg LS, et al. Decline in absolute neutrophil count (ANC) is associated with lower quality of life (QOL) in cancer patients receiving docetaxel. *Proc Annu Meet Am Soc Clin Oncol*. 2002;21:2808. Abstract.

48. Okon TA, Fortner BV, Schwartzberg L, et al. Quality of life (QOL) in patients with grade IV chemotherapy-induced neutropenia (CIN). *Proc Annu Meet Am Soc Clin Oncol*. 2002;21:2920. Abstract.

49. Calhoun EA, Chang CH, Welshman EE, et al. A neutropenia-specific quality of life instrument: rationale for the development of

the FACT-N. *Proc Annu Meet Am Soc Clin Oncol*. 2002;21:1498. Abstract.

50. Lyman GH, Kuderer NM. Incorporation of quality of life considerations into decision models for the use of colony stimulating factors in chemotherapy patients at risk for febrile neutropenia. In: Klastersky JA, ed. *Febrile Neutropenia*. Berlin; New York: Springer; 1997.

51. Lyman GH, Kuderer NM. Filgrastim in patients with neutropenia: potential effects on quality of life. *Drugs*. 2002;62(suppl 1):65-78.

52. Talcott JA, Whalen A, Clark J, et al. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol*. 1994;12:107-114.

53. Rubenstein EB, Rolston K, Benjamin RS, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer*. 1993;71:3640-3646.

54. Sivasubramaniam V, Dale D, Crawford J, et al. Impact of outpatient treatment of febrile neutropenia (FN) on risk thresholds for G-CSF prophylaxis in cancer chemotherapy (CT). *Proc Annu Meet Am Soc Clin Oncol*. 2001;20:1563. Abstract.

55. Lyman GH. A New approach to maintain planned dose chemotherapy on time: a decision-making tool to improve patient care. *Eur J Cancer*. 2000;36(suppl):15-21.

56. Lyman GH. A predictive model for neutropenia associated with cancer chemotherapy. *Pharmacotherapy*. 2000;20:1045-1115.

57. 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.

58. Silber JH, Fridman M, Shpilsky A, et al. Modeling the cost-effectiveness of granulocyte-stimulating factor use in early-stage breast cancer. *J Clin Oncol*. 1998;16:2435-2444.

59. Lyman GH, Crawford J, Dale D, et al. Predicting the risk of chemotherapy-induced neutropenia (CIN) in patients with breast cancer: rationale for prospective risk model development. *Breast Cancer Res Treat*. 2002;76:S537.

60. Repetto L, Bigansoli L, Koehne CH, et al. EORTC Cancer in the Elderly Task Force Guidelines for the use of the colony-stimulating factors in elderly patients with cancer. *Eur J Cancer*. 2003;39:2264-2272.

61. Doorduijn JK, van der Holt B, van Imhoff GW, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2003;21:3041-3050.