Original Article

Guidelines of the National Comprehensive Cancer Network on the Use of Myeloid Growth Factors with Cancer Chemotherapy: A Review of the Evidence

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Key Words

Myeloid growth factors, colony-stimulating factors, chemotherapy, febrile neutropenia, dose intensity

Abstract

The prophylactic use of myeloid growth factors reduces the risk of chemotherapy-induced neutropenia and its complications, including febrile neutropenia and infection-related mortality. Perhaps most importantly, the prophylactic use of colony-stimulating factors (CSFs) has been shown to reduce the need for chemotherapy dose reductions and delays that may limit chemotherapy dose intensity, thereby increasing the potential for prolonged disease-free and overall survival in the curative setting. National surveys have shown that the majority of patients with potentially curable breast cancer or non-Hodgkin's lymphoma (NHL) do not receive prophylactic CSF support. In this issue, the National Comprehensive Cancer Network presents guidelines for the use of myeloid growth factors in patients with cancer. These guidelines recommend a balanced clinical evaluation of the potential benefits and harms associated with chemotherapy to define the treatment intention, followed by a careful assessment of the individual patient's risk for febrile neutropenia and its complications. The decision to use prophylactic CSFs is then based on the patient's risk and potential benefit from such treatment. The routine prophylactic use of CSFs in patients receiving systemic chemotherapy is recommended in patients at high risk (>20%) of developing febrile neutropenia or related complications that may compromise treatment. Where compelling clinical indications are absent, the potential for CSF prophylaxis to reduce or offset costs by preventing hospitalization for FN should be considered. The clinical, economic, and quality of life data in support of these recommendations are reviewed, and important areas of ongoing research are highlighted. (*JNCCN* 2005;3:557–571)

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Chemotherapy-induced neutropenia (CIN), including febrile neutropenia (FN), is the major dose-limiting toxicity of many common systemic chemotherapy regimens. FN and its consequences are associated with substantial morbidity, mortality, and cost.[1–8] Perhaps of even greater concern, CIN and FN are frequently associated with chemotherapy dose reductions and delays, reducing treatment dose intensity and potentially compromising disease control and survival in responsive and potentially curable malignancies.[9–16] The myeloid growth factors or colony-stimulating factors (CSFs) have been shown to reduce the incidence, duration, and severity of CIN and FN, representing an alternative to chemotherapy dose attenuations.[17–22] In this issue, the National Comprehensive Cancer Network (NCCN) has published guidelines for myeloid growth factors, which recommend a risk-adapted strategy for CSF use based on the allocated chemotherapy regimen, patient factors, and treatment intent.[23] The aim of this article is to discuss clinical, economic, and quality-of-life (QOL) data that support these guidelines.

Risks of Severe and Febrile Neutropenia in Patients Receiving Cancer Chemotherapy

The risk of FN and infection in patients with hematologic malignancies and solid tumors relates directly to both the

severity and duration of neutropenia.[24,25] The risk of CIN or FN varies according to the specific agents used and the dose intensity administered (i.e., the amount of drug delivered over a specified time interval). Quantifying the risk of CIN or FN for a given chemotherapy regimen is difficult because hematologic toxicity has been under- and inconsistently reported in randomized controlled trials (RCTs) that use different measures, with reported rates varying widely for commonly studied regimens.[7]

The risk of the initial FN event for many regimens appears to be greatest during the early cycles of chemotherapy. Retrospective practice surveys have shown that approximately half of patients with aggressive non-Hodgkin's lymphoma (NHL) who developed FN after chemotherapy experienced their initial FN episode during the first cycle of treatment (Figure 1).[26] Furthermore, the increased risk of FN seen in elderly NHL patients was found to relate primarily to a doubling of risk during the first cycle (Figure 1). In a nationwide, prospective registry of adult cancer patients treated with chemotherapy in community oncology practices, more than half of episodes of CIN and FN were experienced in the first cycle of chemotherapy across a range of disease categories and chemotherapy regimens.[27] These data show that the reason for the lower risk after the first cycle of chemotherapy relates to reduced dose intensity or starting a myeloid growth factor in subsequent cycles after an initial episode of FN. When prophylactic CSF is not used and dose intensity is maintained, the rates of severe or FN are nearly constant across cycles, with approximately one third of patients experiencing two or more events. When the use of a myeloid growth factor or greater dose reductions are employed in subsequent cycles, the risk of FN falls quickly, resulting in the pattern commonly seen.

In studies performed before the availability of the CSFs, the risk of FN across multiple cycles of chemotherapy remained high when dose intensity was maintained. In small series of patients with small cell lung cancer receiving combination chemotherapy with no growth factor support and doses only reduced by 25% after episodes of FN, the sequential risks of FN over 6 cycles of therapy were 17.9%, 17.6%, 16.1%, 40.0%, 21.4%, and 36.4%, for an overall risk of 22.1% per cycle (Figure 2).[28]

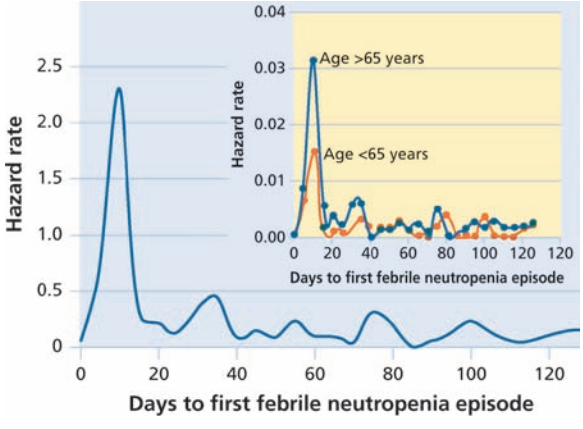

Figure 1 Hazard plot of time to initial episode of FN in 577 patients with NHL receiving chemotherapy with CHOP.[5] Insert illustrates difference in hazard rate based on age < 65 years or ≥ 65 years.

Consequences of FN

FN-Related Hospitalization and Inpatient Mortality

Most patients with FN require hospitalization for prompt clinical evaluation and administration of empiric, broad-spectrum antibiotics to reduce the mortality associated with delayed treatment of serious infections in the neutropenic patient.[29] Researchers have estimated that approximately 60,000 patients with cancer are hospitalized with FN each year in the United States.[3] Analyses of discharge databases show that inpatient mortality rates for FN vary from about 7% to 11%.[3,30] Risk factors for inpatient mortality

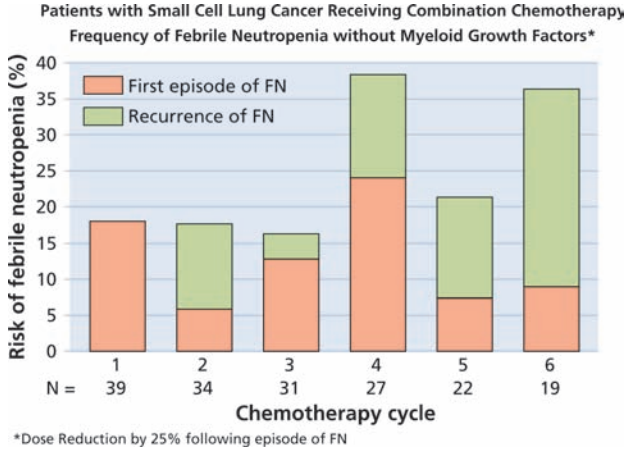

Figure 2 Reported risk of FN by cycle in patients receiving combination chemotherapy for small cell lung cancer without myeloid growth factor support.[28] Orange shading indicates the risk of the initial episode of FN while the green shading indicates recurrent episodes in those with previous FN events. A dose reduction by 25% in subsequent chemotherapy was stipulated in those with a previous episode of FN.

include gram-negative and gram-positive sepsis, pneumonia, fungal infection, leukemia, pulmonary embolism, hypotension, or hypovolemia on admission, and various comorbidities, including cardiac, cerebrovascular, renal, or liver disease. The risk of inpatient mortality has also been shown to increase with the number of major comorbid conditions.[30]

Substantial Cost

Costs associated with hospitalization for FN are substantial and add to the overall costs of cancer care. Recent estimates of the direct medical costs associated with FN-related hospitalization from national hospital discharge databases range from $10,000 to $20,000 per episode of hospitalization.[3,30] Furthermore, the third of patients with the longest hospitalizations with FN (≥ 10 days) accounted for 74% of the hospital days and nearly 80% of the estimated cost.[5,30] These estimates, however, do not account for other important costs, including the direct costs related to professional fees; non-medical direct costs of care, including patient and caregiver time while receiving care; and indirect costs of the disease and its treatment, including morbidity (costs associated with lost or impaired ability to work) and mortality costs (associated with lost productivity because of premature death).[31,32]

Quality of Life

Patients who are hospitalized with FN experience QOL impairments as a result of invasive diagnostic and treatment procedures, separation from family members, and adherence to strict guidelines to reduce the risk of infection. Patients with FN may fear infection, treatment failure, or death.[2] Only recently, however, have validated instruments been used to study QOL in patients with CIN, showing a negative association between the magnitude of the absolute neutrophil count nadir and QOL measures.[2,33–35] A significant worsening of symptoms with febrile status has also been seen.[34,36,37] For example, data pooled from 3 clinical trials in stage II to IV breast cancer show that FN increases the incidence, duration, and severity of common chemotherapy toxicities, including dehydration, anorexia, asthenia, and vomiting.[36]

Reduced Dose Intensity

One of the most-concerning consequences of CIN is its impact on delivered chemotherapy dose intensity because of dose reductions and delays after a previous cycle of chemotherapy. The resulting reduction in dose intensity relative to that showing efficacy in RCTs may diminish the potential for long-term disease control and survival in responsive and potentially curable malignancies. Chu and DeVita[38] have pointed out that, in in vivo models, dose reductions in the linear phase of the dose response curve almost always result in a reduction in cure rates, even before a decrease in response rate is seen. In animal models, Skipper[39] showed that before a significant reduction in response rates was seen, a 20% reduction in dose resulted in an approximately 50% reduction in cure rates. Therefore, complete remissions may continue to be seen with reduced dose intensity, while the potential for disease eradication and cure may be entirely lost.

Although in vitro systems and in vivo animal models do not always parallel results in humans, considerable evidence suggests that chemotherapy for many human malignancies follows a clear dose-response relationship. Early clinical studies in the metastatic setting showed a significant positive relationship between dose intensity and objective tumor response.[38] Retrospective clinical trials also suggest that a reduction in dose intensity can negatively influence patient survival in potentially curable malignancies.

A 20-year follow-up of the early Milan trial of adjuvant chemotherapy with cyclophosphamide, methotrexate, 5-fluorouracil (CMF) in early-stage breast cancer demonstrated that patients who received more than 85% of planned dose intensity experienced better disease-free (42% vs. 26%) and overall survival (40% vs 21%) compared with patients who received lower dose intensity.[12] In fact, patients receiving less than 65% of standard dose intensity experience disease-free and overall survival rates similar to those for untreated controls.

In a previous retrospective study by Kwak et al., patients with NHL receiving 75% or less of standard adriamycin dose intensity experienced significantly shorter survival than patients receiving more than 75% (P = .001).[14] Similarly, inferior survival has been reported in other studies of patients with NHL treated with less-than-standard dose intensity.[15,16] Such studies are limited, however, by their retrospective design.

The overview of all prospective RCTs of adjuvant chemotherapy versus controls in early-stage breast cancer (ESBC) has shown a highly significant reduction in the 15-year recurrence rates, breast cancer mortality, and all cause mortality.[40] Although

randomization to single agent regimens was associated with a significant reduction in the rates of recurrence, combination chemotherapy regimens were significantly superior to single agent regimens and resulted in significant improvements in 15-year recurrence-free rates as well as breast cancer-free survival. Adjuvant combination chemotherapy regimens containing an anthracycline were found to reduce annual breast cancer death rates by 38% in women younger than 50 and 20% in women 50 years of age or older.[40]

The overview clearly shows that a dose response relationship exists for disease-free and overall survival between a chemotherapy dose intensity of zero (controls) and the dose intensity that was actually administered across trials. Somewhere between the dose intensity delivered in the treatment arm and that of the control arm, therapeutic benefit is lost and patient survival compromised. Although few studies reported delivered dose intensity, the authors suggest that the trial results could have been stronger had full adherence with the chemotherapy regimens studied been achieved.[40] The authors also point out that the many adjuvant combination regimens shown in the 1980s to reduce 5-year recurrence rates but not 5-year mortality have now been shown, with further follow-up, to substantially reduce 15-year mortality rates. Finally, they suggest that further improvement in long-term survival may be seen with either better compliance with the older regimens or the newer drugs and regimens currently in use.

Two RCTs of adjuvant chemotherapy in ESBC randomized patients to different dose intensities. A study in patients with ESBC (CALGB 8541) randomized patients to 3 different dose intensities (1.0; 0.67; 0.50) of adjuvant cyclophosphamide, doxorubicin, 5-fluorouracil (CAF). At a median follow-up of 9 years, patients in the low-RDI arm had experienced significantly worse disease-free ($P < .0001$) and overall survival ($P = .004$) than patients in the moderate- and full-RDI arms, respectively.[13] A randomized trial conducted by the French Adjuvant Breast Cancer Study Group demonstrated that a regimen of fluorouracil, epirubicin, and cyclophosphamide was superior when epirubicin was given at a dose of 100 mg/m^2 (FEC100) rather than 50 mg/m^2 (FEC50) for 10-year disease-free (50.7% vs. 45%; $P = .036$) and overall survival (54.8% vs. 50%; $P = .038$).[40]

Recently reported results from a randomized phase II study in elderly patients with small cell lung cancer showed a 1-year survival rate of 39% in patients who received a full-dose regimen of platinum and etoposide with prophylactic CSF, but only 18% in patients who received an attenuated-dose regimen with no CSF.[41] Although dose escalation studies have shown little success in altering patient outcomes, dose-dense regimens with shortened treatment intervals requiring CSF support allowing upwards of 50% increase in RDI have been shown to improve survival over standard regimens in ESBC and NHL.[43,44]

Despite this growing body of data, national practice pattern surveys conducted over the past few years continue to show that large proportions of patients receiving chemotherapy for potentially curable malignancies are being undertreated. In a study of nearly 20,000 women with ESBC treated in 1,200 oncology practices, more than half received less than 85% of the standard dose intensity for their regimen (Figure 3).[9] Two thirds of the reductions in dose intensity were planned from the beginning of treatment, while the remaining reductions were in response to treatment toxicity such that on average women only received 79% of full dose intensity chemotherapy. Leading factors associated with planned reduction in dose intensity were age, obesity and comorbities.[10]

In a similar study of more than 4,500 patients with aggressive NHL receiving cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or CHOP-like chemotherapy, 53% and 48% received less than 85% of the standard dose intensity based on either treatment with 6 cycles or NCCN guidelines, respectively.[11] Such undertreatment was more prevalent among elderly patients, those receiving certain regimens, and overweight and obese patients.[11] The majority of

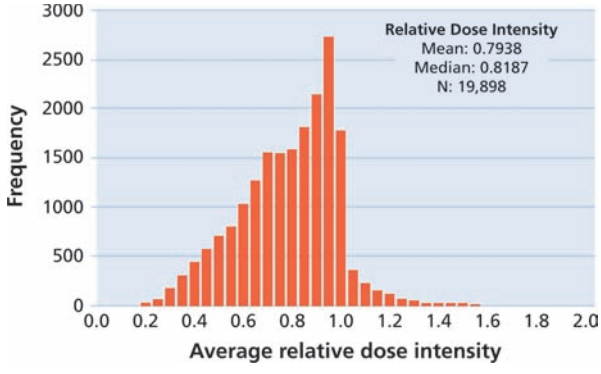

Figure 3 Relative dose intensity in adjuvant chemotherapy among 19,898 women with early-stage breast cancer.[9] More than half (53%) received less than 85% of standard dose intensity for their respective regimen.

patients in each study received no CSF support or received it only after a neutropenic complication. The ease with which major reductions in dose intensity occur is shown in Figure 4, which illustrates the combined effects of dose reduction and treatment delay for either every-3-week schedules of doxorubicin and cyclophosphamide (AC) for breast cancer (Figure 4A) or CHOP for NHL (Figure 4B). Chu and DeVita concluded that such empiric reductions in dose intensity represent a major reason for treatment failure in patients with responsive malignancies in both the adjuvant and advanced disease situation.[38]

It is reasonable to ask why more controlled clinical trials investigating the impact of reductions in dose intensity and the value of sustaining full dose intensity on long-term outcomes have not been performed. Randomization between the dose and schedule shown to be effective in RCTs versus a regimen or schedule at considerably lower dose intensity that will likely be less effective raises important ethical as well as practical recruitment issues. Conversely, the major barrier to studying the impact of smaller reductions in dose intensity is statistical. To provide reasonable power to confidently show the anticipated impact of a 10% to 25% reduction in RDI on patient survival, researchers would need a sample size of many thousands of patients per study arm. None of the studies reported to date have been powered to show the anticipated clinical impact of such reductions in dose intensity.

A RDI Associated with Dose Reductions and Treatment Delays
Example: AC Q 3 Weeks X 4 Cycles

	Total Treatment Delays (weeks)					
Dose Reduction	0	1	2	3	4	5
0	1.00	.92	.86	.80	.75	.70
10%	.90	.83	.77	.68	.64	.60
20%	.80	.74	.68	.64	.60	.56
30%	.70	.65	.60	.56	.53	.49
40%	.60	.55	.51	.48	.45	.42
50%	.50	.46	.43	.40	.37	.35

B RDI Associated with Dose Reductions and Treatment Delays
Example: CHOP Q 3 Weeks X 6 Cycles

	Total Treatment Delays (weeks)					
Dose Reduction	0	1	2	3	4	5
0	1.00	.95	.90	.86	.82	.78
10%	.90	.85	.81	.77	.74	.70
20%	.80	.76	.72	.69	.65	.63
30%	.70	.66	.63	.60	.57	.55
40%	.60	.57	.54	.51	.49	.47
50%	.50	.47	.45	.43	.41	.39

Figure 4 Chart illustrating the impact of dose reduction (%) and treatment delay (weeks) imposed across a course of chemotherapy with either AC every 3 weeks for four cycles in ESBC (A) or CHOP every 3 weeks for six cycles for NHL (B).

Clinical Efficacy of Myeloid Growth Factors

CSF Use Reduces the Risk of FN and FN Hospitalizations

Recombinant granulocyte colony-stimulating factor (G-CSF) consists of a 175 amino acid, 18 kD glycoprotein that binds to specific cell surface receptors, promoting neutrophil proliferation, differentiation, and functional maturation. G-CSF has been shown to reduce the risk of FN across a broad range of malignancies and myelosuppressive chemotherapy regimens with varying levels of risk. When used in pivotal trials as an adjunct to highly myelosuppressive chemotherapy, G-CSF significantly reduced the incidence, duration, and severity of CIN, the risk of FN and infection, and the total days of FN hospitalization and IV antibiotic use compared with placebo in patients with small cell lung cancer.[17,18] A meta-analysis of the initial 8 RCTs in 1,144 patients confirmed that CSF use significantly reduced the risk of FN (OR = 0.38; $P < .0001$) and documented infection (OR = 0.51; $P < .001$).[19] Since that analysis, the results of several additional RCTs have become available, including a large trial of a longer acting G-CSF.

Two additional trials of G-CSF support in elderly NHL patients have been published. The Nordic Lymphoma Group evaluated the efficacy of G-CSF (5 µg/kg/d) in elderly patients with NHL treated with either CHOP or cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP).[45] CNOP was found to be a distinctly inferior regimen in both groups. Alternatively, CHOP with G-CSF support was associated with significantly greater RDI (96% vs. 91.5%, $P < .05$), less severe neutropenia ($P < .001$), fewer episodes of FN (34% vs. 50%; $P < .001$), and improved 5-year survival (60% vs. 45%; $P = .045$). Another trial of CHOP with or without low dose G-CSF (300 µg fixed dose) showed that G-CSF with CHOP was

associated with less severe neutropenia ($P < .001$), fewer first-cycle infections (32% vs. 20%; $P = .01$), and fewer early and infection-related deaths (27% vs. 15%; $P = .04$).[46] A modest difference was seen in RDI (median 92.5% vs. 90.3%) and no difference in 5-year survival. Timmer-Bonte et al.[47] conducted a study of cyclophosphamide, doxorubicin, and etoposide over 3 days with prophylactic antibiotics (ciprofloxacin + roxithromycin) with or without G-CSF 5 µg/kg/d on days 4 to 13. Patients treated with G-CSF experienced fewer episodes of FN in cycle 1 (24% vs. 10%; $P = .01$) and less overall FN (32% vs. 18%; $P = .01$). Of note, two thirds of FN episodes occurred during the first cycle. A modest but significant increase in RDI was seen with G-CSF, but the study was underpowered to address secondary outcomes of infection-related mortality (6% vs. 3%) and tumor response. No data were reported on disease-free or overall survival.

A next-generation G-CSF, pegfilgrastim, was bioengineered for sustained duration of action by the addition of a 20 kD polyethylene glycol (PEG) moiety to the N-terminus of the G-CSF molecule, greatly increasing molecular size and diminishing renal filtration. This results in prolonged circulation in the serum with eventual elimination by binding to G-CSF receptors on recovering neutrophils. Comparative RCTs in breast cancer patients treated with doxorubicin and docetaxel showed that a single injection of pegfilgrastim (100 µg/kg or a 6-mg fixed dose) per cycle is at least as effective as daily injections of filgrastim (5 µg/kg/d) in reducing the incidence, duration, and severity of CIN, and the incidence of FN.[21,22] In a comparable clinical setting without G-CSF support this regimen was associated with a 38% incidence of FN.[48] Systematically combining the results of the pivotal pegfilgrastim trials ($n = 448$) suggests that the risk of FN is significantly lower for pegfilgrastim compared with filgrastim (relative risk = 0.561; 95% CI, 0.35–0.89; Figure 5).

To study the efficacy of pegfilgrastim, in regimens associated with lower risk of neutropenic complications, a large ($n = 928$) randomized double-blind placebo-controlled trial of pegfilgrastim was conducted in breast cancer patients treated with docetaxel 100 mg/m^2 every 3 weeks.[49] In previous clinical trials, this regimen was associated with FN rates of 10% to 20%.[50,51] Compared with the occurrence of FN in the placebo arm (17%), patients in the pegfilgrastim arm experienced significantly fewer episodes of FN (1%;

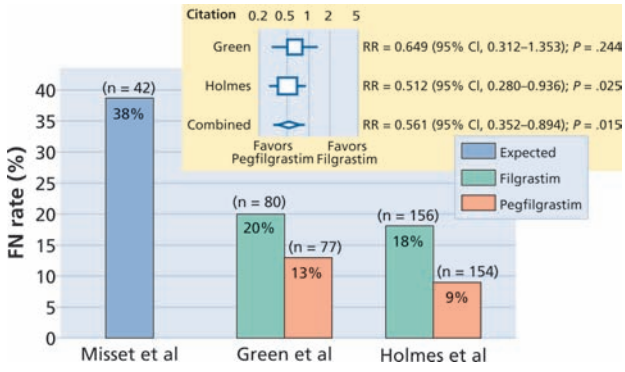

Figure 5 Risk of FN in two pivotal RCTs of a combination of doxorubicin and docetaxel in stages II–IV breast cancer comparing filgrastim at 5 µg/kg/day to a single injection of pegfilgrastim at either 100 µg/kg (Holmes[21]) or 6 mg fixed dose (Green[22]) contrasted to the historical experience with this chemotherapy regimen of approximately 40% without myeloid growth factor support.[48] Insert combines results of two RCTs using a Mantet Haenszel estimation demonstrating a significant reduction in risk of FN with pegfilgrastim compared to filgrastim in these trials ($P = .015$).

$P < .001$), as well as fewer hospitalizations (1% vs. 14%) and reduced anti-infective use (2% vs. 10%; Figure 6). Note that when the studies are formally combined, pegfilgrastim prophylaxis appears to reduce the risk of FN compared with filgrastim by nearly half, with two-thirds of FN episodes occurring during the first cycle of chemotherapy.[49]

The clinical efficacy of G-CSF has recently been confirmed in an updated meta-analysis of 14 RCTs of primary prophylaxis of G-CSF in 3,091 adult cancer patients treated with systemic chemotherapy.[52] This review includes 10 trials of filgrastim, 3 of lenograstim (a glycosylated G-CSF available only in

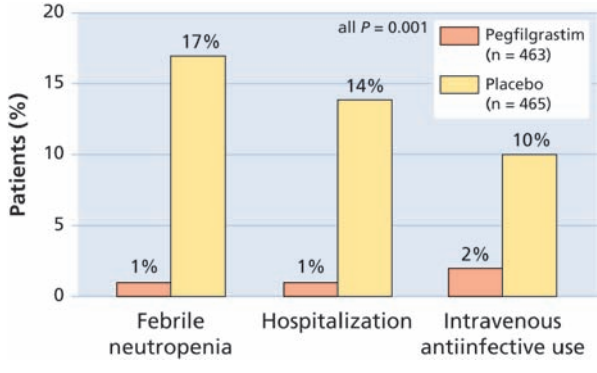

Figure 6 Clinical outcomes including the rates of FN, FN hospitalization and IV antibiotic use from a large ($n = 928$) double-blind, placebo-controlled trial of pegfilgrastim in women with breast cancer receiving a regimen of docetaxel at 100 mg/m^2 every three weeks previously associated with approximately a 20% risk of FN.[49]

Europe), and the one trial of pegfilgrastim. The RCTs in the meta-analysis include 6 in NHL and 8 in solid tumors, including breast, lung, sarcoma, and germ cell malignancies.

CSF Use Reduces the Risk of Febrile Neutropenia

The updated meta-analysis shows that patients randomized to receive G-CSF experienced significantly fewer episodes of FN (316; 20%) than control subjects (576; 37%; $P < .0001$).[52] Significant reductions in the risks of FN were seen in NHL and solid tumor studies, in studies of elderly patients—as well as those including all ages—and with all forms of G-CSF. Of note, the relative risk reduction associated with pegfilgrastim use was significantly greater than with either filgrastim or lenograstim. It should also be noted that the evidence for CSF efficacy provided by the RCTs is based on their use in primary prophylaxis, initiated within 1 to 3 days of chemotherapy and, except for pegfilgrastim, administered daily until neutrophil recovery. A meta-analysis in adult patients with NHL who received CSFs[53] and two meta-analyses of prophylactic G-CSFs in children receiving cancer chemotherapy[54,55] have also shown reductions in the risk of FN as well as the duration of hospitalization.

CSF Use Reduces Infection-Related Mortality

The original meta-analysis of 8 trials[19] found no significant difference in infection-related mortality with G-CSF prophylaxis compared with control (OR = 0.60; 95% CI, 0.30–1.22; $P = .12$), although the study power to show an effect for this outcome was low. The updated meta-analysis included 10 studies that reported rates of infection-related mortality ranging from 0% to 7% among control subjects. Patients randomized to G-CSF were less likely to die of infectious complications while on treatment (21; 1.7%) compared with control subjects (40; 3.3%; $P = .001$).[52] It is important to note that patients eligible for the prophylactic RCTs were generally highly selected, including younger age and few comorbidities. The true infection-related mortality rate and, therefore, the benefit of CSF prophylaxis or treatment may actually be greater. In a Cochrane Collaboration meta-analysis of CSFs used therapeutically (after hospitalization for FN) in patients with established FN treated with antibiotics, Clark et al.[56] noted a significant reduction in infection-related mortality, from 5.7% among control subjects to 3.1% in CSF patients (RR = 0.51; 95% CI, 0.26–1.00, $P = .05$).

Overall Survival

Overall survival is rarely considered the goal of supportive care studies, which are primarily designed to study the impact of care on disease- or treatment-related complications, such as antiemetics, antibiotics, analgesics, bisphosphonates, and the erythroid growth factors. Nevertheless, as discussed previously, there is accumulating evidence based on RCTs that the myeloid growth factors administered prophylactically or therapeutically can reduce the risk of infection-related mortality.[51,55] Therefore, for some patients, the use of the myeloid growth factors is life saving, reducing short-term mortality. Perhaps even more important, the CSFs may enhance the delivery of full dose intensity in conventional regimens as well as enable the delivery of dose-dense regimens, which have been shown to improve survival in both ESBC and aggressive NHL.

Most studies of prophylactic CSF use with conventional chemotherapy considered FN as the primary outcome and were powered accordingly. Only two of the studies included in the updated meta-analysis considered survival as a primary outcome of the study; both were trials in elderly patients receiving CHOP chemotherapy for NHL.[45,46] In one comparison,[45] a significant improvement in survival with G-CSF added to CHOP was seen, but no difference in survival was reported in the other study. Two additional studies reported survival as a secondary outcome but were not powered to show a survival difference.[57,58] Bohlius et al. report survival outcomes from 9 NHL trials.[53] However, two trials were of granulocyte-macrophage colony-stimulating factor (GM-CSF), and one study has never been presented or published. Of the remaining 6 studies, average sample sizes across trials in control and CSF arms were 53 (range, 10–104) and 55 (range, 12–103) patients, respectively. Three of these studies did not initiate CSF until day 15 of the cycle and were not included in the updated meta-analysis of prophylactic G-CSF, and 3 are included as discussed previously. The lack of strong evidence for a survival effect based on a paucity of adequately powered trials should not be considered evidence for the absence of such an effect in some disease settings. More and larger studies are needed in a variety of malignancies to address this issue.

CSF Use Can Sustain Dose Intensity

Perhaps the most important benefit from prophylactic CSF is the potential to sustain full dose intensity

in responsive and potentially curable malignancies. Among the 8 reporting RCTs of conventional dose chemotherapy in the recently updated meta-analysis, the average RDI among control and G-CSF patients was 88% (95% CI: 86%–90%) and 95% (95% CI: 93%–96%), respectively (P <.001).[52] G-CSF-treated patients received 10% greater RDI than control patients among studies that included all ages, compared with a 5% increase in studies limited to elderly patients. Prospective studies of dose dense regimens (every 2 weeks) requiring CSF support in both ESBC and aggressive NHL have the potential for increasing the RDI of administered chemotherapy by 50%.[43,44] At a median follow-up of 36 months, results from CALGB 9741 in node-positive ESBC patients have shown that dose-dense doxorubicin and cyclophosphamide followed by taxol (AC-T) results in reductions in relative risk for disease-free and overall survival of 26% (P = .0072) and 31% (P = .014), respectively.[43] Likewise, a study of dose-dense chemotherapy in patients with NHL by the German High-Grade Lymphoma Group have shown significant improvements for CHOP-14 in time to progression, event-free survival as well as overall survival among older patients.[44] Likewise, younger good prognosis NHL patients randomized to receive dose-dense CHOP experienced a small but significant improvement in overall survival at 5 years.[59]

Economics of Myeloid Growth Factors

When compelling clinical indications for the use of myeloid growth factors do not seem to exist based on reducing the risk of FN or infection-related mortality or for sustaining dose intensity, the decision to use these agents is often based on economic considerations. Unfortunately, only two of the 14 RCTs of prophylactic G-CSF in the updated meta-analysis attempted to capture direct medical costs and each did so only in a subgroup of patients at selected institutions without adequate power to address treatment group comparisons.[46,60] However, several studies based on clinical decision models have been conducted, incorporating FN risk and treatment efficacy estimates derived from RCTs or meta-analyses along with estimates of resource use and direct costs for FN hospitalization derived from single or multiple institution studies.

Cost Minimization

When no difference in patient survival or QOL is assumed, the comparative economic impact of treatment strategies is often expressed in terms of cost minimization or the cost savings associated with the new treatment compared to standard treatment. Such models permit estimation of expected costs associated with treatment options and estimation of variable thresholds where the cost associated with each treatment strategy is equal.

The robustness of model assumptions is often evaluated by performing multiple sensitivity analyses exploring the variation in expected cost or cost-thresholds with changes in the baseline values assigned to each variable. A 1993 cost-minimization model based on the pivotal RCT of Crawford et al.[17] and including limited costs derived from a single institution estimated that the use of CSF reduced overall costs in patients who were treated with chemotherapy regimens associated with a risk of FN greater than 40%.[60,61] A subsequent economic analysis conducted at the same institution was based on cost allocation and accounting functions to capture all direct institutional expenditures for all patients with FN hospitalized over a 2-year period.[62] Based on these updated cost estimates, threshold risks of FN associated with the cost saving use of the CSFs of 20% to 25% have been estimated (Figure 7).[62–64]

Economic studies of hospitalized patients with FN across multiple U.S. institutions have provided very similar estimates of average hospital costs for FN.[3,4,8,64] These studies have shown that a relatively small proportion of patients account for a large proportion of the associated days of hospitalization and costs.[29] A

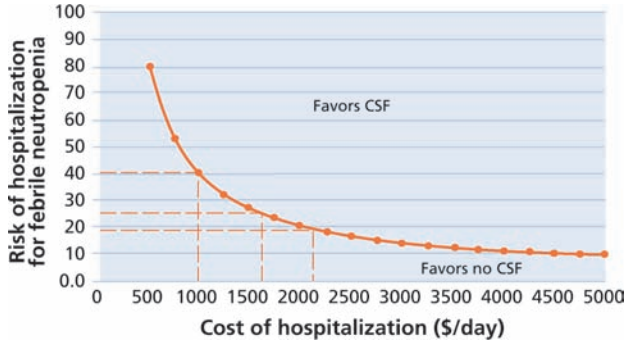

Figure 7 Threshold curve from a cost minimization model of prophylactic G-CSF in patients receiving cancer chemotherapy showing with recent estimates of direct or indirect costs/day associated with hospitalization for FN, the cost neutral risk threshold for FN hospitalization by cycle has decreased compared to estimated 1993 estimates.[32,61,62]

recent cost-minimization analysis of pegfilgrastim based on risk and efficacy estimates from the updated meta-analysis of 14 RCTs[52] and recent multi-institutional hospital and physician cost data have been presented.[65] Risk thresholds for FN under 20% were estimated with increasing cost savings as the risk reduction associated with primary prophylaxis with pegfilgrastim increases (Figure 8). It should be noted that these economic models are based on cycle-specific events, with the assumption that similar risks will be experienced across cycles of the same regimen when administered without reductions in dose intensity or the addition of a myeloid growth factor. The RCTs show that only during the first cycle do all patients receive full-dose intensity chemotherapy with or without CSF support. None of the RCTs permitted unaltered dose delivery in patients experiencing FN in cycle 1 in the absence of a hematopoietic growth factor.

Data from a recent prospective registration study not only show that 50% to 75% of initial severe and febrile neutropenia episodes occur in cycle 1, but also that virtually all such events are followed by subsequent reductions in dose intensity or the addition of a myeloid growth factor.[66] Among those patients receiving full-dose intensity in subsequent cycles without CSF support, the event rate and, therefore, the cost implications are the same or greater than that experienced in cycle 1. It should also be noted that where the expected costs of care with a CSF exceed those without a CSF, the growth factor costs are, nevertheless, partially offset by the reduction in risk of hospitalization for FN in a proportion of patients. A recent study contrasting routine inpatient management of FN with a strategy permitting subsequent outpatient

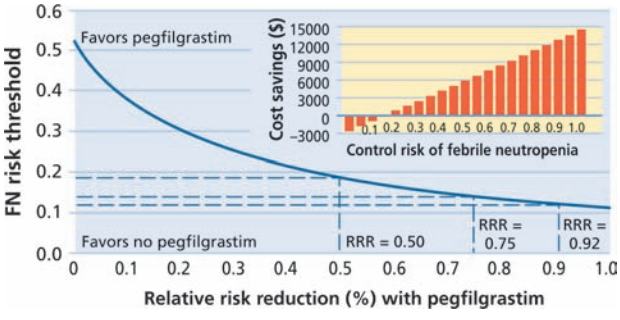

Figure 8 Threshold curve from a cost minimization model of primary prophylaxis with pegfilgrastim in patients receiving cancer chemotherapy showing a decrease in cost neutral risk thresholds for FN hospitalization by cycle with increasing assumed relative risk reduction.[21,22,49,65] The insert displays the estimated cost or cost savings associated with prophylactic pegfilgrastim based on the cycle-specific risk of FN.

care for low risk patients with FN shows minimal differences in the estimated FN risk thresholds because of the limited contribution of low risk patients to the overall costs associated with FN hospitalization.[67] Very little study of non-medical costs, including patient time costs and indirect costs of FN or the myeloid growth factors has been conducted. Cosler et al.[32] found that consideration of indirect and out-of-pocket expenses associated with severe and febrile neutropenia increased the overall cost of CSF and lowered thresholds for CSF use.

Beyond Cost Minimization

Cost-effectiveness models have been developed based on the increasing evidence that CSFs not only decrease the risk of FN, but also reduce the risk of infection-related mortality and may potentially improve long-term disease outcomes by sustaining full-dose intensity in curative settings. These models suggest that prevention of infection-related mortality or disease recurrence in potentially curable malignancies is associated with cost-effectiveness ratios for primary CSF prophylaxis well below the societal benchmark of $50,000 per life-year gained.[63,64,68,69] Similarly, acceptable cost-effectiveness ratios of prophylactic CSF are anticipated in ESBC and other potentially curable malignancies in which more intensive (e.g., docetaxel, doxorubicin, and cyclophosphamide [TAC] or 5-fluorouracil, epirubicin, cyclophosphamide [FEC100], or dose-dense regimens requiring such support are associated with prolongation of disease-free or overall survival. Likewise, the increase in 5-year survival in elderly patents with NHL that has been seen with the addition of CSF to CHOP administered by conventional[45] or dose-dense[44] schedules provides cost-effectiveness ratios well within accepted limits. The previously observed offsetting costs associated with CSF use, because of preventing FN hospitalization, only further improve the cost-effectiveness estimates in such settings.

Cost-utility models have the potential to further clarify the impact of primary prophylaxis with CSFs in support of patients treated with cancer chemotherapy.[2] However, such models are severely limited by the paucity of QOL data, including formally assessed patient preferences in those patients with FN or those receiving myeloid growth factors. Factors that may impact on patient QOL include the prevention of hospitalization for FN and its consequences and the ability to reduce infection-related mortality and sustain dose intensity on

the one hand and the discomfort associated with one or more injections, and the bone pain associated with marrow expansion in some patients treated with CSFs on the other. Further studies are needed to assess the quality of life impact of severe and febrile neutropenia and its alleviation with the myeloid growth factors versus the required injections and bone pain experienced by some patients.

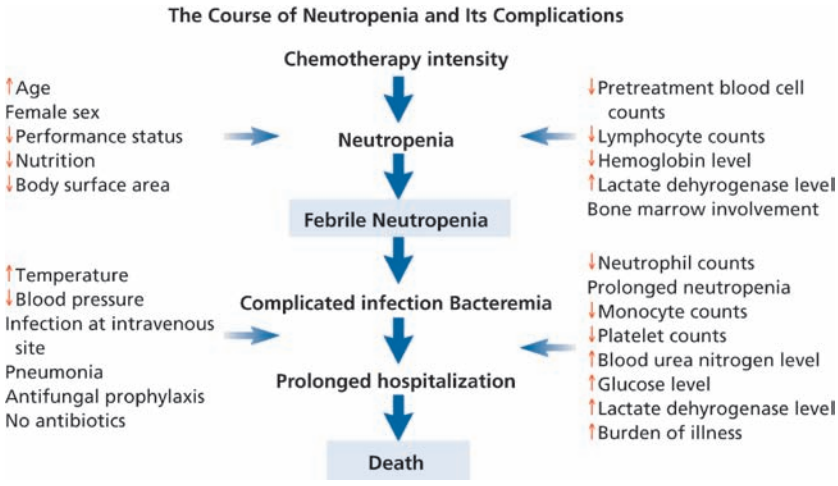

Figure 9 Risk factors identified in a systematic review of risk models for FN and its complications.[65] Only risk factors found to be statistically significant in multivariate models from two or more studies are included.

Risk Factors and Risk Models

The decision to use primary CSF prophylaxis to support patients receiving cancer chemotherapy is generally based on clinical judgment including: (1) the estimated risk of neutropenic complications expected based on the treatment regimen; (2) patient-specific characteristics, including age, functional status, and comorbidities; and (3) the treatment intention, balancing the anticipated *benefit* of chemotherapy with the *risk* of serious and life-threatening complications.[70] Treatment intention determines the relevance or potential harm associated with alternative options to the addition of CSF support, such as dose reduction, treatment delay, use of an alternative chemotherapy regimen, or withholding treatment altogether.

All of the risk factor studies reported to date are based on retrospective studies, which looked at different outcomes and measured different risk factors. Table 1 and Figure 9 summarize the results of a systematic review of risk factor studies for FN, adverse consequences or death from FN, and reduced dose intensity.[71] The chemotherapy regimen is one of the primary determinants of the risk of FN. Regimens that are associated with a high risk of FN include dose-dense regimens (for which CSF use is mandatory),[43,44,59] or those with high-dose intensity, for example TAC in breast cancer.[37,72,73] Older age is consistently identified as a predictor of neutropenic complications, including dose reductions and delays.[9,11] Other predictors include poor performance status, the presence of comorbid conditions, and baseline laboratory abnormalities (e.g., elevated levels of lactate dehydrogenase or serum albumin < 3.5 g/dL).[5,6,9,11,25,74,75] A risk model for time to initial FN in NHL patients receiving CHOP was derived from a retrospective series of 577 patients and included 6 independent risk factors: age, baseline hemoglobin, heart disease, renal disease, planned dose intensity, and no CSF prophylaxis (Figure 10).[5] A risk model for first-cycle severe or FN based on a prospective registry of nearly 3,000 patients treated with a new chemotherapy regimen at 115 randomly selected practices in the United States is under development.[66] Independent risk factors in multivariate analysis included the type of cancer, treatment regimen, age, body surface area, certain comorbidities (liver

Figure 10 Cumulative risk of the initial episode of FN in a retrospective study of 577 patients with aggressive NHL receiving CHOP based on a multivariate risk model incorporating age, baseline hemoglobin, heart disease, renal disease, planned dose intensity and use of growth factor.[5] The cumulative risk by risk score is found to differ primarily in the risk during the first cycle of treatment.

Table 1 Risk Factors for Febrile Neutropenia, Adverse Consequences or Death from FN, and Reduced Dose Intensity[28]

Risk Factors for FN	
Treatment-related	Previous history of severe neutropenia with similar chemotherapy
	Type of chemotherapy (anthracyclines)
	Planned relative dose intensity >80%
	Pre-existing neutropenia or lymphocytopenia
	Extensive prior chemotherapy
	Concurrent or prior radiation therapy to marrow containing bone
Patient-related	Age
	Female gender
	Poor performance status
	Poor nutritional status (e.g., low albumin)
	Decreased immune function
Cancer-related	Bone marrow involvement with tumor
	Advanced cancer
	Elevated lactate dehydrogenase (lymphoma)
Conditions associated with risk of serious infection	Open wounds
	Active tissue infection
Comorbidities	Chronic obstructive pulmonary disease (COPD)
	Cardiovascular disease
	Liver disease (elevated bilirubin, alkaline phosphatase)
	Diabetes mellitus
	Low baseline hemoglobin
Risk Factors for Adverse Consequences/Death from FN	
Hematologic complications	Severe and prolonged neutropenia
	Anemia
	Thrombocytopenia, monocytopenia
Age	
Cancer-related	Leukemia
	Lymphoma
	Lung cancer
	Other advanced or uncontrolled cancer
Comorbidities	Cardiovascular disease
	COPD
	Renal failure
	Liver disease
	Cerebrovascular
	Pulmonary embolism
	Diabetes mellitus
Infectious complications	High temperature
	Hypotension (shock, hypovolemia, tachycardia)
	Sepsis (gram –, gram +, polymicrobial)
	Pneumonia
	Fungal infection
	IV site infection
	Antifungal prophylaxis
Risk Factors for Reduced Dose Intensity	
Neutropenic events	Febrile neutropenia, particularly first cycle
	Severe neutropenia, particularly first cycle
Patient factors	Age
	Ethnicity
	Education
	Compliance
Comorbidities	Cardiovascular disease
	Renal disease
	Obesity or BSA >2 m^2
	Poor functional or nutritional status
	Connective tissue disease
Disease factors	Stage
	Prior treatment
	Marrow involvement
Treatment variables	Prior treatment
	Chemotherapy regimen
	Treatment intent, dose and schedule
Physician/practice variables	Practice site
	Practice setting
	Training/experience

disease, renal disease, diabetes), baseline blood counts, the intention to provide full-dose chemotherapy, and no prophylactic CSF support. Once validated, such a risk model may guide clinicians and patients on the most effective and cost-effective use of myeloid growth factors in patients at greatest risk and most likely to benefit.

The NCCN guidelines frame the clinical decision to use myeloid growth factor support in cancer chemotherapy patients in a clinically relevant context based on risk assessment and treatment intention (Figure 11). The initial step is to characterize the risk associated with the chemotherapy regimen selected. An effort should then be made to identify patient-specific risk factors for severe neutropenia and its consequences, including FN. The ultimate decision on the use of a prophylactic CSF is then made based on the overall assessment of risk against the treatment intent, which defines the importance of preserving dose intensity. The goal of this process is ultimately to target prophylactic CSF support toward individual patients who are at greatest risk as well as most likely to benefit from CSF use. In the future, these decisions will hopefully be aided by fully validated risk models, which identify patients who are at greatest risk of these complications of cancer treatment.

Conclusions and Recommendations

The NCCN guidelines presented in this issue incorporate the most recent evidence on the use of CSFs to support patients receiving cancer chemotherapy. For high-risk patients (risk > 20%), first- and subsequent-cycle CSF use is recommended for most treatment settings. For patients with intermediate risk (10% to 20%), CSF prophylaxis should be considered based on treatment intention and the potential for benefit versus harm. If no compelling clinical indications are seen for the use of prophylactic CSF support, economic considerations may be relevant. For low-risk patients (risk < 10%), routine CSF prophylaxis is not recommended, In subsequent cycles of chemotherapy, patients initially considered to be low risk who, nevertheless, experienced severe or febrile neutropenia should be considered for subsequent myeloid growth factor support. Clinicians should always base the decision of whether to offer growth factor support on their unique understanding of the potential for benefit and harm from cancer treatment including the patient's risk for serious and life threatening complications with and without the support of the myeloid growth factors.

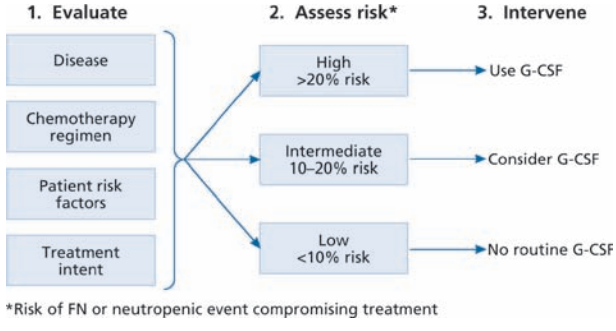

Figure 11 Schema summarizing recommendations of the NCCN Myeloid Growth Factor Guidelines based on (1) evaluation, (2) risk assessment and (3) intervention.

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