**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](http://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](http://nccn.org).
Updates in Version 2.2014 of the NCCN Guidelines for Myeloid Growth Factors from Version 1.2014 include:

**MS-1**
- The Discussion section was updated to reflect the changes in the algorithm.

Updates in Version 1.2014 of the NCCN Guidelines for Myeloid Growth Factors from Version 2.2013 include:

**Global**
"Hematopoietic cell transplant (HCT)" replaced "bone marrow transplant (BMT)."

**MGF-A 1 of 4**
- Myelodysplastic syndromes: Decitabine was removed.

**MGF-A 2 of 4**
- Breast Cancer: TC (docetaxel, cyclophosphamide) was added.
- Footnote was added: "Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study."
- Footnote "†" was modified: "A small retrospective trial had a 17% risk of FN in neoadjuvant setting and a randomized trial had a 5.4% in metastatic setting (G-CSF was administered to 42.5% of patients who received FOLFIRINOX). While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features."

**MGF-A 3 of 4**
- References were updated. (Also on MGF-A 4 of 4)

**MGF-B**
- The last bullet was added: "HIV-infected patients."

**MGF-C**
- Footnote was added: "Lyman et al reported an increase in absolute and relative risk of AML/MDS of 0.41% and 1.92, respectively, related to G-CSF. Overall mortality was decreased. See discussion for details and reference."

**MGF-F 1 of 2**
- "Filgrastim" replaced "G-CSF" on this page.
EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLEa

<table>
<thead>
<tr>
<th>Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignanciesb</th>
<th>RISK ASSESSMENT FOR FEBRILE NEUTROPENIAc</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease</td>
<td>High (&gt;20%)</td>
</tr>
<tr>
<td>• Chemotherapy regimend</td>
<td>Intermediate (10%-20%)</td>
</tr>
<tr>
<td>→ High-dose therapy</td>
<td>Low (&lt;10%)</td>
</tr>
<tr>
<td>• Dose-dense therapy</td>
<td>Treatment intent (curative vs. palliative)</td>
</tr>
<tr>
<td>• Standard-dose therapy</td>
<td></td>
</tr>
<tr>
<td>• Patient risk factorsd</td>
<td></td>
</tr>
<tr>
<td>• Treatment intent</td>
<td></td>
</tr>
</tbody>
</table>

**PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIAc,e**

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

CSFs= Colony-stimulating factors

---

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

bFor use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes, and in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia.

cFebrile neutropenia is defined as 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 NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

dThere 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).

eSee Toxicity Risks with Growth Factors (MGF-C).

fThe confounding effects of chemotherapy dose and schedule, 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.

gThere 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.)

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

iThe 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.

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.
EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

Prior use of CSFs

Consider chemotherapy
dose reduction or change
in treatment regimen

No prior use of CSFs

Consider CSFs
(See Risk Assessment for
Febrile Neutropenia, MGF-1)

Febrile neutropenia or dose-limiting
neutropenic event

Repeat assessment after
each subsequent cycle

No febrile neutropenia or dose-limiting
neutropenic event

Evaluate patient prior to second and subsequent chemotherapy cycles

Febrile neutropenia is defined as, 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 NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

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.
**Presentation**

Patients receiving prophylactic CSFs (filgrastim or sargramostim)

Patients who have received prophylactic pegfilgrastim

Patients who did not receive prophylactic CSFs

**CSF Use During Current Chemotherapy Cycle**

Present with febrile neutropenia

Patients who have received prophylactic pegfilgrastim

Patients who did not receive prophylactic CSFs

**Management of Patients With Febrile Neutropenia**

Continue CSFs

No additional CSFs

Consider CSFs

Risk factors not present for an infection-associated complication

Risk factors present for an infection-associated complication

---

**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%)

- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-B)
- 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)

Acute Lymphoblastic Leukemia (ALL)
- ALL induction regimens (See NCCN Guidelines for ALL)

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)\(^1\)

Breast Cancer
- Dose-dense AC followed by T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)\(^3\)
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)\(^4\)

Esophageal and Gastric Cancers
- Docetaxel/cisplatin/fluorouracil\(^5\)

Hodgkin Lymphoma
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)\(^6\)

Kidney Cancer
- Doxorubicin/gemcitabine\(^7\)

Non-Hodgkin’s Lymphomas
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory)\(^8,9\)
- ICE (ifosfamide, carboplatin, etoposide) (DLBCL, PTCL, 2nd line, salvage)\(^10\)
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)\(^11\)
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab\(^12,13\)
- MINE (mesna, ifosfamide, novantrone, etoposide) (DLBCL, PTCL, 2nd line, refractory)\(^14\)
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd line)\(^15\)
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (DLBCL, PTCL, 2nd line, recurrent)\(^16\)
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)\(^17,18\)

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)\(^19\)
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)\(^19\)

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine\(^20\)

Ovarian Cancer
- Topotecan\(^21\)
- Paclitaxel\(^22\)
- Docetaxel\(^23\)

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)\(^24\)
- Doxorubicin\(^25\)
- Ifosfamide/doxorubicin\(^26\)

Small Cell Lung Cancer
- Topotecan\(^27\)

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)\(^28\)
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)\(^29,30\)
- TIP (paclitaxel, ifosfamide, cisplatin)\(^31\)

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

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 an Intermediate Risk for Febrile Neutropenia (10%-20%)

- The type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-B).
- 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)

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel³²

Breast Cancer
- Docetaxel every 21 days³³
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)³⁴
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)³⁵
- AC + sequential docetaxel + trastuzumab (adjuvant)³⁶
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel³⁷
- Paclitaxel every 21 days (metastatic or relapsed)³⁸
- TC (docetaxel, cyclophosphamide)³⁹,³⁹

Cervical Cancer
- Cisplatin/topotecan (recurrent or metastatic)⁴⁰,⁴¹,⁴²
- Paclitaxel/cisplatin⁴³
- Topotecan (recurrent or metastatic)⁴³
- Irinotecan (recurrent or metastatic)⁴⁴

Colorectal Cancer
- FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin)⁴⁵

Esophageal and Gastric Cancers
- Epirubicin/cisplatin/5-fluorouracil⁴⁷
- Epirubicin/cisplatin/capecitabine⁴⁷

Hodgkin Lymphoma
- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)⁴⁸
- Stanford V (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)⁴⁹

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)⁵⁰
- DT-PACE + bortezomib (VTD-PACE)⁵¹

Non-Hodgkin’s Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt lymphoma, recurrent)⁵²
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, DLBCL, recurrent)⁵²
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)⁵³
- GDP (gemcitabine, dexamethasone, cisplatin) (DLBCL, PTCL, 2nd line)⁵⁴
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (DLBCL, 2nd line)⁵⁴
- FMR (fludarabine, mitoxantrone, rituximab)⁵⁵
- CHOEP (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)⁵⁶,⁵⁷ including regimens with pegylated liposomal doxorubicin⁵₈,⁵₉ or mitoxantrone⁶₀ substituted for doxorubicin

Non-Small Cell Lung Cancer
- Carboplatin/paclitaxel (adjuvant, advanced/metastatic)⁶¹
- Carboplatin/vinorelbine (adjuvant, advanced/metastatic)⁶²
- Carboplatin/docetaxel (adjuvant, advanced/metastatic)⁶¹,⁶³
- Carboplatin/irinotecan (advanced/metastatic)⁶⁴
- Carboplatin/etoposide (adjuvant, advanced/metastatic)⁶⁵
- Docetaxel (advanced/metastatic)⁶³

Ovarian Cancer
- Carboplatin/docetaxel⁶⁶

Pancreatic Cancer
- FOLFIRINOX†

Prostate Cancer
- Cabazitaxel⁶⁷

Small Cell Lung Cancer
- Etoposide/carboplatin⁶⁸

Testicular Cancer
- Etoposide/cisplatin⁶⁹

Uterine Sarcoma
- Docetaxel (advanced or metastatic)⁷⁰

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

†A small retrospective trial had a 17% risk of FN in neoadjuvant setting⁷² and a randomized trial had a 5.4% in metastatic setting (G-CSF was administered to 42.5% of patients who received FOLFIRINOX).⁷³ While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

‡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.

³Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

See Chemotherapy Regimen References, MGF-A (4 of 4)

See Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia, MGF-A (1 of 4)
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.


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.

**CHEMOTHERAPY REGIMEN REFERENCES**


77. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer following docetaxel treatment: A randomised open-label trial. Lancet 2010;376:1147-1154.


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 Guidelines for Senior Adult Oncology)
- 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
- HIV-infected patient

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

**Filgrastim and derivative products including pegfilgrastim**¹,²,³

- **Warnings**
  - Allergic reactions
    - ◊ Skin: rash, urticaria, facial edema
    - ◊ Respiratory: wheezing, dyspnea
    - ◊ Cardiovascular: hypotension, tachycardia, anaphylaxis
  - Bleomycin-containing regimens: pulmonary toxicity⁴
  - Splenic rupture
  - Acute respiratory distress syndrome
  - Alveolar hemorrhage and hemoptysis
  - Sickle cell crises (only in patients with sickle cell disease)
  - MDS and AML⁵

- **Precautions**
  - Cutaneous vasculitis
  - Immunogenicity

- **Adverse reactions**
  - Bone pain

**Sargramostim**¹,³

- **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 hematopoietic cell transplant or peripheral blood progenitor cell transplant - asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder
  - Allogeneic hematopoietic cell 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

¹See full prescribing information for specific product information.
²Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim and pegfilgrastim.
³The toxicities listed are from the prescribing information and are based on studies from different patient populations. For filgrastim and derivative products, the toxicities are based on non-myeloid malignancies. For sargramostim, the toxicities are based primarily on studies from leukemia and transplant patients and the listed toxicities may reflect intravenous route of administration and may differ from those of subcutaneous administration.
⁴See Discussion for details.
⁵Lyman et al reported an increase in absolute and relative risk of AML/MDS of 0.41% and 1.92, respectively, related to G-CSF. Overall mortality was decreased. See Discussion for details and reference.

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 or tbo-filgrastim\(^1\) (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 the next day up to 3-4 days after completion of chemotherapy and treat through post-nadir recovery.

• Pegfilgrastim (category 1) (For prophylactic use only)
  - One dose of 6 mg per cycle of treatment.
  - The majority of trials administered pegfilgrastim the day after chemotherapy (category 1).
  - Administration of pegfilgrastim up to 3-4 days after chemotherapy is also reasonable based on trials with filgrastim.
  - Limited data suggest that same-day administration of pegfilgrastim may be considered in certain circumstances.\(^2\)

  - There is evidence to support use for chemotherapy regimens given every 3 wks (category 1).
  - There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 wks.
  - There are insufficient data to support use for weekly chemotherapy regimens; therefore, use of pegfilgrastim cannot be recommended.

• Sargramostim\(^3\) (category 2B)
  - Used in clinical trials at a dose of 250 mcg/m\(^2\)/day (rounding to the nearest vial size by institution-defined weight limits).
  - Start the next day up to 3-4 days after completion of chemotherapy and treat through post-nadir recovery.

• Prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.
• Subcutaneous route is preferred for all 4 agents.
• Prophylactic antibiotics are not routinely recommended for standard-dose chemotherapy. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

\(^1\)Tbo-filgrastim is a human G-CSF approved by the FDA through an original biologic license application, not as a biosimilar to filgrastim. Like other G-CSFs, it is indicated for reducing the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.

\(^2\)For references for pegfilgrastim, see MGF-E 2 of 2.

\(^3\)There is category 1 evidence to support filgrastim, tbo-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. Sargramostim is also indicated for mobilization of hematopoietic progenitor cells and acceleration of myeloid recovery in patients receiving hematopoietic cell transplantation (HCT), and for patients who have undergone HCT in whom engraftment is delayed or has failed. Studies are ongoing in other areas.

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.
REFERENCES FOR PEGIFLGRASITM


Summary of 4 prospective trials.


Retrospective study supports same-day administration.

Whitworth JM, Matthews KS, Shipman KA, et al. The safety and efficacy of day 1 vs day 2 administration of peg in patients receiving myelosuppressive chemotherapy for gynecologic malignancies. Gynecol Oncol 2009;112:601-604.

Retrospective study supports same-day administration.


Prospective randomized trial showing no difference between same-day and next-day administration.


Prospective randomized trial favored next-day administration.


Prospective randomized trial favored next-day administration.
**Mobilization of hematopoietic progenitor cells in autologous setting**

- Single-agent growth factor: Filgrastim dose range 10-32 mcg/kg/day by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5.¹
- Combination of similar doses of filgrastim after chemotherapy (e.g., cyclophosphamide,² ICE,³ DHAP,³ VTD-PACE,⁴ and others) with the goal of mobilization during count recovery. Filgrastim is started about 24 hours after completion of chemotherapy.

**Combination of filgrastim with plerixafor (for selected patients with non-Hodgkin’s lymphoma or multiple myeloma)**

- Filgrastim 10 mcg/kg/day x 4 days, then plerixafor 240 mcg/kg/day (dose adjusted for GFR <50 mL/min, maximum dose 40 mg/day, maximum 4 days) by subcutaneous injection the evening of day 4 prior to collection beginning the next morning (day 5):
  - For patients who were heavily pre-treated⁵ or patients who exhibit risk factors for being poor mobilizers or who have failed prior collection attempts.
  - As “just in time” or “rescue” if circulating CD34+ cell count is below target.⁶-⁸

**Mobilization of allogeneic donors**

- Allogeneic stem cell donors: Filgrastim 10 mcg/kg/day by subcutaneous injection, start collection on day 4 or 5.⁹-¹¹
- Use of plerixafor in normal donors is under study.
- Allogeneic donors for granulocyte transfusion: one dose of filgrastim 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8-24 hours prior to collection.¹²

**Supportive care**

- Post autologous stem cell or cord blood transplant: Filgrastim dose 5 mcg/kg/day. Begin day +5 post transplant until recovery of absolute neutrophil count (ANC) (e.g., >1.5 x 10⁹/L times 2 days).¹³,†

**Role of pegfilgrastim in mobilization and post transplant**

- Limited data suggest that pegfilgrastim may be equivalent to filgrastim in this setting.¹⁴,¹⁵

**Role for GM-CSF in mobilization, post autologous transplant, and delayed hematopoietic recovery**

- Mobilization as single agent¹⁶,¹⁷,‡
- Mobilization in combination: Filgrastim 7.5 mcg/kg each morning, GM-CSF 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.¹⁸
- Post autologous stem cell transplant or for delayed hematopoietic engraftment after transplant: 250 mcg/m²/day until ANC >1.5 x 10⁹/L times 3 days.¹⁹-²¹

---

¹Filgrastim accelerates neutrophil recovery but has not impacted survival. See Discussion for details.

‡However, filgrastim is more widely utilized than GM-CSF for mobilization.

---

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.
Myeloid Growth Factors

**MYELOID GROWTH FACTORS IN MOBILIZATION AND POST STEM CELL TRANSPLANT**

**REFERENCES**


**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.
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.

Table of Contents

Overview ............................................................... MS-2
Benefits and Risks of CSFs ....................................................... MS-3
Prophylactic Use of CSFs .......................................................... MS-5
   Risk Assessment ...................................................................... MS-5
   Chemotherapy Regimens and Risk for FN ......................... MS-6
Patient Risk Factors for Developing FN ............................... MS-6
Patients at High Risk for FN .................................................. MS-6
Patients at Intermediate Risk for FN ...................................... MS-7
Patients at Low Risk for FN ....................................................... MS-8
Evaluation of Subsequent Chemotherapy Cycles ............... MS-8
Dosing and Administration ..................................................... MS-8
   Filgrastim ........................................................................... MS-8
   Tbo-filgrastim ..................................................................... MS-8
   Pegfilgrastim ...................................................................... MS-9
   Sargramostim ..................................................................... MS-10
Therapeutic Use of CSFs .................................................... MS-10
   Dosing and Administration .................................................. MS-11
CSFs in the Hematopoietic Cell Transplant Setting ............. MS-11
   Mobilization with Growth Factors ...................................... MS-11
   Growth Factors as Part of Supportive Care After Transplant... MS-12
   Dosing and Administration .................................................. MS-12
   Filgrastim ........................................................................... MS-12
   Pegfilgrastim ...................................................................... MS-13
   Sargramostim ..................................................................... MS-13
Severe Chronic Neutropenia ................................................. MS-13
References ................................................................................ MS-14
Overview

Myeloid growth factors (MGFs) are a class of biologic agents that regulate the proliferation, differentiation, survival, and activation of cells in the myeloid lineage. In cancer patients receiving myelosuppressive chemotherapy, MGFs are primarily used to reduce the incidence of neutropenia. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 neutrophils/mcL or an ANC of less than 1000 neutrophils/mcL and a predicted decline to less than or equal to 500 neutrophils/mcL over the next 48 hours. Neutropenia can progress to febrile neutropenia (FN, ≥38.3°C orally or ≥38.0°C over 1 hour), which is a major dose-limiting toxicity of chemotherapy that often requires prolonged hospitalization and broad-spectrum antibiotic use (reviewed by Lyman and Kuderer\(^1\)). In turn, these can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome. A review by Dale et al\(^2\) showed that about 25% to 40% of treatment-naive patients develop FN with common chemotherapy regimens. Development of FN 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.\(^3\)

The risk of FN is usually based on the treatment regimen and delivered dose intensity. However, 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 that the rates of myelosuppression and delivered dose intensity are underreported.\(^4\) Even when reported, the rates of myelosuppression with the same or similar regimens varied greatly, making it difficult to determine the actual risk for neutropenic complications associated with common chemotherapy regimens.\(^4\) Treatment dose intensity was reported with even less consistency, complicating interpretation of the reported rates of toxicity or treatment efficacy. Differences in the reported rates of myelotoxicity may be attributed to intrinsic variation in the patient population as well as differences in the delivered dose intensities.

Studies have demonstrated that prophylactic use of MGFs can reduce the risk, severity, and duration of FN, but the cost has prevented its routine use in all patients receiving myelosuppressive chemotherapy. However, selective use of MGFs in patients at increased risk for neutropenic complications may enhance the cost-effectiveness. Although early studies investigated a role for macrophage-colony stimulating factor\(^5,6\) and interleukin-3\(^7-9\) in alleviating FN, this guideline will focus on the two MGFs that have shown the most promise in terms of clinical use: granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). For simplicity, the use of the term colony stimulating factor (CSF) will be utilized when the data are supported by studies for both G-CSF and GM-CSF.

Filgrastim, tbo-filgrastim, and pegfilgrastim are G-CSFs currently approved by the U.S. Food and Drug Administration (FDA) for use in the prevention of chemotherapy-induced neutropenia. Both tbo-filgrastim and pegfilgrastim are restricted in the FDA approval for use in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. Filgrastim is approved for these applications as well as for broader patient populations that include patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy, cancer patients receiving bone marrow transplant, patients undergoing peripheral blood progenitor cell collection and therapy, and patients with severe chronic neutropenia. While the European guidelines also include lenograstim as a recommended G-CSF in solid tumors and non-myeloid malignancies,\(^10\) it is not approved
for use in the United States outside of myeloid malignancies and is therefore, not addressed in this guideline.

The only GM-CSF that is FDA-approved is sargramostim, although clinical trials have used the GM-CSF molgramostim. Molgramostim is not recommended by the panel due to the increased adverse events compared to sargramostim\(^1\) as well as the lack of FDA approval. Sargramostim is limited to use following induction therapy for AML and in various stem cell transplantation settings. It should be noted that there is a lack of head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs.

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

Benefits and Risks of CSFs

There are several circumstances in which CSFs are incorporated into cancer regimens to improve the care of patients. CSFs are used in the prophylactic and therapeutic treatment of FN as well as in the hematopoietic cell transplant setting for mobilization and supportive care. CSFs may also be incorporated into the treatment of severe chronic neutropenia.

The prophylactic use of CSFs reduced the incidence, length, and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, solid tumors, non-small cell lung cancer, and NHL.\(^12-26\) Additionally, the benefit of GM-CSF therapy was seen in the treatment of myeloid malignancies.\(^29\) CSFs improved the delivery of full dose-intensity chemotherapy at the planned schedule, although this has not been shown to lead to better response or higher overall survival in most studies.\(^12,14,16,19-22,26,30,31\) However, in node-positive breast cancer and aggressive lymphoma,\(^28,33,34\) dose-dense regimens supported by CSFs improved disease-free and/or overall survival compared to conventional chemotherapy.

Meta-analyses confirmed the efficacy of prophylactic CSFs in decreasing rates of infection and risk of neutropenia.\(^35-37\) The meta-analysis from Clark et al\(^37\) included 13 studies, in which 6 studies treated patients with G-CSF, 6 studies treated patients with GM-CSF, and one 3-arm study included G-CSF, GM-CSF, or a placebo in the treatment. In total, 1518 patients were evaluated for overall mortality, infection-related mortality, length of hospitalization, and time to neutrophil recovery. While overall mortality did not appear to reach statistical significance (odds ratio [OR], 0.68; 95% CI, 0.43–1.08; \(P = .1\)), the infection-related mortality had a borderline significant benefit with the use of CSFs (OR, 0.51; 95% CI, 0.26–1.00; \(P = .05\)). However, a clear reduction in the length of hospitalization (hazard ratio [HR] = 0.63; 95% CI, 0.49–0.82; \(P = .0006\)) and time to neutrophil recovery (HR = 0.32; 95% CI, 0.23–0.46; \(P < .0001\)) was observed with the addition of CSFs.

In a systematic review of 17 randomized trials of prophylactic G-CSFs, including 3493 adult patients with solid tumor and lymphoma,\(^36\) G-CSF as primary prophylaxis reduced the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; \(P < .001\)) and improved relative dose intensity of the chemotherapy delivered with an average difference between study arms of 8.4% (\(P = .001\)). For the first time, this analysis also reported a substantial reduction in risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; \(P = .018\)) and of early death during chemotherapy (RR, 0.5...
The survival advantage was confirmed in a systematic review by Lyman et al\textsuperscript{39} of 25 randomized controlled trials that involved 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 a 3.40% and 0.90 reduction in absolute and relative risk for all-cause mortality, respectively, although an increased risk for AML and myelodysplastic syndromes (MDS) was observed (see later discussion). The degree of benefit correlated with the chemotherapy dose intensity.

There are toxicity risks reported with the use of CSFs (see Toxicity Risks with Growth Factors on page MGF-C). To date, the main consistently observed toxicity associated with G-CSF therapy is mild to moderate bone pain in 10% to 30% of patients.\textsuperscript{40-46} This is usually effectively controlled by non-narcotic analgesics.\textsuperscript{40,41} The meta-analysis by Kuderer et al\textsuperscript{47} confirmed a heightened risk of musculoskeletal pain associated with CSF (RR, 4.03; 95% CI, 2.15–7.52; \(P < .001\)).\textsuperscript{38} There have also been reports of rare cases of splenic rupture with G-CSF usage, some of which were fatal.\textsuperscript{50-52} 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). Other warnings from the prescribing information include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.\textsuperscript{40,41,49} Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease, but not for patients with sickle cell trait.\textsuperscript{50-52} Similar toxicities are expected for filgrastim and pegfilgrastim, although not all toxicities have been reported with each preparation.

Adverse events have been reported with GM-CSF. An early study of patients with advanced malignancy evaluated side effects following administration of GM-CSF. Adverse reactions were seen in 65% of these patients, though they were not severe and were reversible. These reactions included mild myalgias, facial flushing, low-grade fever, headache, bone discomfort, nausea, and dyspnea.\textsuperscript{55} A side-effect profile of GM-CSF, completed several years later, reported a lower rate of 20% to 30% mild-to-moderate adverse events, and attributed this decline to improved dosing and delivery.\textsuperscript{56} Though uncommon, significant side effects have been reported for GM-CSF. Less than 1% of patients will develop blood clots.\textsuperscript{57-59} Though blood clots rarely lead to pulmonary embolus or stroke, these life-threatening conditions are possible. There have been reports in clinical
trials of capillary leak syndrome, a condition in which fluids move from the vascular system into the interstitial space resulting in hypotension and reduced blood flow to internal organs. While this is more common with GM-CSF, it has also been reported to occur with G-CSF therapy. Worsening of amyloidosis following G-CSF administration has been reported; however, this is based on two case reports in patients that were already prone to life-threatening complications.

Although there have been suggestions of potentially increased risk of AML/MDS with CSF administration from epidemiologic studies, this was not observed in individual randomized trials. The recent analysis by Lyman et al 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. These data mirror an earlier report based on the SEER database that showed an elevated risk of developing AML/MDS in patients with either G-CSF or GM-CSF therapy. One caveat of the study is that it could not exclude the possibility that this increase was due to the use of growth factors in cases that were more likely to progress into AML/MDS, regardless of the presence or absence of adjuvant therapy.

In addition to evaluating the clinical benefits and risks of CSF therapy, an increasing number of studies have assessed the financial implications of its use. 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. While the addition of CSFs to treatment regimens inevitably raises the drug cost, it may actually equate to substantial savings in comparison to the cost of hospitalization and subsequent treatment of neutropenia.

Despite the increasing number of economic analyses available, 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. Therefore, the following section will provide an indication for prophylactic CSF use based on the risk of FN or other neutropenic events that can potentially compromise treatment.

**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 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 towards prolongation of survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to either an overall high-risk group (>20% risk of FN), intermediate-risk group (10%–20% risk), or 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 the assessment of FN risk, independent clinical judgment should be exercised based on the patient’s situation. In addition to assessing patient and treatment-related risk, consideration should be given to the intent of cancer treatment when determining the appropriate use of CSFs. For example, a patient with a previous neutropenic complication in the
immediately prior cycle of chemotherapy, with no plan to reduce the
dose intensity, should be considered high risk.

**Chemotherapy Regimens and Risk for FN**

The development of FN is a common dose-limiting toxicity of many single agent and combination chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Clinical trial data of chemotherapy regimens that have an incidence of FN greater than 20% in chemotherapy-naive patients are considered by the panel as high risk. It is emphasized that the type of chemotherapy regimen is only one component of the risk assessment and needs to be combined with patient risk factors for an estimation of the overall risk for FN.

The algorithm includes lists of common chemotherapy regimens associated with a high risk or intermediate risk of developing FN based on published data (see Examples of Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia on page MGF-A 1 of 4; and Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia (10%–20%) on page MGF-A 2 of 4). These lists are not comprehensive and are meant to serve as examples only, as the exact risk will depend on the agent, dose, and treatment setting. It should be noted that some regimens, such as the RICE and CHOP-14 regimen for NHL, have only been tested with growth factor support.

Evens et al\(^76\) showed that standard chemotherapy for Hodgkin 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 the risks and benefits with the patient.

**Patient Risk Factors for Developing FN**

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\(^77\)). 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 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 Guidelines for Senior Adult Oncology).\(^78-83\) 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, HIV-infection, and pre-existing conditions such as neutropenia and infection (see Patient Risk Factors for Developing Febrile Neutropenia on page MGF-B). 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 3760 cancer patients beginning chemotherapy treatment.\(^84\)

**Patients at High Risk for FN**

NCCN Panel discussions have focused on defining a risk level of FN that would warrant routine use of prophylactic growth factors. The guidelines recommend prophylactic CSF if the risk of FN is greater than
20%. The most recent update of the ASCO guidelines and the EORTC both adopted the 20% threshold for considering routine prophylactic treatment.\textsuperscript{85,86}

These consistent recommendations are based on the results of several large randomized trials that have documented a significant reduction of FN following primary prophylaxis when the risk of FN without prophylaxis is 20%. For example, Vogel and colleagues\textsuperscript{15} 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{15} 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\textsuperscript{2} every 3 weeks. Four hundred 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 a 17% overall incidence of FN. By contrast, the pegfilgrastim group had a 1% incidence. In the pegfilgrastim group, 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 being statistically significant ($P < .001$).

In cycle 1, there was an 11% rate of FN in the first cycle for the placebo group versus a less than 1% rate in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN with a less than 1% rate 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.\textsuperscript{13} 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 of FN were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis was 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 high 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 are at high risk for 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 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-patient discussion of the risk-benefit ratio with respect to 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 the increased risk of FN is a result of patient risk factors, CSF is 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.
Patients at Low Risk for FN
For low-risk patients, as defined by risk less than 10%, routine use of CSFs is not recommended as alternative treatment options are appropriate and more cost-effective.\(^{70,85,87,88}\) 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 of chemotherapy, 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 benefitting from chemotherapy, the previous assessment should be repeated after each subsequent cycle.

Dosing and Administration
Currently used or approved CSFs for the prophylaxis of FN and maintenance of scheduled dose delivery include filgrastim, tbo-filgrastim, pegfilgrastim, and sargramostim, preferably given subcutaneously. While data from randomized studies support the use of filgrastim, tbo-filgrastim, and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on its use following induction therapy for AML and in various stem cell transplantation settings. Therefore, when choosing among CSFs for the prophylactic treatment of FN, filgrastim, tbo-filgrastim, and pegfilgrastim are considered category 1 recommendations, while sargramostim is considered a category 2B recommendation. The NCCN Panel does not routinely recommend use of prophylactic antibiotics in these settings. In addition, prophylactic use of CSFs in patients given concurrent chemotherapy and radiation has not been evaluated and is therefore not recommended.

Filgrastim
Initial doses of filgrastim are initiated the next day or up to 3 to 4 days after completion of chemotherapy in a daily dose of 5 mcg/kg until post-nadir ANC recovery is to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits.

Tbo-filgrastim
As patents for oncology biologics begin to expire, the United States is developing an abbreviated regulatory pathway for the approval of similar follow-on formulations, termed biosimilars.\(^{89}\) The NCCN Biosimilars Work Group published a white paper identifying the challenges in the incorporation of these agents into health care practice.\(^{90}\) In August 2012, the FDA announced the approval of tbo-filgrastim, describing it as “a leukocyte growth factor indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.” Approval was based on 3 randomized clinical trials involving 680 cancer patients.
One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo. Tbo-filgrastim was equivalent to filgrastim and superior to placebo in reducing the duration of severe neutropenia and incidence of FN. Two other randomized studies of patients with lung cancer and NHL receiving chemotherapy also reported similar efficacy of tbo-filgrastim and filgrastim. Toxicities were similar between the 2 agents. A meta-analysis of the 3 trials concluded tbo-filgrastim to be non-inferior to filgrastim for the reduced incidence of FN, irrespective of the myelotoxicity of the chemotherapy regimen.

Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.

Although tbo-filgrastim is available in the European Union as a biosimilar to filgrastim, it was approved by the FDA in an original biologic license application because the biosimilar approval process has not yet been finalized. In April 2013, the FDA Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee released the briefing materials for the use of tbo-filgrastim.

The panel recommends a dose of 5 mcg/kg daily until expected neutrophil nadir is achieved and neutrophil count has recovered to the normal range. The first dose should not be given within the 24 hours preceding nor following myelosuppressive chemotherapy.

**Pegfilgrastim**

The NCCN Panel discussed 2 issues that have emerged regarding the use of pegfilgrastim. The first is the timing of administration after chemotherapy. Since most clinical studies administer the agent the day after chemotherapy completion, this is a category 1 recommendation. Based on trials of filgrastim, panelists agreed that giving pegfilgrastim up to 3 to 4 days after chemotherapy is also reasonable. In addition, panelists pointed out that some institutions practice “same-day” pegfilgrastim, defined as administration of pegfilgrastim on the day during which patients receive chemotherapy. This is done for logistical reasons and to minimize burdens on long-distance patients.

Clinical trials both in support of and against same-day pegfilgrastim have been published. The original rationale for not giving same-day CSF was the potential for increased neutropenia resulting from CSF stimulation of myeloid progenitors at the time of cytotoxic chemotherapy. In a direct comparison, Kaufman et al administered either same-day or next-day pegfilgrastim in women with breast cancer receiving docetaxel, doxorubicin, and cyclophosphamide. Febrile neutropenia was observed in 33% of patients treated in the same-day group compared with only 11% of patients in the next-day group. A similar trend was seen in a prospective randomized double-blind trial of patients receiving CHOP or CHOP-like therapy for NHL where same-day pegfilgrastim was associated with enhanced myelosuppression and no reduction in leukopenia was seen. However, despite longer duration of grade 4 neutropenia in the same-day group, there was no increase in the overall incidence of neutropenia and the increased duration did not meet the non-inferiority margin. While the study recommends administration of pegfilgrastim 24 hours after chemotherapy, it is acknowledged that same-day administration may be an acceptable alternative for some patients.

Vance et al published a retrospective review of same-day pegfilgrastim in patients with breast cancer receiving dose-dense doxorubicin and no increased neutropenia was observed. Another retrospective study from a community-based oncology practice showed similar incidence of myelosuppressive adverse events when comparing the two groups. This study of 159 patients spanned 15 different tumor types and 50 different chemotherapy regimens. A double-blind phase
Myeloid Growth Factors


II study in patients with non-small cell lung cancer treated with carboplatin and docetaxel showed no increase of neutropenia nor any adverse events in patients receiving same-day pegfilgrastim compared with patients receiving next-day pegfilgrastim treatment. The benefit of same-day pegfilgrastim was also observed in patients with non-small cell lung cancer treated with weekly chemotherapy regimens. Same-day pegfilgrastim in these patients was shown to be beneficial not only from a safety perspective but also from a logistical one where next-day pegfilgrastim would have compromised the weekly chemotherapy schedule. Another study in patients with lung cancer showed an unexpected low rate of severe neutropenia (only 2 patients per group), suggesting that same-day filgrastim is a reasonable option. More recent retrospective studies in patients with gynecologic malignancies demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours of chemotherapy.

Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient per chemotherapy cycle. Administration of pegfilgrastim next day or up to 3 to 4 days following chemotherapy is preferred; however, the panel agreed that same-day administration of pegfilgrastim may be considered under certain circumstances. The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle length. Based on phase III clinical trials, use of pegfilgrastim after chemotherapy given every 3 weeks is a category 1 recommendation. Pegfilgrastim treatment is a category 2A recommendation for chemotherapy regimens administered every 14 days based on phase II studies. There are insufficient data to support the dose and schedule for weekly regimens; therefore, these cannot be recommended.

Sargramostim

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. Administration of 250 mcg/m²/day sargramostim, rounding to the nearest vial size by institution-defined weight limits, should start the next day or up to 3 to 4 days after completion of chemotherapy, and treatment should continue through post-nadir recovery.

Therapeutic Use of CSFs

Compared to prophylactic use, there is less evidence supporting the therapeutic use of CSFs for FN as an adjunct to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials, Clark and colleagues reported a shorter length of hospitalization (HR, 0.63; 95% CI, 0.49–0.82; \( P = .0006 \)), and a shorter time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; \( P < .00001 \)), but no improvement in overall survival to be associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al also 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 or placebo. In this study, 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, \( P = .015 \)).

The NCCN Panel recommends that patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, since pegfilgrastim is long-acting, those who have
received prophylactic pegfilgrastim should not be treated with additional CSF. As there is currently a lack of evidence for the therapeutic use of pegfilgrastim and tbo-filgrastim, 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 neutrophils/mcL) or anticipated prolonged (>10 days) neutropenia, pneumonia, invasive fungal infections or other clinically documented infections, hospitalization, and prior episode of FN. If risk factors are present, CSFs should be considered.

**Dosing and Administration**

Filgrastim and sargramostim are currently the only recommended CSFs for the therapeutic treatment of FN in selected high-risk patients as outlined above. Both are considered category 2A recommendations. Filgrastim should be given as a daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) or sargramostim should be given at a dose of 250 mcg/m$^2$/day (rounding to the nearest vial size by institution-defined weight limits). Treatment should continue through post-nadir recovery.

**CSFs in the Hematopoietic Cell Transplant Setting**

CSFs are commonly administered in the transplant setting, either for mobilization of hematopoietic progenitor cells or as supportive care after transplantation.

**Mobilization with Growth Factors**

Mobilization of peripheral blood stem cells (PBSCs) by G-CSF has largely replaced bone marrow collection for autologous transplantation due to ease of collection, avoidance of general anesthesia, and more rapid recovery of blood counts. Most data are focused on filgrastim, although studies suggest that single-dose pegfilgrastim has similar efficacy. G-CSF can be administered as a single agent or as part of a chemo-mobilization regimen, starting on the day after completion of chemotherapy.

While apheresis usually commences on the fourth or fifth day of G-CSF initiation when it is used as a single agent, recent studies have shown that the addition of the CXCR4 inhibitor plerixafor to chemo-mobilization accelerated the increase in PBSC count. This may be used as a rescue strategy when PBSC yield is poor, or when the CD34+ cell count does not reach the target level. One retrospective analysis demonstrated that pegfilgrastim resulted in a better PBSC yield than filgrastim, requiring less use of rescue plerixafor, but there have not been any randomized trials that address the effect of plerixafor when used in combination with pegfilgrastim.

G-CSF is also used to mobilize PBSCs in the allogeneic setting. Initially, there were concerns about normal donor toxicity and the risk of graft-versus-host disease (GVHD) in the recipient, but studies have demonstrated G-CSF to be well-tolerated by donors without an effect on long-term survival. The use of plerixafor in normal donors is currently under study. Tbo-filgrastim has also been shown to mobilize PBSC for allogeneic transplantation in both healthy donors and in patients with multiple myeloma and lymphoma, but the data are limited and mobilization is not listed as an approved indication.

Studies using GM-CSF as a single mobilization agent or in sequential combination with G-CSF reported good yields of PBSC in normal donors. Although both CSFs have been used for mobilization, G-CSF has been favored for this purpose.
Growth Factors as Part of Supportive Care After Transplant

Consensus is lacking on the use of growth factors in the post-transplant setting. G-CSF administration after high-dose chemotherapy and autologous PBSC transplantation has been shown to expedite neutrophil recovery in prospective randomized trials. However, results were mixed on the impact of G-CSF on duration of hospital stay, infections, and survival. A systematic review comparing filgrastim and pegfilgrastim in the autologous setting, including a randomized trial of 80 patients, concluded that the two are at least equally effective.

Similarly, data are conflicting on G-CSF as a supportive care measure for allogeneic transplant recipients, with some studies associating G-CSF with worse clinical outcome. However, it has been used routinely to alleviate the delayed recovery of blood counts after umbilical cord blood transplant because there is a significant delay in the rate and kinetics of neutrophil and platelet engraftment after cord blood transplant as compared to marrow or mobilized PBSC grafts.

GM-CSF has been demonstrated to promote hematopoietic recovery after autologous hematopoietic cell transplantation or delayed autologous engraftment. GM-CSF therapy has been shown to improve treatment outcome in patients with hematological malignancies who previously had graft failure following bone marrow transplant. GM-CSF has also been administered to patients with hematologic malignancies leading to decreased neutropenia, decreased morbidity, and decreased hospitalization during autologous hematopoietic cell transplant.

Dosing and Administration

Use of filgrastim or sargramostim is a category 2A recommendation for supportive care after transplant. While filgrastim is recommended in mobilization for both autologous and allogeneic transplants, sargramostim is recommended for mobilization only in the autologous setting. There are limited data available for the use of tbo-filgrastim in mobilization, therefore, it is not currently recommended by the NCCN Panel for mobilization.

Filgrastim

Filgrastim effectively mobilizes hematopoietic progenitor cells for transplant both as a single-agent therapy or in combination with plerixafor.

For mobilization of hematopoietic progenitor cells in an autologous setting, the panel recommends single-agent filgrastim at a dose range from 10 to 32 mcg/kg/day by subcutaneous injection, in daily or twice-daily dosing. Several regimens are effective in chemo-mobilization of hematopoietic progenitors, including cyclophosphamide, ICE, DHAP, VTD-PACE, and others. Filgrastim begins 24 hours after completion of chemotherapy and continues through completion of collection, typically at a dose of at least 10 mcg/kg/day. Apheresis begins upon rise of the white blood cell count, when the circulating CD34+ cell count reaches target levels.

In allogeneic stem cell donors, single-agent filgrastim is given at 10 mcg/kg/day. Allogeneic granulocyte donors receive single-agent filgrastim as a single dose of 5 mcg/kg with 10 mg oral dexamethasone given 8 to 24 hours prior to collection. For patients with NHL or multiple myeloma, filgrastim can be given at 10 mcg/kg/day for 4 days followed by plerixafor at 240 mcg/kg/day (dose adjusted for glomerular filtration rate < 50 mL/min, maximum dose 40 mcg/day, maximum 4 days) on the evening of day 4 prior to collection that begins on the morning of day 5. The combination of filgrastim with plerixafor is beneficial for patients who were heavily pre-treated or patients who exhibit risk factors for
being poor mobilizers or who have failed prior collection attempts. It also serves as a useful treatment for patients with CD34+ cell counts below the target range.

For myeloid reconstitution post autologous stem cell transplant, 5 mcg/m²/day filgrastim should be administered at day 5 or later post-transplant until ANC is greater than 1.5 x 10⁹ neutrophils/L for 2 consecutive days.

**Pegfilgrastim**

Pegfilgrastim is approved for use after myelosuppressive chemotherapy, which could therefore be interpreted to include high-dose chemotherapy. It is administered as a single dose of 6 mg by subcutaneous injection.

**Sargramostim**

Sargramostim can be given in the setting of mobilization of hematopoietic progenitor cells for autologous transplant as a single or in combination with filgrastim as 7.5 mcg/kg filgrastim each morning and 7.5 mcg/kg of sargramostim each evening. Leukopheresis begins on day 5. It is not approved for mobilization in the allogeneic setting.

Sargramostim is an approved treatment for the myeloid reconstitution of cells following both allogeneic and autologous stem cell transplant. It is also used in cases of delayed hematopoietic engraftment after autologous or allogeneic transplant. In the supportive care setting, sargramostim should be given at a dose of 250 mcg/m²/day until ANC greater than 1.5 x 10⁹ neutrophils/L for 3 days is achieved.

**Severe Chronic Neutropenia**

The NCCN Guidelines for Myeloid Growth Factors focuses on chemotherapy-induced neutropenia in the cancer setting; therefore, severe chronic neutropenia that requires G-CSF therapy is only briefly discussed below. 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 observational studies showed that patients with idiopathic and cyclic neutropenia generally responded to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF (1–3 mcg/kg/day). Congenital neutropenia patients generally require 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 for 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 website developed by The Severe Chronic Neutropenia International Registry: [http://depts.washington.edu/registry/index.html](http://depts.washington.edu/registry/index.html).
References


69. Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte...


83. Morrison VA, Picozzi V, Scott S, et al. The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in...


102. 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.


105. Hoffmann PS. Administration of pegfilgrastim on the same day or next day of chemotherapy. Journal of Clinical Oncology 2005;23(Suppl 16):Abstract 8137. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/8137.


109. Whitworth JM, Matthews KS, Shipman KA, et al. The safety and efficacy of day 1 versus day 2 administration of pegfilgrastim in patients receiving myelosuppressive chemotherapy for gynecologic
NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.


135. Cavallaro AM, Lilley KM, Majolino I, et al. Three to six year follow-up of normal donors who received recombinant human granulocyte


