Myeloid Growth Factors

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Myeloid Growth Factors

Clinical Practice Guidelines in Oncology™

Jeffrey Crawford, MD; James Armitage, MD; Lodovico Balducci, MD; Charles Bennett, MD, PhD; Douglas W. Blayney, MD; Spero R. Cataland, MD; David C. Dale, MD; George D. Demetri, MD; Harry P. Erba, MD, PhD; James Foran, MD; Alison G. Freifeld, MD; Marti Goemann, RPh; Mark L. Heaney, MD, PhD; Sally Httoy, PharmD; Susan Hudock, PharmD; Dwight D. Kloth, PharmD; David J. Kuter, MD, PhD; Gary H. Lyman, MD, MPH; Laura Boehnke Michaud, PharmD; Sarah C. Miyata, RN, MSN, ACNP-CS; Martin S. Tallman, MD; Saroj Vadhan-Raj, MD; Peter Westervelt, MD, PhD; and Michael K. Wong, MD, PhD

Overview

Neutropenia (< 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 hours) and resulting febrile neutropenia (FN; ≥ 38.3°C orally or ≥ 38.0°C over 1 hour) can be induced by myelosuppressive chemotherapy. FN is a major dose-limiting toxicity of chemotherapy, often necessitating hospitalization for evaluation and empiric broad-spectrum antibiotics. These complications often result in dose reductions or treatment delays, which may compromise clinical outcomes. The prophylactic use of colony-stimulating factors (CSFs) can reduce the risk, severity, and duration of FN.

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

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Disclosures for the NCCN Myeloid Growth Factors Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and on-line. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Myeloid Growth Factors Guidelines Panel members can be found on page 82. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

Myeloid Growth Factors Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, myeloid growth factors, neutropenia, fever, chemotherapy (JNCCN 2009;7:64–83)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Despite these benefits, CSFs are not administered to all patients undergoing myelosuppressive chemotherapy because of the costs associated with routine use. Selective use of CSFs in patients at increased risk for neutropenic complications may, however, enhance cost-effectiveness by directing treatment toward patients most likely to benefit.

The risk for FN is usually based on the treatment regimen and delivered dose intensity. A survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin’s lymphoma (NHL) has shown, however, that the rates of myelosuppression and delivered dose intensity are underreported.1 When reported, the rates of myelosuppression with the same and similar regimens varied greatly, making it difficult to determine the actual risk for neutropenic complications associated with common chemotherapy regimens.1 Differences in the reported rates of neutropenic complications may relate to differences in study patient populations as well as delivered dose intensity. Treatment dose intensity was reported with even less consistency, making it very difficult to interpret differences in reported rates of toxicity or treatment efficacy.

A review by Dale2 showed that approximately 25% to 40% of treatment-naive patients develop FN with common chemotherapy regimens.2 Occurrence of FN may delay subsequent chemotherapy courses or result in dose reductions that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. Prolonged hospitalizations are...
### EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE

Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies:

- **High** (> 20%)
- **Intermediate** (10% - 20%)
- **Low** (< 10%)

- Disease
- Chemotherapy regimen
  - High dose therapy
  - Dose-dense therapy
  - Standard dose therapy
- Patient risk factors
- Treatment intent (curative vs. palliative)

### RISK ASSESSMENT FOR FEBRILE NEUTROPENIA

- Predicted risk of neutropenia
- Neutrophil count
- Temperature
- Infection
- Other factors

### PROPHYLAXIS USE OF CSF FOR FEBRILE NEUTROPENIA

<table>
<thead>
<tr>
<th>CHEMOTHERAPY TREATMENT INTENT</th>
<th>CURATIVE/ADJUVANT</th>
<th>PROLONG SURVIVAL/QUALITY OF LIFE</th>
<th>SYMPTOM MANAGEMENT/QUALITY OF LIFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF (category 1 for G-CSF)</td>
<td>CSF (category 1 for G-CSF)</td>
<td>CSF</td>
<td></td>
</tr>
<tr>
<td>Consider CSF</td>
<td>Consider CSF</td>
<td>Consider CSF</td>
<td></td>
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<tr>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td></td>
</tr>
</tbody>
</table>

CSF = Colony-stimulating factors

### Clinical Trials

The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

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EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

- Evaluate patient prior to second and subsequent chemotherapy cycles
  - Febrile neutropenia or dose-limiting neutropenic event
    - Prior use of CSF
      - Consider dose reduction or change in treatment regimen
    - No prior use of CSF
      - Consider CSF (See Risk Assessment For Febrile Neutropenia, previous page)
  - No febrile neutropenia or dose-limiting neutropenic event
    - Repeat assessment after each subsequent cycle

SECONDARY PROPHYLAXIS

*To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

*Febrile neutropenia is defined as, single temperature ≥ 38.3°C orally or ≥ 38.0°C over 1 h; neutropenia < 500 neutrophils/mcl. or < 1000 neutrophils/mcl. and a predicted decline to ≤ 500/mcl over the next 48 h. See the NCCN Prevention and Treatment of Cancer-Related Infections Guidelines.*
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

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Examples of Chemotherapy Regimens with a High Risk of Febrile Neutropenia (> 20%)

- **This list is not comprehensive;** there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment naive vs. heavily pretreated patients; see page 66).
- **The type of chemotherapy regimen is only one component of the risk assessment** (See Patient Risk Factors for Developing Febrile Neutropenia, page 74).
- Pegfilgrastim has not been documented to have benefit in regimens given for less than a 2-wk duration.
- **Note:** The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

**Bladder Cancer**
- MVAC (methotrexate, vinblatistone, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)¹
- Docetaxel + trabuzumab (metastatic or relapsed)²
- Dose dense AC→T* (doxorubicin, cyclophosphamide, paclitaxel)³ (adjuvant)
- AT (doxorubicin, paclitaxel) (metastatic or relapsed)⁴
- AT (doxorubicin, docetaxel) (metastatic or relapsed)⁵
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)⁶

**Esophageal and Gastric Cancer**
- Docetaxel/cisplatin/fluorouracil⁷

**Non-Hodgkin’s Lymphoma**
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphomas, 2nd-line, salvage)⁸
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)⁹
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone)¹⁰
- MINE (mesna, ifosfamide, novantrone, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphomas 2nd-line, refractory)¹¹
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd-line)¹²
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, 2nd-line, recurrent)¹³
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)¹⁴
- HyperCVAD + Rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab) (Burkitt’s Lymphoma)¹⁵,¹⁶

**Melanoma**
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)¹⁷
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)¹⁷

**Myelodysplastic syndrome**
- Decitabine¹⁸

**Ovarian Cancer**
- Topotecan¹⁹
- Paclitaxel²⁰
- Docetaxel²¹

**Pancreatic Cancer**
- Gemcitabine/docetaxel²²

**Sarcoma**
- MAID (MESNA, doxorubicin, ifosfamide, dacarbazine)²³
- Doxorubicin²⁴

**Small Cell Lung Cancer**
- Topotecan²⁵

**Testicular Cancer**
- VeIP (vinblastine, ifosfamide, cisplatin)²⁶
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)²⁷

*In general, dose dense regimens require growth factor support for chemotherapy administration.

See Chemotherapy Regimen References (pages 71 and 72)  
See Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (page 70)
Examples of Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (10%-20%)

- **This list is not comprehensive**, there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment naive vs. heavily pretreated patients; see page 66)
- The type of chemotherapy regimen is only one component of the risk assessment (See Patient Risk Factors for Developing Febrile Neutropenia, page 74).
- Pegfilgrastim has not been documented to have benefit in regimens given under a 2-week duration.
- **Note:** The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

### Occult Primary/Adenocarcinoma
- Gemcitabine, docetaxel\(^8\)
- Docetaxel every 21 d\(^9\)
- Epirubicin (adjuvant)\(^10\)
- Epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil (adjuvant)\(^10\)
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)\(^10\)
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)\(^11\)
- AC + sequential docetaxel + trastuzumab (adjuvant)\(^12\)
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel\(^13\)
- Paclitaxel every 21 d (metastatic or relapsed)\(^14\)
- Vinblastine (metastatic or relapsed)\(^15\)

### Cervical Cancer
- Cisplatin + topotecan (recurrent or metastatic)\(^16\)
- Topotecan (recurrent or metastatic)\(^17\)
- Irinotecan (recurrent or metastatic)\(^18\)

### Colon Cancer
- FOLFIRI (fluorouracil, leucovorin, oxaliplatin)\(^19\)
- Capecitabine (adjuvant)\(^20\)
- Epirubicin/cisplatin\(^21\)
- Epirubicin/cisplatin/oxaliplatin\(^22\)
- Epirubicin/cisplatin/oxaliplatin/5-fluorouracil\(^23\)
- Epirubicin/cisplatin/oxaliplatin/capecitabine\(^24\)

### Hodgkin Lymphoma
- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)\(^25\)
- Stanford II (methotrexate, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)\(^26\)

\(^1\)There is one retrospective review that suggests pulmonary toxicity may be increased using G-CSF in bleomycin-containing regimens. (See discussion for further detail.)

### Non-Hodgkin’s Lymphoma
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt’s, recurrent)\(^27\)
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, diffuse large B-cell lymphoma, recurrent)\(^28\)
- Rituximab + hyperCVAD alternating with methotrexate + cytarabine (CVAD template) (cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen included IT methotrexate\(^29\)
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)\(^30\)
- GDP (gemcitabine, dexamethasone, cisplatin) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd-line)\(^31\)
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (diffuse large B-cell lymphoma, 2nd-line)\(^32\)
- Filgrastim, mitoxantrone\(^33\)
- CHOP + R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)\(^34\)

### Non-Small Cell Lung Cancer
- Carbo/etoposide (adjuvant, advanced/metastatic)\(^35\)
- Carbo/etoposide (adjuvant, advanced/metastatic)\(^36\)
- Carbo/etoposide (adjuvant, advanced/metastatic)\(^37\)
- Carboplatin/paclitaxel (adjuvant, advanced/metastatic)\(^38\)
- Docetaxel (advanced/metastatic)\(^39\)

### Ovarian Cancer
- Carboplatin/docetaxel\(^40\)
- Carboplatin/docetaxel\(^41\)
- Carboplatin/docetaxel\(^42\)

### Small Cell Lung Cancer
- Etoposide/carboplatin\(^43\)
- Etoposide/docetaxel\(^44\)

### Testicular Cancer
- Etoposide/cisplatin\(^45\)

### Uterine Cancer
- Docetaxel (uterine sarcoma, advanced or metastatic)\(^46\)
CHEMOTHERAPY REGIMEN REFERENCES


References continued on page 72
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
CHEMOTHERAPY REGIMEN REFERENCES


PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

In addition to the risk of the chemotherapy regimen and specific malignancy being treated, these factors need to be considered when evaluating a patient’s overall risk for febrile neutropenia:

- Older patient, notably patients aged 65 y and older
- History of previous chemotherapy or radiation therapy
- Pre-existing neutropenia or bone marrow involvement with tumor
- Pre-existing conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

MYELOID GROWTH FACTORS FOR PROPHYLAXIS AND TREATMENT OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start 24-72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.
- Pegfilgrastim (category 1; for prophylactic use only)
  - One dose of 6 mg per cycle of treatment.
  - Start 24-72 h after completion of chemotherapy.
  - Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after chemotherapy have shown less benefit in 2 studies of regimens associated with moderate- to high-risk neutropenia,\(^1,2^) and comparable benefit in 1 study of a regimen with low-risk neutropenia where pegfilgrastim would not be routinely indicated.\(^3^) Therefore, administration of growth factor on same day as chemotherapy is not recommended.
  - There is evidence to support use for chemotherapy regimens given every 3 wk (category 1).
  - Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 wk.
  - There are insufficient data to support dose and schedule of weekly regimens or chemotherapy schedules < 2 wk and these cannot be recommended.
- Sargramostim\(^4\) (category 2B)
  - Used in clinical trials at a dose of 250 mcg/m\(^2\)/d (rounding to the nearest vial size by institution-defined weight limits).
  - Start 24-72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.
- Prophylactic use of CSF in patients given concurrent chemotherapy and radiation is not recommended.
- Subcutaneous route is preferred for all 3 agents.
- No data support alternative dosing schedules in intermediate- and high-risk patients.
- The safety data appear to be similar between filgrastim and pegfilgrastim.
- Prophylactic antibiotics are not routinely recommended for standard-dose chemotherapy (see NCCN Prevention and Treatment of Cancer-Related Infections Guidelines. To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.)

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4. There is category 1 evidence to support filgrastim or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence for a category 1 recommendation for sargramostim in this setting. Sargramostim is indicated for use following induction chemotherapy in older adult patients with AML. Studies are ongoing in other areas.
### Myeloid Growth Factors Version 1:2009

**TOXICITY RISKS WITH GROWTH FACTORS**

<table>
<thead>
<tr>
<th>Filgrastim&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Sargramostim&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warnings</strong></td>
<td><strong>Warnings</strong></td>
</tr>
<tr>
<td>- Allergic reactions</td>
<td>- Fluid retention: edema, capillary leak syndrome, pleural and/or pericardial effusion</td>
</tr>
<tr>
<td>- Skin: rash, urticaria, facial edema</td>
<td>- Respiratory symptoms: sequestration of granulocytes in pulmonary circulation dyspnea</td>
</tr>
<tr>
<td>- Respiratory: wheezing, dyspnea</td>
<td>- Cardiovascular symptoms: occasional transient supraventricular arrhythmia. Use with caution in patients with preexisting cardiac disease</td>
</tr>
<tr>
<td>- Cardiovascular: hypotension, tachycardia</td>
<td>- Renal and hepatic dysfunction: elevation of serum creatinine or bilirubin and hepatic enzymes. Monitor patients who display renal or hepatic dysfunction prior to initiation of treatment</td>
</tr>
<tr>
<td>- Splenic rupture</td>
<td>- Adverse reactions with autologous bone marrow transplant or peripheral blood progenitor cell transplant</td>
</tr>
<tr>
<td>- Adult respiratory distress syndrome</td>
<td>- Asthenia, diarrhea, rash</td>
</tr>
<tr>
<td>- Precipitate sickle cell disease crisis</td>
<td>- Adverse reactions with allogeneic bone marrow transplant or peripheral blood progenitor cell transplant</td>
</tr>
<tr>
<td><strong>Adverse reactions</strong></td>
<td></td>
</tr>
<tr>
<td>- Medullary bone pain (&gt; 10%)</td>
<td></td>
</tr>
<tr>
<td>- Precautions</td>
<td>- Abdominal pain, chest pain, diarrhea, nausea, vomiting, GI hemorrhage, pruritus, bone pain, eye hemorrhage, hyperglycemia, hypomagnesemia, pharyngitis, insomnia, anxiety, high BUN, high cholesterol</td>
</tr>
<tr>
<td>- Cutaneous vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

**Pedfilgrastim<sup>2</sup>**

<table>
<thead>
<tr>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Splenic rupture</td>
</tr>
<tr>
<td>- Adult respiratory distress syndrome</td>
</tr>
<tr>
<td>- Allergic reactions</td>
</tr>
<tr>
<td>- Skin: rash, urticaria</td>
</tr>
<tr>
<td>- Respiratory: anaphylaxis</td>
</tr>
<tr>
<td>- Precipitate sickle cell disease crisis</td>
</tr>
<tr>
<td><strong>Adverse reactions</strong></td>
</tr>
<tr>
<td>- Bone pain</td>
</tr>
</tbody>
</table>

<sup>1</sup>To view filgrastim prescribing information, see http://www.fda.gov/cder/foi/label/2006/103353s008BL.pdf.

<sup>2</sup>To view pedfilgrastim prescribing information, see http://www.fda.gov/cder/foi/label/2007/125031s082bl.pdf.

<sup>3</sup>To view sargramostim prescribing information, see http://berlex.bayerhealthcare.com/html/products/pl/Leukine_PI.pdf.

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**PATIENT RISK FACTORS FOR POOR CLINICAL OUTCOMES OR FOR DEVELOPING INFECTION-ASSOCIATED COMPLICATIONS**<sup>1,2</sup>

<table>
<thead>
<tr>
<th>Patient risk factors include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sepsis syndrome</td>
</tr>
<tr>
<td>- Age &gt; 65 y</td>
</tr>
<tr>
<td>- Severe neutropenia (absolute neutrophil count &lt; 100/mcL)</td>
</tr>
<tr>
<td>- Neutropenia expected to be more than 10 d in duration</td>
</tr>
<tr>
<td>- Pneumonia</td>
</tr>
<tr>
<td>- Invasive fungal infection</td>
</tr>
<tr>
<td>- Other clinically documented infections</td>
</tr>
<tr>
<td>- Hospitalization at the time of fever</td>
</tr>
</tbody>
</table>

<sup>1</sup>The decision to use or not use CSF in the treatment of febrile neutropenia is controversial. See discussion for further detail.

the dominant factor in the high cost of cancer care. Prevention of adverse effects associated with cancer treatment, including limitation of mobility, emotional distress, and decreased energy, has a major impact on patient quality of life.1

Filgrastim and pegfilgrastim, both granulocyte colony-stimulating factors (G-CSF), currently have FDA approval for use in the prevention of chemotherapy-induced neutropenia. In contrast, the labeled indication for sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), is limited to use after induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. Recommendations are based on evidence derived mainly from studies on G-CSFs. Head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs are lacking.

These guidelines focus on the use of CSFs in the cancer setting; specifically they address adult patients with solid tumors and nonmyeloid malignancies. Growth factors in the treatment of myeloid malignancies are discussed in the NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes and Acute Myeloid Leukemia (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

Benefits and Risks of CSFs

The prophylactic use of G-CSFs has been shown to reduce the incidence, length, and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, and NHL.4–15 G-CSFs also improved delivery of full dose intensity chemotherapy at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival.4,6,8,11,13–17 However, in node-positive breast cancer18 and NHL,19 dose-dense regimens supported by G-CSFs improved disease-free and/or overall survival compared with conventional chemotherapy.

Meta-analyses have confirmed the efficacy of prophylactic CSFs in decreasing rates of infection,20,21 risk for neutropenia,20,21 length of hospitalization,21 and time to neutrophil recovery.22 Clark et al.22 found a marginal benefit of CSF in lowering infection-related mortality (odds ratio [OR], 0.51; 95% CI, 0.26–1.00; P = .05). In a recent meta-analysis of 17 randomized trials of prophylactic G-CSFs, including 3493 adult patients with nonmyeloid malignancies,23 G-CSF as primary prophylaxis reduces risk for FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; P < .001) and improves relative dose-intensity of the chemotherapy delivered (average difference between study arms, 8.4%; P = .001). For the first time, this analysis also reports a substantial reduction in risk for infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; P = .018) and all early deaths during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; P = .002).

Over the past decade, costs for inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.24 Economic analyses of CSFs have yielded mixed results, depending on the context of use.25–29 However, the policy of the NCCN Myeloid Growth Factors Panel is to look primarily at issues of therapeutic efficacy and clinical benefit, rather than cost. The indication for prophylactic CSF use depends on the risk for FN or other neutropenic events that can potentially compromise treatment.

To date, the main consistently observed toxicity associated with G-CSF therapy was mild to moderate bone pain.30 This is usually effectively controlled by nonnarcotic analgesics. The meta-analysis by Kuderer et al.31 confirmed a heightened risk for musculoskeletal pain associated with CSF (RR, 4.03; 95% CI, 2.15–7.52; P < .001). In a retrospective review, a heightened rate of bleomycin pulmonary toxicity was linked to G-CSF use in patients with Hodgkin lymphoma undergoing bleomycin-containing therapy.31

Rare cases of splenic rupture with G-CSF use, some of which were fatal, have also been reported.32 These cases occurred in patients and healthy donors in the stem cell transplantation setting. Some patients develop allergic reactions in the skin, respiratory system, or cardiovascular system (filgrastim only). Although a potentially increased risk for acute leukemia with G-CSF administration has been suggested, the Research on Adverse Drug Events and Reports (RADAR) group concluded that long-term safety data are still lacking to confirm this relationship.33 Toxicity risks associated with G-CSFs and GM-CSF are listed on page 75.

Prophylactic Use of CSFs

Risk Assessment

The guidelines begin with an evaluation of risk for chemotherapy-induced FN before the first cycle. The risk assessment involves major components, including...
disease type, chemotherapeutic regimen (high-dose, dose–dense, or standard-dose therapy), patient risk factors, and treatment intent. The NCCN panel designated 3 categories based on the intent of chemotherapy, including curative/adjuvant therapy, treatment directed toward prolongation of survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors (pages 69, 70, and 74), the patient is assigned to a high-risk group (> 20% risk for FN), intermediate group (10%–20% risk), or low-risk group (< 10% risk). Notably, no consensus nomogram for risk assessment currently exists. Although the NCCN panel outlines criteria to aid in assessment, independent clinical judgment should be exercised based on the patient’s situation. When determining the appropriate use of CSFs, along with assessing patient and treatment-related risks, the intent of cancer treatment should be considered. For example, one criterion identifying patients as high-risk is a previous neutropenic complication in the immediate previous cycle with no plan to reduce the dose intensity.

**Patients at High Risk for FN**

NCCN panel discussions have focused on defining a risk level for FN that would warrant routine use of prophylactic growth factors. The guidelines recommended prophylactic CSF if the risk for FN was 20% or greater. The most recent update of the ASCO guidelines and EORTC adopted the 20% threshold for considering routine prophylactic treatment.33,38

These consistent recommendations are based on results of several large randomized trials showing that the risk for FN can be significantly reduced with primary prophylaxis when the risk without prophylaxis is 20%. For example, Vogel et al.7 reported on the results of a double-blind, randomized, placebo-controlled multicenter study on whether first and subsequent cycle prophylactic CSF support with pegfilgrastim would significantly reduce FN in a regimen that had previously been associated with an expected FN incidence of 20%. This is the largest randomized study of prophylactic growth factor support performed. Women with breast cancer received docetaxel at 100 mg/m² every 3 weeks. In this double-blind study, designed with FN as the primary end point, 465 women received a placebo injection and 463 received pegfilgrastim, each administered 24 hours after chemotherapy. The placebo group had an overall incidence of FN of 17%, whereas the pegfilgrastim group had a 1% incidence. The incidence of hospitalization decreased from 14% to 1%, and the use of intravenous anti-infectives decreased from 10% to 2%, with all of these differences statistically significant (P < .001). The placebo group had an 11% rate of FN in the first cycle versus less than 1% in the pegfilgrastim group. For cycles 2 through 4, the rate of FN was 6% in the placebo group and less than 1% in the pegfilgrastim group.

A second trial reported the results of 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF.3 In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with 9 patients (10%) in the antibiotics plus FN group (P = .01); in cycles 2 to 5, the incidences were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis is effective in reducing FN and infections in patients with small cell lung cancer with the first cycle of chemotherapy. Furthermore, this strategy could be applied to other cancer patients with a similar risk for FN.

The NCCN, ASCO, and EORTC guidelines all recognize various special circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens may nonetheless be at high risk for FN from bone marrow compromise or comorbidity (see page 74).

Prophylactic CSF is recommended for any patient considered at high risk, regardless of whether the treatment is intended to be curative, prolong survival, or manage symptoms.

**Patients at Intermediate Risk for FN**

The NCCN panel defines intermediate risk as a 10% to 20% probability of developing FN or a neutropenic event that would compromise treatment. In all 3 categories of treatment intent, the panel recommends individualized consideration of CSF use based on physician and patient discussion of the risk–benefit ratio of the likelihood of developing FN, potential consequences of a neutropenic event, and implications of reduced chemotherapy dose delivery. When the intent of chemotherapy is to prolong survival or for symptom management, using CSFs is a difficult decision that requires careful discussion between physician and patient. If inalterable patient risk factors determine the risk, CSF is reasonable.
or dose reduction, if of comparable benefit, should be explored.

**Patients at Low Risk for FN**

For low-risk patients, as defined by a less than 10% risk, routine use of CSFs is not considered cost-effective and alternative treatment options are appropriate.\(^{24-26}\) However, CSFs may be considered if the patient is undergoing curative or adjuvant treatment and is at significant risk for serious medical consequences of FN, including death.

**Evaluation of Subsequent Chemotherapy Cycles**

After the first cycle, patient evaluation should be performed before each subsequent cycle to determine the risk categorization and treatment intent. If the patient experienced a previous episode of FN or a dose-limiting neutropenic event during the previous cycle of treatment with the same dose and schedule planned for the current cycle, this patient is now in the high-risk group.

If the patient experiences an episode such as this despite receiving CSF, the panel recommends a chemotherapy dose reduction or change in treatment regimen unless this will impact patient survival. If the patient does not develop FN or a dose-limiting neutropenic event and is believed to be benefiting from chemotherapy, the previous assessment should be repeated after each subsequent cycle.

**Chemotherapy Regimens and Risk for FN**

The development of FN is a common dose-limiting toxicity of many single agents and combination chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy-naïve patients who have an incidence of FN greater than 20% undergoing chemotherapy regimens in clinical trials are considered at high risk by the panel, and CSF-prophylaxis is recommended. Some regimens, such as the RICE (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-14 (mesna, ifosfamide, mitoxantrone, and etoposide) regimen for NHL, have only been tested with growth factor support. Benefits of pegfilgrastim have not been shown in regimens given over less than a 2-week duration. Pegfilgrastim should be avoided in patients undergoing weekly chemotherapy and should not be used with the FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen. Controversy surrounds the use of G-CSFs for patients with Hodgkin lymphoma undergoing bleomycin-containing chemotherapy. An increased risk for bleomycin pulmonary toxicity has been reported with G-CSF use for this disease in a retrospective study on 141 patients.\(^{31}\) In a systematic review of case reports by Azoulay et al.,\(^{37}\) 70 cases of G-CSF-related pulmonary toxicity was identified in cancer patients with neutropenia. Of these, 36 patients had received bleomycin, but most were those with NHL who have also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate).

Evens et al.\(^{38}\) showed that standard chemotherapy for Hodgkin lymphoma (ABVD [doxorubicin, bleomycin, vinblastine and dacarbazine]) can be safely administered at full dose without G-CSF support. However, this requires treatment with ABVD in some patients at the time of neutropenia. Until further evidence from larger prospective studies becomes available, prophylactic G-CSF use with ABVD can be considered after risks and benefits are discussed with the patient.

**Patient Risk Factors for Developing FN**

Patient risk factors are an important consideration in estimating the overall risk for FN, particularly when chemotherapy regimens are considered an intermediate risk.\(^{39}\) Patient factors may elevate the overall risk to a high-risk category, where prophylactic CSFs are more routinely recommended. For example, many regimens for breast and lung cancer are associated with an intermediate risk for neutropenic complications, and it is important to identify which of these patients would be considered at high risk. Higher age, notably older than 65 years, is the most important risk factor for developing severe neutropenia.\(^{40-46}\) Other risk factors include poor performance status; comorbidities, including renal or liver dysfunction; and preexisting conditions, such as neutropenia and infection.\(^{49}\)

**Therapeutic Use of CSFs**

Compared with prophylactic use, less evidence supports therapeutic use of CSFs for FN as an adjunctive to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials, Clark et al.\(^{73}\) reported a shorter length of hospitalization (HR, 0.63; 95% CI, 0.49–0.82; \(P = .0006\)), shorter time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; \(P < .00001\)), but no improvement in overall survival associated with therapeutic CSF. In an earlier meta-analysis, Berghmans et al.\(^{47}\) again found no difference in
mortality but were unable to assess other clinical benefits. Notably, this analysis did not include a multi-center trial of 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor who were randomized to treatment with G-CSF or placebo. The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days; \( P = .0004 \)), antibiotic therapy (median 5 vs. 6 days; \( P = .013 \)), and hospital stay (median 5 vs. 7 days; \( P = .015 \)).

Patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, because pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional CSFs. So, as there is currently a lack of evidence for therapeutic use of pegfilgrastim, only filgrastim or sargramostim should be administered in the therapeutic setting. For patients who have not received prophylactic CSFs, the panel recommends an evaluation for risk factors for infection-related complications or poor clinical outcome. These include old age (> 65 years), sepsis syndrome, severe (absolute neutrophil count [ANC] < 100/\( \mu l \)) or anticipated prolonged (> 10 days) neutropenia, pneumonia, invasive fungal infection, or other clinically-documented infections. If risk factors are present, CSFs should be considered.

**Dosing and Administration**

Currently used myeloid growth factors for the prophylaxis of FN and maintenance of scheduled dose delivery include filgrastim, pegfilgrastim, and sargramostim. Although data from randomized studies support the use of filgrastim and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on its use after induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. Therefore, when choosing among myeloid growth factors, filgrastim and pegfilgrastim are considered category 1 recommendations, while sargramostim is considered a category 2B recommendation.

Initial doses of filgrastim are initiated beginning within 1 to 3 days after completion of chemotherapy in a daily dose of 5 mcg/kg until post-nadir ANC recovery is at normal or near-normal ANC levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. There is also evidence to support use of pegfilgrastim 24 hours after completion of chemotherapy given every 3 weeks in one dose of 6 mg per cycle of treatment. There are insufficient data to support dose and schedule of weekly regimens or schedules less than 2 weeks and these cannot be recommended. Same day administration of pegfilgrastim is also not recommended. Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after have shown less benefit in 2 studies of regimens associated with moderate to high-risk neutropenia. Same day pegfilgrastim showed comparable benefit in one study of a regimen with low risk neutropenia, but pegfilgrastim would not be routinely indicated. There is insufficient evidence from randomized trials to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. It is indicated for use following induction chemotherapy in older adult patients with AML. Again, administration of sargramostim the same day as chemotherapy is not recommended.

The subcutaneous route is preferred for all 3 agents. There are no data to support alternative dosing schedules in intermediate- and high-risk patients. The NCCN Myeloid Growth Factors Panel Members do not routinely recommend use of prophylactic antibiotics in these settings. In addition, prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.

**Severe Chronic Neutropenia**

These guidelines focus on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia requiring G-CSF therapy is briefly discussed in this section. G-CSF is established as an effective treatment for cyclic, congenital, and idiopathic neutropenia (types of severe chronic neutropenia), based on a randomized control trial involving 123 patients. In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers, and infections. Subsequent observation studies show that patients with idiopathic and cyclic neutropenia generally respond to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF (1–3 mcg/kg/d). Patients with congenital neutropenia generally require somewhat higher doses (3–10 mcg/kg/d). All patients should have doses adjusted to maintain a blood neutrophil
level in the normal or low-normal range. Acute adverse
effects include bone pain, arthralgias, and myalgias,
which usually diminish in the first few weeks of
treatment.

The greatest concern is that patients with severe
congenital neutropenia, but not all patients with
chronic neutropenia, are at risk for developing
myelodysplasia and leukemia, with or without G-CSF
treatment. More severely affected patients, as reflected
by the requirement of higher doses of G-CSF, seem
to be at greater risk. These considerations emphasize
the importance of making a correct diagnosis and fol-
lowing up these patients carefully. Currently, the only
alternative therapy is hematopoietic stem cell trans-
plantation. For further reading on chronic neutro-
penia, refer to the Web site developed by the Severe
Chronic Neutropenia International Registry (http://
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The NCCN guidelines staff have nothing to disclose.

*All guidelines panel members will be required to provide financial disclosures by 12/31/08. Go to www.nccn.org for updates.