Neutropenia is the primary dose-limiting toxicity in patients with cancer treated with systemic chemotherapy. The risk of febrile neutropenia (FN) has been estimated on the basis of the chemotherapy regimen, but studies are now finding a number of patient-related and disease-related risk factors for FN and other complications, such as hospitalization, chemotherapy dose reductions and delays, and mortality. These patient-related risk factors have been incorporated into clinical guidelines for managing neutropenia. The newly released guidelines on the use of myeloid growth factors with cancer chemotherapy of the National Comprehensive Cancer Network use disease- and patient-related factors along with the chemotherapy regimen risk. These guidelines also differ from previous guidelines in that they recommend the routine use of colony-stimulating factors (CSFs) in patients in whom the risk of neutropenia is > 20% (the previous threshold was ≥ 40%); this recommendation is based on recent data that show the clinical benefits of filgrastim (Neupogen) and pegfilgrastim (Neulasta) in studies in which the overall populations had FN risks of between 20% and 40%. The use of guidelines such as these in clinical practice will make it possible to target CSFs to appropriate patients in the first cycle of chemotherapy, when the risk of neutropenia is highest.

Chemotherapy-induced neutropenia (CIN) is the primary dose-limiting toxicity in patients with cancer treated with chemotherapy, with potentially severe clinical consequences such as febrile neutropenia (FN), infection, sepsis, and death. In addition, chemotherapy alterations such as dose reductions and delays that are triggered by CIN may also compromise long-term treatment outcomes.[1] The use of colony-stimulating factors (CSFs) such as filgrastim (Neupogen) and pegfilgrastim (Neulasta) reduces the rates of FN and of FN-associated hospitalization and the use of intravenous anti-infectives and also helps maintain the chemotherapy at full dose and on schedule.[2] The use of CSFs in all patients treated with myelosuppressive chemotherapy is not considered cost-effective, however, and a more appropriate strategy may be to target them to patients who are at increased risk for neutropenia and its complications.[3]

Most efforts to define the risk of neutropenia have focused on the prescribed chemotherapy regimen. It is difficult, however, to determine the actual risk for neutropenia and its complications with common chemotherapy regimens, for many reasons.[4] As discussed in a report of the findings in a survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin's lymphoma, the rates of neutropenia with the same and similar regimens varied greatly. Some of this variation may be due to underreporting of the rates of myelosuppression and the relative dose intensity (RDI) of the chemotherapy. In addition, the differences in the rates of neutropenia may also reflect differences in patient characteristics. It is therefore likely that estimating the risk of neutropenia and targeting CSF therapy to appropriate patients can be improved by assessing not only the planned chemotherapy regimen but also patients' individual risk factors.[3]

This article reviews patient-related risk factors for neutropenia and its complications, as well as the recently published guidelines of the National Comprehensive Cancer Network (NCCN), which make recommendations for appropriate use of CSFs in patients with cancer.
Risk Assessment and Guidelines for First-Cycle Colony-Stimulating Factor Use in the Management of Chemotherapy-Induced Neutropenia

Published on Cancer Network (http://www.cancernetwork.com)

first cycle, when the risk is highest.
A number of pretreatment factors have been found that predict the risk of FN, FN mortality, chemotherapy dose alterations, and related events. These risk factors fall into three major categories: disease-related, patient-related, and treatment-related (Table 1).[1,3]

Table 1

<table>
<thead>
<tr>
<th>Disease-Related</th>
<th>Patient-Related</th>
<th>Treatment-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia, lymphoma</td>
<td>Age &gt; 65 years</td>
<td>Intensity of regimen</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Female sex</td>
<td>Chemotherapy regimen</td>
</tr>
<tr>
<td>Marrow involvement</td>
<td>Poor performance status</td>
<td>• Etoposide</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>(Eastern Cooperative Oncology Group ≥ 2)</td>
<td>• High-dose</td>
</tr>
<tr>
<td>Uncontrolled cancer</td>
<td>Poor nutritional status, low albumin level</td>
<td>cyclophosphamide</td>
</tr>
<tr>
<td>Elevated lactate dehydrogenase level (lymphoma)</td>
<td>Immunodeficiency, neutropenia, leukemia</td>
<td>• High-dose anthracycline</td>
</tr>
<tr>
<td></td>
<td>Open wounds</td>
<td>Concurrent or previous radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Tissue infection</td>
<td>Extensive previous chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Comorbidities</td>
<td>Absence of CSF therapy</td>
</tr>
<tr>
<td></td>
<td>• Chronic obstructive pulmonary disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liver disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low hemoglobin level</td>
<td></td>
</tr>
</tbody>
</table>

CSF = colony-stimulating factor; FN = febrile neutropenia


Disease-related risk factors indicate the degree to which the underlying disease may render a patient susceptible to chemotherapy-induced myelosuppression. For example, FN-related hospitalizations are longer and inpatient mortality higher in patients with leukemia than in those with solid tumors.[7] In addition, the risk is also higher in patients with bone marrow involvement of the disease, advanced cancer, and cancer that is not controlled by antineoplastic therapy.[8]

Patient-related risk factors pertain to the patient's general health. The most widely used patient risk factor is advanced age, generally defined as 65 years or older.[6,9-12] A number of comorbidities have also been found to be risk factors, including lung disease, renal disease, liver disease, cerebrovascular disease, cardiovascular disease, and diabetes mellitus.[3,6,10] Other patient risk factors are poor performance status, existing immunodeficiency or neutropenia, female sex, active tissue infections, open wounds, and low pretreatment hemoglobin level.[8]

Treatment-related risk factors involve the inherent risk of the regimen, as well as the patient's treatment history. Frequently cited risk factors are the planned intensity of the chemotherapy regimen and the absence of CSF.[11,12] Some cytotoxic agents have also been found to have a high risk, such as etoposide, cyclophosphamide (Cytoxan, Neosar), and anthracyclines. The primary risk factors in the patient's treatment history are extensive previous chemotherapy and previous radiotherapy (specifically, radiation to marrow-containing anatomic structures).[8]

The risk factors mentioned here provide an opportunity to assess the risk of FN and other complications of neutropenia before the first cycle of chemotherapy, making it possible to target CSFs to those patients who are at increased risk at the time of greatest potential danger.[3]

Guidelines for the Use of Colony-Stimulating Factors in Managing Neutropenia

Several of the risk factors mentioned above have been incorporated into clinical guidelines for
targeted use of CSFs in high-risk patients. The guidelines of the American Society of Clinical Oncology (ASCO), last updated in 2000, recommend the use of CSFs in the first cycle only with regimens associated with an FN risk of 40% or greater. These recommendations were based on the initial randomized clinical trials that showed the benefit of G-CSF prophylaxis with a rate of FN of greater than 40% in the control group. In addition, early economic analyses showed that the cost of filgrastim could be offset by the savings from fewer hospitalizations when the risk of FN was greater than 40%. Few commonly used regimens, however, are associated with a risk of FN greater than 40%. The ASCO guidelines also recommended that first-cycle use of CSFs be considered for patients with high-risk characteristics, including immunodeficiency due to the underlying disease or extensive previous treatment, history of FN during treatment with chemotherapy, poor performance status, advanced cancer, open wounds, and active tissue infections.[8]

More recently, the NCCN published its guidelines for myeloid growth factors in cancer treatment.[13] The NCCN guidelines incorporate the most up-to-date information on risk factors for CIN, FN, hospitalization, chemotherapy dose alterations, and related events, as well as the latest data on the clinical benefit of first-cycle CSFs.[1,14] These guidelines also reflect the consensus of the panel's 16 members and member institutions.

The NCCN guidelines base the decision to use CSF on: (1) the patient's risk factors and the myelotoxicity of the chemotherapy regimen and (2) the intent of the treatment-cure, prolongation of survival, or palliation (Figure 1). The guidelines acknowledge the importance of maintaining the dose and schedule of the chemotherapy and recommend the use of CSFs to help ensure that the chemotherapy is given at full dose and on schedule. The goal is to target CSFs to those patients who are at increased risk and are therefore most likely to benefit from them, by preventing toxic complications and by maximizing the long-term therapeutic outcomes.[1]

Before the first cycle of the chemotherapy, patients are assessed for the risk of neutropenia and its complications and are categorized as high risk (> 20%), intermediate risk (10%-20%), or low risk (< 10%). The pretreatment risk assessment considers the three types of risk factors discussed above-disease-related factors, patient-related factors, and treatment-related factors.[13] Examples of high-risk and intermediate-risk regimens are shown in Tables 2 and 3.[13]
<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples of High-Risk Regimens (Risk &gt; 20%)</strong></td>
</tr>
</tbody>
</table>

**Bladder cancer**
TC (paclitaxel, cisplatin)
MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)

**Breast cancer**
AC→T (doxorubicin, cyclophosphamide, docetaxel)
AT (doxorubicin, paclitaxel)
TAC (docetaxel, doxorubicin, cyclophosphamide)

**Cervical cancer**
TC (paclitaxel, cisplatin)

**Head and neck cancers**
TIC (paclitaxel, ifosfamide, mesna, cisplatin)

**Non-Hodgkin’s lymphoma**
VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin)
A(N)CVB (doxorubicin or mitoxantrone, cyclophosphamide, vindesine, bleomycin)
DHAP (dexamethasone, cisplatin, cytarabine)
ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine)

**Non-small-cell lung cancer**
VIG (gemcitabine, ifosfamide, vinorelbine)
DP (docetaxel, carboplatin)

**Small-cell lung cancer**
CAE (cyclophosphamide, doxorubicin, etoposide)
Topotecan
TopT (topotecan, paclitaxel)

**Ovarian cancer**
Topotecan
Paclitaxel
Docetaxel

**Sarcoma**
MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
Doxorubicin
Doxorubicin, ifosfamide

**Testicular cancer**
VIP (vinblastine, ifosfamide, cisplatin)

The routine use of CSFs in the first and subsequent chemotherapy cycles is recommended in high-risk patients. Their use in intermediate-risk patients in the first and subsequent cycles should be considered, with the intent of treatment taken into account. For example, in patients treated with potentially curative regimens, CSF support may help in maintaining the dose intensity of the chemotherapy and therefore in maximizing the likelihood of long-term disease-free and overall survival.[15,16] In intermediate-risk patients treated with chemotherapy with palliative intent, however, the use of CSFs may not be warranted, and other alternatives, such as less myelosuppressive chemotherapy, should also be considered. The routine first-cycle use of CSFs in low-risk patients is not recommended unless the patient is at risk for severe consequences of FN such as death.[13]

<p>| Table 3 |</p>
<table>
<thead>
<tr>
<th>Examples of Immediate-Risk Regimens (Risk 10%–20%)[9]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma</strong></td>
</tr>
<tr>
<td>GPT (gemcitabine, carboplatin, paclitaxel)</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
</tr>
<tr>
<td>Docetaxel</td>
</tr>
<tr>
<td>AC (doxorubicin, cyclophosphamide)</td>
</tr>
<tr>
<td>DX (docetaxel, capecitabine)</td>
</tr>
<tr>
<td><strong>Hodgkin disease</strong></td>
</tr>
<tr>
<td>Stanford V (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)</td>
</tr>
<tr>
<td><strong>Non-Hodgkin’s lymphoma</strong></td>
</tr>
<tr>
<td>CHOP (doxorubicin, cyclophosphamide, vincristine, prednisone)</td>
</tr>
<tr>
<td>FM (fludarabine, mitoxantrone)</td>
</tr>
<tr>
<td>CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)</td>
</tr>
<tr>
<td><strong>Non–small-cell lung cancer</strong></td>
</tr>
<tr>
<td>TC (cisplatin, paclitaxel)</td>
</tr>
<tr>
<td><strong>Small-cell lung cancer</strong></td>
</tr>
<tr>
<td>TopC (cisplatin, topotecan)</td>
</tr>
<tr>
<td>EP (etoposide, carboplatin)</td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
</tr>
<tr>
<td>Topotecan</td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
</tr>
<tr>
<td>IG (irinotecan, gemcitabine)</td>
</tr>
<tr>
<td><strong>Testicular cancer</strong></td>
</tr>
<tr>
<td>EC (etoposide, cisplatin)</td>
</tr>
</tbody>
</table>

By defining the threshold for high risk and routine use of CSFs as > 20%, the NCCN guidelines differ from the earlier ASCO guidelines, which define high risk as ≥ 40%.[8] This difference is due to the results of recent trials that showed the efficacy of filgrastim and pegfilgrastim in patients in whom the risk of FN was between 20% and 40%. In one study, patients with small-cell lung cancer treated with a regimen with a risk of FN of approximately 30% were randomized to treatment with either
prophylactic antibiotics alone or prophylactic antibiotics and filgrastim.[17] The FN rate was more than halved by the use of prophylactic filgrastim (10% vs 24%, \( P = .01 \)), and infection-related deaths were reduced from nine patients to five.

As detailed in the previous paper,[18] 928 patients with breast cancer who were treated with a regimen with an approximately 20% risk of FN were randomized to placebo or pegfilgrastim in the largest study ever performed of prophylactic CSF in the setting of CIN.[14] The rate of FN was reduced from 17% to 1% (\( P < .001 \)), hospitalization for FN from 14% to 1% (\( P < .001 \)), and use of intravenous anti-infectives from 10% to 2% (\( P < .001 \)). With the clear demonstration in this trial of the benefit of first-cycle use of CSF in a population with an overall risk of neutropenia of 17%, the threshold of 20% was established for routine use of prophylactic CSFs in the first cycle of chemotherapy. The NCCN guidelines were based on clinical outcomes and did not consider economic outcomes; nonetheless, the 20% level of risk of FN is consistent with the risk at which the routine use of pegfilgrastim has been determined to be cost-effective.[19] It should also be noted that based on the results of the Vogel trial, the pegfilgrastim product label has recently been changed to recommend first-cycle use with chemotherapy regimens associated with a risk of FN of 17% or greater.[20]

As shown in Figure 2, in addition to pretreatment risk assessments, the NCCN guidelines recommend ongoing monitoring and evaluation of the treatment intent and risk for neutropenia before each cycle, so that CSFs can be used in the later cycles if FN or dose-limiting events occurred in an earlier cycle. The modification of the chemotherapy regimen dose can be considered for patients in whom neutropenia occurred despite the use of prophylactic CSFs or in whom such modifications are not likely to affect the clinical benefit of the treatment.[13]

![Figure 2: NCCN recommendations for evaluating risk after each cycle](image)

With respect to the choice of CSF, the two growth factors that are currently in clinical use are recombinant human granulocyte CSF (G-CSF; filgrastim, pegfilgrastim, and lenograstim [Granocyte]) and granulocyte-macrophage CSF (GM-CSF; sargramostim [Leukine]). The two agents differ substantially in their mechanisms of action, however, and the results of randomized clinical trials of prophylactic CSF in the setting of CIN reflect those differences. While trials with G-CSF in patients with nonmyeloid malignancies have shown significant and consistent reductions in the risk of neutropenia and its complications, including FN,[2] the results of randomized trials with GM-CSF have been inconsistent.[21] In addition, while the clinical trials of G-CSF have shown bone pain to be the most common clinical toxicity, GM-CSF has also been associated with bone pain as well as a higher
incidence of thrombocytopenia and of symptoms such as fever, myalgia, edema, and rash.\cite{21}
GM-CSF has not been approved for an indication in CIN\cite{22}; however, as an adjunct to treatment in acute leukemia and bone marrow transplantation, both G-CSF and GM-CSF are approved by the United States Food and Drug Administration (FDA).

The NCCN has initially limited their recommendations to the prophylaxis of CIN in patients with nonmyeloid malignancies. In this setting, the NCCN guidelines list filgrastim, pegfilgrastim, and sargramostim as possible choices. Filgrastim and pegfilgrastim are given category 1 recommendations (uniform consensus based on high-level evidence), while sargramostim is given a category 2B recommendation (nonuniform NCCN consensus but no major disagreement, based on lower-level evidence, including clinical experience).\cite{13}

Guidelines for the Use of Colony-Stimulating Factors in Elderly Patients

Advanced age is an important independent risk factor, and older patients are often treated with lower chemotherapy doses in order to lessen the occurrence of neutropenia and its complications.\cite{11,12} Growing consensus suggests that older patients with cancer can obtain the same benefits from aggressive chemotherapy as younger patients.\cite{23} In a recently reported clinical trial of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab (Rituxan) in patients with intermediate- or high-grade non-Hodgkin's lymphoma (NHL), filgrastim was given in the first and subsequent cycles in all patients older than 60 years.\cite{24} The incidence of FN in these older patients was 22%-significantly lower than the incidence of 41% in this age group in a nearly identical trial in which filgrastim was not used ($P = .005$).\cite{25} More important, the RDI of the chemotherapy was similar in both older patients given filgrastim and in younger patients (94% and 95%), as was the complete response rate (91% and 97%).

These results indicate that older patients who are treated with full-dose chemotherapy obtain almost the same benefits from it as younger patients.\cite{23} The growing sense is that age itself should not be considered a contraindication to full-dose cancer treatment.\cite{26} Instead, it has been proposed that the approach to treating older patients should incorporate full-dose treatment with curative intent in the setting of thorough risk assessment and prophylaxis with CSFs, where appropriate.\cite{9,23,27}

Consistent with this change in the approach to treating older patients, two organizations have developed guidelines for the use of CSFs in elderly patients. The Senior Adult Oncology Panel of the NCCN recommends prophylactic CSFs in patients aged 65 years or older who are treated with CHOP or CHOP-like regimens for lymphoma and in patients aged 60 years or older who are treated with induction or consolidation therapy for acute myelogenous leukemia.\cite{9} The Cancer in the Elderly Task Force of the European Organization for Research and Treatment of Cancer has published guidelines that, recognizing the higher risk of myelosuppression in elderly patients, recommend prophylactic G-CSFs in patients aged 60 years or older who are treated with chemotherapy for a variety of malignancies, including NHL, small-cell lung cancer, and urothelial tumors.\cite{26}

Conclusions

The body of data on disease-related, patient-related, and treatment-related risk factors for the development of FN and other complications of neutropenia is growing.\cite{3} These data provide improved opportunities for pretreatment risk assessments so that CSF therapy can be administered in patients at increased risk starting in cycle 1, when the risk of FN is highest.\cite{6}

A greater understanding of disease- and patient-related risk factors also provides an opportunity to refine risk assessments beyond the rates of neutropenia that have been associated with the prescribed regimen. The newly released NCCN guidelines incorporate disease- and patient-related risk factors to a greater degree than has been seen in previous guidelines.\cite{1,13} The NCCN guidelines also substantially differ from the 2000 ASCO guidelines in recommending the use of CSFs in patients in whom the risk of neutropenia is greater than 20%.\cite{1,13} This recommendation is based in part on recent data that show significant clinical benefits with first-cycle use of pegfilgrastim in patients with a lower risk.\cite{14}

The NCCN guidelines also consider the intent of treatment, with greater emphasis on prophylaxis with CSFs and maintaining the dose intensity of potentially curative chemotherapy regimens.\cite{13} It is hoped that the new guidelines will help promote delivery of full standard doses of chemotherapy as a quality measure. The current focus on identification of patient risk factors will further refine our ability to deliver chemotherapy more safely and more effectively.

**Disclosures:**
Dr. Crawford has received research funding from and has served on advisory boards for Amgen.
References:


17. Timmer-Bonte JN, de Boo TM, Smit HJ, et al: Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in


**Source URL:**
http://www.cancernetwork.com/oncology-journal/risk-assessment-and-guidelines-first-cycle-colony-stimulating-factor-use-management-chemotherapy

**Links:**
[1] http://www.cancernetwork.com/review-article
[2] http://www.cancernetwork.com/oncology-journal
[4] http://www.cancernetwork.com/authors/jeffrey-crawford-md