Myeloid Growth Factors

Version 1.2012

NCCN.org
NCCN Guidelines Version 1.2012 Panel Members
Myeloid Growth Factors

* Jeffrey Crawford, MD/Chair †‡
Duke Cancer Institute

Jeffrey Allen, MD †
St. Jude Children’s Research Hospital/
University of Tennessee Cancer Institute.

James Armitage, MD †‡
UNMC Eppley Cancer Center at
The Nebraska Medical Center

Lodovico Balducci, MD †‡
H. Lee Moffitt Cancer Center & Research Institute

Douglas W. Blayney, MD †
Stanford Cancer Institute

Spero R. Cataland, MD †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Mark L. Heaney, MD, PhD †‡ pró
Memorial Sloan-Kettering Cancer Center

Susan Hudock, PharmD Σ
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Dwight D. Kloth, PharmD Σ
Fox Chase Cancer Center

David J. Kuter, MD, DPhil †‡
Massachusetts General Hospital Cancer Center

Gary H. Lyman, MD, MPH †‡
Duke Cancer Institute

Brandon McMahon, MD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Sepidah Shayani, PharmD Σ
City of Hope Comprehensive Cancer Center

David P. Steensma, MD †
Dana-Farber/Brigham and Women’s Cancer Center

Saroj Vadhvan-Raj, MD †þ
The University of Texas MD Anderson Cancer Center

Peter Westervelt, MD, PhD †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Michael Westmoreland, PharmD Σ
The University of Texas MD Anderson Cancer Center

NCCN
Mary Dwyer, MS
Maria Ho, PhD

† Medical oncology
‡ Hematology/Hematology oncology
þ Internal medicine
Σ Pharmacology
* Writing Committee Member
**NCCN Myeloid Growth Factors Panel Members**

**Summary of the Guidelines Updates**

**Evaluation, Risk Assessment, and Prophylactic Use (MGF-1)**

**Evaluation Prior to Second and Subsequent Chemotherapy Cycles (MGF-2)**

**Therapeutic Use of CSF for Febrile Neutropenia (MGF-3)**

**Examples of Disease Settings and Chemotherapy Regimens and Risk for Febrile Neutropenia (MGF-A)**

**Patient Risk Factors for Developing Febrile Neutropenia (MGF-B)**

**Toxicity Risks with Growth Factors (MGF-C)**

**Patient Risk Factors for Poor Clinical Outcomes or for Developing Infection-Associated Complications (MGF-D)**

**Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-E)**

---

**Clinical Trials:** NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html.

**NCCN Categories of Evidence and Consensus:** All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

---

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN 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® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2012.
Updates in Version 1.2012 of the NCCN Myeloid Growth Factors Guidelines from Version 1.2011 include:

**MGF-1**
- Footnote “d” was modified by combining with another footnote as, “There are many factors that need to be evaluated to determine a patient’s risk categorization; these include type of chemotherapy regimen (See MGF-A) and patient risk factors including a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity (See MGF-B).”
- Footnote “f” was modified as, “The confounding effects of anthracycline and alkylating agent chemotherapy dose and schedule, additional radiation dose and field size, and colony stimulating factors use on the slight excess risk of leukemia and MDS in patients treated with these agents and modalities are currently unquantified being evaluated. See Discussion for further details.” and removing, “The associated risk of leukemia and MDS has been suggested by epidemiologic studies. A systematic review of randomized clinical trials of patients receiving chemotherapy with or without primary G-CSF support with at least two years of follow-up reported relative and absolute risk increase of AML/MDS of 1.92 and 0.41%, respectively. The relative risk and absolute risk reduction for all-cause mortality with an average follow-up of five years were 0.897 and 3.40%, respectively, and correlated with chemotherapy relative dose intensity with G-CSF support (Lyman GH, Dale DC, Wolff DA, et al. J Clin Oncol 2010;28: 2914-2924).”
- Footnote, “This table applies to prophylaxis beginning with the first cycle of chemotherapy for solid tumors and non-myeloid malignancies. (See MGF-E)” was removed.

**MGF-3**
- Patients receiving prophylactic CSF (filgrastim or sargramostim), footnote “n” was added to the management “Continue CSFs.”

**MGF-A 1 of 5**
- Regimens with a High-Risk for Febrile Neutropenia
  - Non-Hodgkin’s Lymphomas, for CHOP-14, “± rituximab” was added with a corresponding reference.
  - The note regarding bleomycin was changed from “There is one retrospective review that suggests pulmonary toxicity may be increased using G-CSF in bleomycin containing regimens” to “When using G-CSFs with bleomycin-containing regimens, there may be an increased risk for pulmonary toxicity.” (Also for MGF-A 2 of 5)

**MGF-A 2 of 5**
- Regimens with an Intermediate-Risk for Febrile Neutropenia
  - Non-small cell lung cancer, a note was added for the carboplatin/paclitaxel regimen: “If carboplatin dose is AUC >6 and/or Japanese ancestry.”

**MGF-C**
- Filgrastim
  - Footnote 2, “There may be an increased risk for pulmonary toxicity in bleomycin-containing regimens (See discussion for further details.)” was added.
  - Warnings, “Alveolar hemorrhage and hemoptysis” was added.
  - Precautions, “Immunogenecity” was added.
- Pegfilgrastim
  - Adverse reactions, “Pain in extremity” was added.
- Sargramostim
  - The adverse events section was updated.
**EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE**

<table>
<thead>
<tr>
<th>Risk Assessment for Febrile Neutropenia</th>
<th>CHEMOTHERAPY TREATMENT INTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies</td>
<td>PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA</td>
</tr>
<tr>
<td>- Disease</td>
<td>- CSFs (category 1 for G-CSFs)</td>
</tr>
<tr>
<td>- Chemotherapy regimen</td>
<td>- CSFs (category 1 for G-CSFs)</td>
</tr>
<tr>
<td>- High-dose therapy</td>
<td>- CSFs</td>
</tr>
<tr>
<td>- Dose-dense therapy</td>
<td></td>
</tr>
<tr>
<td>- Standard-dose therapy</td>
<td></td>
</tr>
<tr>
<td>- Patient risk factors</td>
<td>- Consider CSF</td>
</tr>
<tr>
<td>- Treatment intent</td>
<td>- Consider CSF</td>
</tr>
<tr>
<td>(curative vs. palliative)</td>
<td></td>
</tr>
<tr>
<td>- High (&gt;20%)</td>
<td>- Consider CSF</td>
</tr>
<tr>
<td>- Intermediate (10-20%)</td>
<td></td>
</tr>
<tr>
<td>- Low (&lt;10%)</td>
<td>- No CSFs</td>
</tr>
</tbody>
</table>

| CSFs= Colon-stimulating factors |

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

The NCCN Myeloid Growth Factors Guidelines were formulated in reference to adult patients.

For use of growth factors in Myelodysplastic Syndromes (MDS), see the NCCN Myelodysplastic Guidelines, and in Acute Myeloid Leukemia (AML), see the NCCN Acute Myeloid Leukemia Guidelines.

Febrile neutropenia is defined as a single temperature ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 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.

There are many factors that need to be evaluated to determine a patient’s risk categorization; these include type of chemotherapy regimen (See MGF-A) and patient risk factors including a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity (See MGF-B).

Only consider CSFs if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

The use of CSFs in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is 10-20%, CSFs are reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

The confounding effects of chemotherapy dose and schedule, additional radiation, and CSFs use on the excess risk of leukemia and MDS in patients treated with these agents and modalities are currently being evaluated. See Discussion for further details.

There is category 1 evidence for G-CSFs for a reduction of: risk of febrile neutropenia, hospitalization, and intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSFs for a reduction in infection-related mortality during the course of treatment. (See Discussion for further details.)

Only consider CSFs if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

The use of CSFs in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is 10-20%, CSFs are reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

See Toxicity Risks with Growth Factors (MGF-C).
**EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES**

- **Febrile neutropenia\(^c\) or dose-limiting neutropenic event\(^j\)**
  - Prior use of CSFs
    - Consider dose reduction or change in treatment regimen
  - No prior use of CSFs
    - Consider CSFs (See Risk Assessment for Febrile Neutropenia, MGF-1)
- **No febrile neutropenia\(^c\) or dose-limiting neutropenic event\(^j\)**
  - Repeat assessment after each subsequent cycle

\(^c\)Febrile neutropenia is defined as, single temperature: $\geq 38.3^\circ C$ orally or $\geq 38.0^\circ C$ over 1 h; neutropenia: $< 500$ neutrophils/mcL or $< 1,000$ neutrophils/mcL and a predicted decline to $\leq 500$/mcL over the next 48 h. See NCCN Prevention and Treatment of Cancer-Related Infections Guidelines.

\(^j\)Dose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy.

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Patients receiving prophylactic CSFs (filgrastim or sargramostim) → Continue CSFs

Patients who have received prophylactic pegfilgrastim → No additional CSFs

Patients who did not receive prophylactic CSFs → Consider CSFs

Risk factors not present for an infection-associated complication → No CSFs

Risk factors present for an infection-associated complication → Consider CSFs

Febrile neutropenia is defined as, single temperature: ≥ 38.3°C orally or ≥ 38.0°C over 1 h; neutropenia: < 500 neutrophils/mL or < 1,000 neutrophils/mL and a predicted decline to ≤ 500/mL over the next 48 h. See the NCCN Prevention and Treatment of Cancer-Related Infections Guidelines.

For antibiotic therapy recommendations for fever and neutropenia, see the NCCN Prevention and Treatment of Cancer-Related Infections Guidelines.

The decision to use CSFs in the therapeutic setting is controversial. See Discussion for further details.

See Patient Risk Factors for Poor Clinical Outcomes or for Developing Infection-Associated Complications (MGF-D).

There are no data on pegfilgrastim in the therapeutic setting. Either filgrastim or sargramostim should be used with initial dosing as outlined in Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-E) and discontinued at time of neutrophil recovery.

There are no studies that have addressed therapeutic use of filgrastim for febrile neutropenia in patients who have already received prophylactic pegfilgrastim. However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggests that additional CSFs will not be beneficial.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Examples of Disease Settings and Chemotherapy Regimens with a High Risk for 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 the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-B)
- Pegfilgrastim has not been documented to have benefit in regimens given under a 2-week duration.
- 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, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)\(^1\)
- Docetaxel + trastuzumab (metastatic or relapsed)\(^2\)
- Dose-dense AC→T\(^+\) (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)\(^3\)
- AT (doxorubicin, paclitaxel) (metastatic or relapsed)\(^4\)
- AT (doxorubicin, docetaxel) (metastatic or relapsed)\(^5\)
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)\(^6\)

Breast Cancer
- BEACOPP\(^1\) (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)\(^8\)

Kidney Cancer
- Doxorubicin/gemcitabine\(^9\)

Hodgkin Lymphoma
- BEACOPP\(^1\) (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)\(^8\)

Non-Hodgkin's Lymphomas
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory)\(^10,11\)
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphomas, 2nd line, salvage)\(^12\)
- RICE \(^*\) (rituximab, ifosfamide, carboplatin, etoposide)\(^13\)
- CHOP-14\(^*\) (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab\(^14,15\)
- MINE (mesna, ifosfamide, novantrone, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphomas, 2nd line, refractory)\(^16\)
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd line)\(^17\)
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, 2nd line, recurrent)\(^18\)
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)\(^19,20\)

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)\(^21\)
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)\(^22\)

Multiple Myeloma
- BEAM (cyclophosphamide, etopooside, Ara-C, melphalan)\(^23\)
- Bortezomib + dexamethasone\(^24\)
- Velcade + dexamethasone\(^25\)

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine\(^23\)
- Decitabine\(^24\)

Ovarian Cancer
- Topotecan\(^26\)
- Paclitaxel\(^27\)
- Docetaxel\(^27\)

Testicular Cancer
- VelIP (vinblastine, ifosfamide, cisplatin)\(^31\)
- VIP (etoposide, ifosfamide, cisplatin)\(^31\)
- BEP\(^*\) (bleomycin, etoposide, cisplatin)\(^32\)
- TIP (paclitaxel, ifosfamide, cisplatin)\(^33\)

*In general, dose-dense regimens require growth factor support for chemotherapy administration.
†When using G-CSFs with bleomycin-containing regimens, there may be an increased risk for pulmonary toxicity. (See Discussion for further details.)

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia MGF-A (2 of 5)

See Chemotherapy Regimen References MGF-A (3 of 5)
Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk for 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 the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-B)

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

Breast Cancer
- Docetaxel every 21 days
- Epirubicin (adjuvant)
- Epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil (adjuvant)
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)
- AC + sequential docetaxel + trastuzumab (adjuvant)
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel
- Paclitaxel every 21 days (metastatic or relapsed)
- Vinblastine (metastatic or relapsed)

Cervical Cancer
- Cisplatin + topotecan (recurrent or metastatic)
- Topotecan (recurrent or metastatic)
- Irinotecan (recurrent or metastatic)

Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)
- Etoposide and Gastric Cancers
- Irinotecan/cisplatin
- Epirubicin/cisplatin/5-fluorouracil
- Epirubicin/cisplatin/capcitabine

Hodgkin Lymphoma
- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)
- Stanford V (mekloretamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)

Non-Hodgkin's Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt's lymphoma, recurrent)
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, diffuse large B-cell lymphoma, recurrent)
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)
- GDP (gemcitabine, dexamethasone, cisplatin) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd line)
- GDP (gemcitabine, dexamethasone, cisplatin) + Rituximab (diffuse large B-cell lymphoma, 2nd line)
- FM (fludarabine, mitoxantrone)
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone)
- Cisplatin/paclitaxel (adjuvant, advanced/ metastatic)
- Cisplatin/vinorelbine (adjuvant, advanced/ metastatic)
- Cisplatin/docetaxel (adjuvant, advanced/ metastatic)
- Cisplatin/irinotecan (advanced/metastatic)
- Cisplatin/etoposide (adjuvant, advanced/ metastatic)
- Carboplatin/paclitaxel* (adjuvant, advanced/ metastatic)
- Docetaxel (advanced/metastatic)

Ovarian Cancer
- Carboplatin/docetaxel
- Prostate Cancer
- Cabazitaxel
- Small Cell Lung Cancer
- Etoposide/carboplatin
- Testicular Cancer
- Etoposide/cisplatin
- Uterine Cancer
- Docetaxel (uterine sarcoma, advanced or metastatic)

†When using G-CSFs with bleomycin-containing regimens, there may be an increased risk for pulmonary toxicity. (See Discussion for further details.)

*If carboplatin dose is AUC >6 and/or Japanese ancestry.

**The published results for cabazitaxel have an 8% rate of febrile neutropenia and neutropenic deaths were reported. Primary prophylaxis with G-CSFs should be considered in patients with high-risk clinical features.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CHEMOTHERAPY REGIMEN REFERENCES (3 of 5)


Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**CHEMOTHERAPY REGIMEN REFERENCES (4 of 5)**


Continued on next page
Myeloid Growth Factors

CHEMOTHERAPY REGIMEN REFERENCES (5 of 5)


Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

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

- Older patient, notably patients age 65 and older (See NCCN Senior Adult Oncology Guidelines)
- Previous chemotherapy or radiation therapy
- Preexisting neutropenia or bone marrow involvement with tumor
- Preexisting conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
TOXICITY RISKS WITH GROWTH FACTORS

Filgrastim1,2

• Warnings
  ➤ Allergic reactions
    ◦ Skin: rash, urticaria, facial edema
    ◦ Respiratory: wheezing, dyspnea
    ◦ Cardiovascular: hypotension, tachycardia
  ➤ Splenic rupture
  ➤ Acute respiratory distress syndrome
  ➤ Alveolar hemorrhage and hemoptysis
  ➤ Sickle cell crises
  ➤ MDS and AML (See Discussion for details)

• Precautions
  ➤ Cutaneous vasculitis
  ➤ Immunogenicity

• Adverse reactions
  ➤ Medullary bone pain

Pegfilgrastim3

• Warnings
  ➤ Splenic rupture
  ➤ Acute respiratory distress syndrome
  ➤ Allergic reactions, including anaphylaxis
  ➤ Sickle cell crises

• Adverse reactions
  ➤ Bone pain
  ➤ Pain in extremity

Sargramostim4,5

• Warnings
  ➤ Fluid retention: edema, capillary leak syndrome, pleural and/or pericardial effusion
  ➤ Respiratory symptoms: Sequestration of granulocytes in pulmonary circulation, dyspnea
  ➤ Cardiovascular symptoms: Occasional transient supraventricular arrhythmia. Use with caution in patients with preexisting cardiac disease.
  ➤ 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.

• Adverse events occurring in >10% of patients receiving sargramostim in controlled clinical trials and reported in a higher frequency than placebo
  ➤ AML - fever, skin reactions, metabolic disturbances, nausea, vomiting, weight loss, edema, anorexia
  ➤ Autologous bone marrow transplant or peripheral blood progenitor cell transplant - asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder
  ➤ Allogeneic bone marrow transplant or peripheral blood progenitor cell transplant - abdominal pain, chills, chest pain, diarrhea, nausea, vomiting, hematemesis, dysphagia, GI hemorrhage, pruritus, bone pain, arthralgia, eye hemorrhage, hypertension, tachycardia, bilirubinemia, hyperglycemia, increased creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high BUN, and high cholesterol

1 View filgrastim prescribing information.
2 There may be an increased risk for pulmonary toxicity in bleomycin-containing regimens (See Discussion for further details.).
3 View pegfilgrastim prescribing information.
4 View sargramostim prescribing information.
5 Toxicity data are based primarily on studies from leukemia and transplant patients.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PATIENT RISK FACTORS FOR POOR CLINICAL OUTCOMES OR FOR DEVELOPING INFECTION-ASSOCIATED COMPLICATIONS¹,²

Patient risk factors include:
- Sepsis syndrome
- Age > 65 years
- Severe neutropenia (absolute neutrophil count <100/mcl)
- Neutropenia expected to be more than 10 days in duration
- Pneumonia
- Invasive fungal infection
- Other clinically documented infections
- Hospitalization at the time of fever
- Prior episode of febrile neutropenia

¹The decision to use or not to use CSFs in the treatment of febrile neutropenia is controversial. See Discussion for further details.
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 the 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. Administration of growth factor on the same day as chemotherapy is not recommended.
  - There is evidence to support use for chemotherapy regimens given every 3 wks (category 1).
  - Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 wks.
  - There are insufficient data to support dose and schedule of weekly regimens or chemotherapy schedules less than 2 wks, and these cannot be recommended.

- Sargramostim (category 2B)
  - Used in clinical trials at a dose of 250 mcg/m²/day (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 the same day as chemotherapy is not recommended.

- Prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.
- Subcutaneous route is preferred for all 3 agents.
- There are no data to 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.

---

1 Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after chemotherapy have shown an increase in febrile neutropenia and/or other adverse events. See Discussion for details.

2 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.
The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Neutropenia (< 500 neutrophils/mcl or < 1,000 neutrophils/mcl and a predicted decline to ≤ 500/mcl over the next 48 h) and resulting febrile neutropenia (≥ 38.3°C orally or ≥ 38.0°C over 1 h) can be induced by myelosuppressive chemotherapy. Febrile neutropenia (FN) in turn is a major dose-limiting toxicity of chemotherapy, often requiring prolonged hospitalization and broad-spectrum antibiotic use (reviewed by Lyman and Kuderer). These can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome. Studies have demonstrated that prophylactic use of colony-stimulating factors (CSFs) can reduce the risk, severity, and duration of FN, but its cost has prevented its routine use for all patients receiving myelosuppressive chemotherapy. Selective use of CSFs in patients at increased risk for neutropenic complications may, however, enhance the cost-effectiveness.

The risk of 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.

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. Differences in the reported rates of neutropenic complications may relate to differences in study patient populations as well as the 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 Dale et al showed that about 25-40% of treatment-naive patients develop FN with common chemotherapy regimens. Occurrence of FN may delay subsequent chemotherapy courses or result in dose reduction that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. In addition, correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.

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 following induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. It should be noted that recommendations are based on evidence derived
mainly from studies on G-CSFs. There is a lack of head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs.

The NCCN Myeloid Growth Factors Guidelines is focused on the use of CSFs in the cancer setting. Specifically, the guidelines address adult patients with solid tumors and non-myeloid malignancies. Growth factors in the treatment of myeloid malignancies are discussed in the NCCN Myelodysplastic Syndromes Guidelines and the NCCN Acute Myeloid Leukemia Guidelines.

**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 non-Hodgkin’s lymphoma. G-CSFs also improved delivery of full dose intensity of chemotherapy at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival. However, in node-positive breast cancer and aggressive lymphoma, dose-dense regimens supported by G-CSFs improved disease-free and/or overall survival compared to conventional chemotherapy.

Meta-analyses have confirmed the efficacy of prophylactic CSFs in decreasing rates of infection, and risk of neutropenia. In a meta-analysis of seventeen randomized trials of prophylactic G-CSFs including 3493 adult patients with solid tumor and lymphoma, G-CSF as primary prophylaxis reduces risk of FN (RR = 0.54; 95% CI, 0.43 to 0.67; P < 0.001) and improves relative dose-intensity of the chemotherapy delivered (average difference between study arms 8.4%; P = 0.001). For the first time, this analysis also reported a substantial reduction in risk of infection-related mortality (RR = 0.55; 95% CI, 0.33 to 0.90; P = 0.018) and all early deaths during chemotherapy (RR = 0.60; 95% CI, 0.43 to 0.83; P = 0.002). The survival advantage is confirmed in a recent systematic review by Lyman et al of 25 randomized controlled trials involving over 12,000 patients undergoing chemotherapy with or without G-CSF support. With an average follow-up of 5 years, G-CSF was associated with 3.40% and 0.90 reduction in absolute and relative risk for all-cause mortality, respectively, although this comes with an increase in risk for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (see below). The degree of benefit correlated with chemotherapy dose intensity.

Over the last decade, the costs of inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%. Economic analyses of CSFs have yielded mixed results, depending on the context of usage. However, the policy of the NCCN Myeloid Growth Factors guidelines 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 of 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. This is usually effectively controlled by non-narcotic analgesics. The meta-analysis by Kuderer et al confirmed a heightened risk of musculoskeletal pain associated with CSF (RR = 4.03; 95% CI, 2.15 to 7.52; P < 0.001). In a retrospective review, a heightened rate of bleomycin pulmonary toxicity has been linked to G-CSF use in Hodgkin’s lymphoma patients receiving bleomycin-containing therapy, especially ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). This toxicity potential is unclear for BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), although bleomycin is given every three weeks in this regimen as opposed to every two weeks in ABVD. Clinicians should be alert to signs and
symptoms of this complication for both regimens. An increase in bleomycin pulmonary toxicity has not been reported with G-CSF use in bleomycin-containing testicular cancer chemotherapy regimens.\textsuperscript{18}

There have also been reports of rare cases of splenic rupture with G-CSF usage, some of which were fatal.\textsuperscript{31, 32} These cases occurred in patients and healthy donors in the stem cell transplantation setting. Some patients develop allergic reactions in the skin, the respiratory system, or the cardiovascular system (filgrastim only).

Although there have been suggestions of potentially increased risk of AML/MDS with G-CSF administration from epidemiological studies, this was not observed in individual randomized trials.\textsuperscript{34} The recent analysis by Lyman et al\textsuperscript{24} reported an increase in absolute and relative risk of AML/MDS of 0.41\% and 1.92, respectively, related to G-CSF. It is not possible from this meta-analysis to determine whether the risk of AML/MDS is secondary to G-CSF or related to the higher total doses of chemotherapy. As discussed above, overall mortality was nevertheless decreased.

**Prophylactic Use of CSFs**

**Risk Assessment**

The guidelines begin with an evaluation of risk for chemotherapy-induced FN prior to the first cycle. The risk assessment involves varied components including the disease type, chemotherapeutic regimen (high dose, dose dense or standard dose therapy), patient risk factors, and treatment intent. Three categories based on the intent of chemotherapy have been designated by the NCCN panel. These include curative/adjuvant therapy, treatment directed toward prolongation of survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to a high risk group (> 20\% risk of FN), an intermediate group (10-20\% risk) and low risk group (< 10\% risk). Of note, there is currently no consensus nomogram for risk assessment. While 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, in addition to assessing patient and treatment-related risk, consideration should be given to the intent of cancer treatment. For example, one criterion that identifies a high risk patient is a previous neutropenic complication in the immediate previous cycle with no plan to reduce the dose intensity.

**Patients at High Risk of FN**

NCCN panel discussions have focused on defining a risk level of FN that would warrant routine use of prophylactic growth factors. The guidelines recommended prophylactic CSF if the risk of FN was 20\% or greater. The most recent update of the ASCO guidelines and the European Organisation for Research and Treatment of Cancer (EORTC) both adopted the 20\% threshold for considering routine prophylactic treatment.\textsuperscript{35, 36}

These consistent recommendations are based on the results of several large randomized trials that have documented that the risk of FN can be significantly reduced by primary prophylaxis when the risk of FN without prophylaxis is 20\%. For example, Vogel and colleagues reported on the results of a double blind, randomized, placebo-controlled multicenter study to demonstrate 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\%.\textsuperscript{8} This is the largest randomized study of prophylactic growth factor support that has been performed. Women with breast cancer received docetaxel at 100 mg/m\(^2\) every 3 weeks. Four hundred
and sixty five women received a placebo injection and 463 women received pegfilgrastim, each administered 24 hours after chemotherapy in a double blind study designed with FN as the primary endpoint. The placebo group had an overall incidence of FN of 17%. By contrast, the pegfilgrastim group had a 1% incidence. The incidence of hospitalization was reduced from 14% to 1%, and the use of IV anti-infectives was reduced from 10% to 2%, with all of these differences statistically significant (p<0.001). In cycle 1, there was an 11% rate of FN in the first cycle for the placebo group versus <1% in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN with <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. In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with nine patients (10%) in the antibiotics plus FN group (P = 0.01). In cycles 2 to 5, the incidences of FN 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 considered for other cancer patients with a similar risk of FN.

The NCCN, ASCO and EORTC guidelines all recognize a variety of special circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens may nonetheless be at high risk of FN due to bone marrow compromise or comorbidity.

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

Patients at Intermediate Risk of FN
The NCCN panel defines intermediate risk as a 10-20% probability of developing FN or a neutropenic event that would compromise treatment. In all three categories of treatment intent, the panel recommends individualized consideration of CSF use based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing FN, the potential consequences of a neutropenic event and the implications of reduced chemotherapy dose delivery. When the intent of chemotherapy is designed to prolong survival or for symptom management, the use of CSF is a difficult decision and requires careful discussion between the physician and patient. If patient risk factors determine the risk, CSF is reasonable. If the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

Patients at Low Risk of FN
For low-risk patients, as defined by a <10% risk, routine use of CSFs is not considered cost-effective and alternative treatment options are appropriate. However, CSFs may be considered if the patient is receiving 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 prior to 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 (a nadir or a day-of-treatment count impacting the planned dose of chemotherapy) 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 such an episode despite receiving CSF, the panel recommends a chemotherapy dose reduction or change in treatment regimen unless there is an impact on patient survival. If the patient does not develop FN or a dose-limiting neutropenic event and is thought to be benefiting from chemotherapy, the previous assessment should be repeated after each subsequent cycle.

Chemotherapy Regimens and Risk of 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. As discussed above, chemotherapy regimens that have an incidence of FN greater than 20% in clinical trials in chemotherapy-naive patients are considered by the panel at ‘high risk,’ and CSF-prophylaxis is recommended. It should be noted that some regimens, such as the RICE and CHOP-14 regimen for non-Hodgkin’s lymphoma have only been tested with growth factor support. Benefits of pegfilgrastim have not been shown in regimens given under a two-week duration. Pegfilgrastim should be avoided in patients receiving weekly chemotherapy.

There has been controversy surrounding the use of G-CSFs for patients with Hodgkin’s lymphoma undergoing bleomycin-containing chemotherapy. An increased risk of bleomycin pulmonary toxicity has been reported with G-CSF use for this disease in a retrospective study on 141 patients. In a systematic review of case reports by Azoulay and colleagues, 70 cases of G-CSF-related pulmonary toxicity was identified in cancer patients with neutropenia. 36 patients had received bleomycin, but the majority of these were non-Hodgkin’s lymphoma patients who have also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). Of note, this possible risk of increased pulmonary toxicity was not seen with bleomycin-containing testicular cancer chemotherapy.

Evens et al showed that standard chemotherapy for Hodgkin’s lymphoma (ABVD) 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 discussion of risks and benefits with the patient.

Patient Risk Factors for Developing FN

As previously mentioned, patient risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk (reviewed by Lyman et al). 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 of neutropenic complications, and it is important to identify which of these patients would be considered at high risk. Even a low-risk regimen does not necessarily preclude the use of CSFs in a patient with high risk factors.

Higher age, notably over 65 years, is the most important risk factor for developing severe neutropenia (see NCCN Senior Adult Oncology Guidelines). Other risk factors include previous chemotherapy or radiotherapy, pre-existing neutropenia or tumor involvement in the bone marrow, poor performance status, comorbidities including renal or liver dysfunction, and pre-existing conditions such as neutropenia and infection. Most of these have been confirmed as independent risk factors for neutropenic complications in a risk model developed by...
Lyman and colleagues that was validated in a study population of 3,760 cancer patients beginning chemotherapy.48

**Therapeutic Use of CSFs**

Compared to prophylactic use, there is less evidence supporting therapeutic use of CSFs for FN as an adjunctive to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials 49, Clark and colleagues reported a shorter length of hospitalization (HR = 0.63; 95% CI, 0.49 to 0.82; P = 0.0006), shorter time to neutrophil recovery (HR = 0.32; 95% CI, 0.23 to 0.46; P < 0.00001), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al 50 again found no difference in mortality, but they were unable to assess other clinical benefits. Of note, Berghmans’ analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF. The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days, P = 0.0004), antibiotic therapy (median 5 vs. 6 days, P = 0.013) and hospital stay (median 5 vs. 7 days, P = 0.015).

Patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, since pegylgrastim is long-acting, those who have received prophylactic pegylgrastim should not be treated with additional CSF.52 Also, as there is currently a lack of evidence for therapeutic use of pegylgrastim, only filgrastim or sargramostim should be administered in the therapeutic setting. For patients who have not received prophylactic CSFs, the NCCN panel recommends an evaluation for risk factors for infection-related complications or poor clinical outcome. These include: old age (> 65 years), sepsis syndrome, severe (ANC < 100/mcl) or anticipated prolonged (> 10 days) neutropenia, pneumonia, invasive fungal infection or other clinically-documented infections, hospitalization, and prior episode of FN. 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, pegylgrastim and sargramostim. While data from randomized studies support the use of filgrastim and pegylgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on its use following induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. Therefore, when choosing among myeloid growth factors, filgrastim and pegylgrastim 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 to normal or near-normal ANC levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits.

Because pegylgrastim is longer-acting than filgrastim, a single injection of 6 mg, given 1 to 3 days after administration of chemotherapy, is sufficient per chemotherapy cycle. There is evidence to support use of pegylgrastim 1 day after completion of chemotherapy given every 3 weeks.8, 53 There are insufficient data to support dose and schedule of weekly regimens or schedules less than 2 weeks and these cannot be recommended. However, the panel agreed that pegylgrastim can be given every 2 weeks.54 Same day administration of pegylgrastim is not recommended. Phase II studies of pegylgrastim administration the
same day as chemotherapy versus administration the day after chemotherapy have demonstrated increased incidence of FN and/or adverse events in breast cancer and lymphoma.55-57 Same day pegfilgrastim showed comparable benefit in one study of a regimen with low risk neutropenia, but in this setting pegfilgrastim would not be routinely indicated.58

There is insufficient evidence from randomized trials to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. Sargramostim is indicated for use following induction chemotherapy in older adult patients with AML.59 Again, administration of sargramostim on the same day as chemotherapy is not recommended. The subcutaneous route is preferred for all three 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

The NCCN Myeloid Growth Factors Guidelines is focused on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia that requires G-CSF therapy is briefly discussed below. G-CSF is established as an effective treatment for cyclic, congenital and idiopathic neutropenia (types of severe chronic neutropenia), based a randomized control trial involving 123 patients.60 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/day). Congenital neutropenia patients generally require somewhat higher doses (3-10 mcg/kg./day). 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 the diagnosis of severe congenital neutropenia, but not all patients with chronic neutropenia, are at risk of evolving to myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, as reflected by the requirement of higher doses of G-CSF, appear to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following these patients carefully. Currently the only alternative therapy is hematopoietic stem cell transplantation. For further reading on chronic neutropenia, refer to the web site developed by The Severe Chronic Neutropenia International Registry: http://depts.washington.edu/registry/index.html.
References


14. Osby E, Hagberg H, Kvaloy S, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group


55. Kaufman PA, Paroly W, Rinaldi D. Randomized double blind phase 2 study evaluating same-day vs. next-day administration of pegfilgrastim with docetaxel, doxorubicin and cyclophosphamide (TAC) in women with early stage and advanced breast cancer [abstract]. Presented at the SABCS. Abstract 1054.


