National Comprehensive Cancer Network®

## NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Myeloid Growth Factors

Version 2.2016

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# NCCN Guidelines Version 2.2016 Panel Members
# Myeloid Growth Factors

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Discussion

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

*Pamela Sue Becker, MD/PhD/Vice Chair ‡ Þ ξ
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

James O. Armitage, MD † ξ ‡
Fred & Pamela Buffett Cancer Center

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

Peter Curtin, MD ‡ ξ
UC San Diego Moores Cancer Center

Thomas Fynan, MD †
Yale Cancer Center/
Smilow Cancer Hospital

Elizabeth A. Griffiths, MD ‡ Þ
Roswell Park Cancer Institute

Shannon Hough, PharmD, BCOP ∑
University of Michigan
Comprehensive Cancer Center

Dwight D. Kloth, PharmD, BCOP ∑
Fox Chase Cancer Center

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

Gary H. Lyman, MD, MPH † ‡
Fred Hutchinson Cancer
Research Center/
Seattle Cancer Care Alliance

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

Sudipto Mukherjee, MD, PhD, MPH ‡
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Eric Padron, MD †
Moffitt Cancer Center

Jacqueline Parpal, PharmD, BCOP ∑
University of Colorado
Cancer Center

Raajit Rampal, MD, PhD ‡ Þ †
Memorial Sloan Kettering
Cancer Center

Vivek Roy, MD ‡
Mayo Clinic Cancer Center

Hope S. Rugo, MD † ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

Ayman A. Saad, MD ‡ ξ
University of Alabama at Birmingham
Comprehensive Cancer Center

Lee S. Schwartzberg, MD † ‡ Þ
St. Jude Children's Research Hospital/
The University of Tennessee
Health Science Center

Sepideh Shayani, PharmD ∑ ‡
City of Hope Comprehensive Cancer Center

Mahsa Talbott, PharmD ‡ ∑
Vanderbilt-Ingram Cancer Center

Saroj Vadhan-Raj, MD † Þ
The University of Texas
MD Anderson Cancer Center

Martha Wadleigh, MD ‡ †
Dana-Farber/Brigham and
Women's Cancer Center

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

**NCCN**
Jennifer Burns
Courtney Smith, PhD

† Medical oncology
‡ Hematology/Hematology oncology
Þ Internal medicine
∑ Pharmacology
ξ Bone marrow transplantation
* Discussion writing committee member

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**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.

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# NCCN Guidelines Version 2.2016 Updates Myeloid Growth Factors

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## Updates in Version 2.2016 of the NCCN Guidelines for Myeloid Growth Factors from Version 1.2016 include:

**MS-1**

- The Discussion section has been updated to reflect the changes in the algorithm.

## Updates in Version 1.2016 of the NCCN Guidelines for Myeloid Growth Factors from Version 1.2015 include:

**General**

- "Colony stimulating factors (CSF)" has been changed to "Myeloid growth factors (MGF)" throughout.

**MGF-1**

- This page has been significantly revised.
- In the prophylactic setting, "CSF" has been changed to "G-CSF," and footnote "d" has been added: "G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B)." (Also on MGF-2 and MGF-3)

**MGF-2**

- This page has been added. Patient Risk Factors for Developing Febrile Neutropenia have been moved from the former page MGF-B to this page, and MGF-B was eliminated.

**MGF-4**

- The top pathway has been revised: "Patients receiving prophylactic ~~CSFs~~ *filgrastim, filgrastim-sndz, or tbo-filgrastim*".
- Footnote "o" has been revised: "...However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggest that additional G-CSF ~~will~~ *may* not be beneficial; *but in patients with prolonged neutropenia additional G-CSF may be considered."*

**MGF-B (1 of 2)**

- Sargramostim has been removed from the list of recommended prophylactic options based on limited clinical use.

**MGF-C**

- The page has been retitled to "Myeloid Growth Factors for Therapeutic Use."
- For Possible Indications of Therapeutic MGF for Management of Febrile Neutropenia:
  - The third bullet has been revised: "~~Severe neutropenia (~~Absolute neutrophil count [ANC] <100/mcL."
  - The fifth bullet has been revised: "Pneumonia *or other clinically documented infections"*
  - The following bullet has been removed: "Other clinically documented infections."
- The list of MGF for Therapeutic Use and Maintenance of Scheduled Dose Delivery has been added.
- Footnote "c" has been added: "Tbo-filgrastim and pegfilgrastim have only been studied for prophylactic use. See Discussion for further details."

**MGF-D (1 of 3)**

- Recommendations have been reorganized into three sections: mobilization (autologous), mobilization (allogeneic), and supportive care.
- "Concurrent filgrastim/filgrastim-sndz + sargramostim" has been made a category 2B recommendation.
- Tbo-filgrastim has been added as an option in the following areas:
  - Following "Filgrastim or filgrastim-sndz" under "Single-agent growth factor"
  - Following "Combination chemotherapy followed by filgrastim/filgrastim-sndz"
  - Following "Filgrastim/filgrastim-sndz" under "Dosing" In combination with plerixafor.
- Under "Combination of filgrastim/filgrastim-sndz with plerixafor," the plerixafor dose has been revised: "0.24 mg/kg/d *for patients weighing >83 kg; 20 mg (fixed dose), or 0.24* mg/kg/d *for patients weighing ≤83 kg*, maximum 4 doses (if creatinine clearance >50 mL/min, maximum dose 40 mg/d)."

**MGF-D (2 of 3)**

- Under "Mobilization of Allogeneic Donors":
  - Filgrastim has been made the "preferred" option
  - Plerixafor has been made a category 2B recommendation.
- Tbo-filgrastim has been added as an option for the following indications:
  - As addition to first sub-bullet for Allogeneic hematopoietic cell donors under Mobilization of Allogeneic Donors as a category 2B recommendation.
  - As addition to first sub-bullet for granulocyte transfusion under Mobilization of Allogeneic Donors as a category 2B recommendation.
  - As addition to first bullet under Supportive Care Options.
- Footnote "†" has been added: "For additional dosing information refer to the package insert: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=97cc73cc-b5b7-458a-a933-77b00523e193. (Accessed March 14, 2016.)"

**MGF-D (3 of 3)**

- References have been updated.

**EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE[a]**

**RISK ASSESSMENT[b] FOR FEBRILE NEUTROPENIA[c]**

**PROPHYLACTIC USE OF G-CSF FOR FEBRILE NEUTROPENIA**
**Curative/Adjuvant or Palliative Setting[e]**

**Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies[f]**

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

**High (>20%)** → **Granulocyte colony-stimulating factors (G-CSF)[d,g] (category 1)** → See Evaluation Prior to Second and Subsequent Chemotherapy Cycles (MGF-3)

**Intermediate (10%–20%)** → **Consider G-CSF[g] based on patient risk factors** → See MGF-2

**Low (<10%)** → **No G-CSF** → See Evaluation Prior to Second and Subsequent Chemotherapy Cycles (MGF-3)

[a]The NCCN Guidelines for Myeloid Growth Factors were formulated in reference to adult patients.

[b]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 (See MGF-2).

[c]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 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

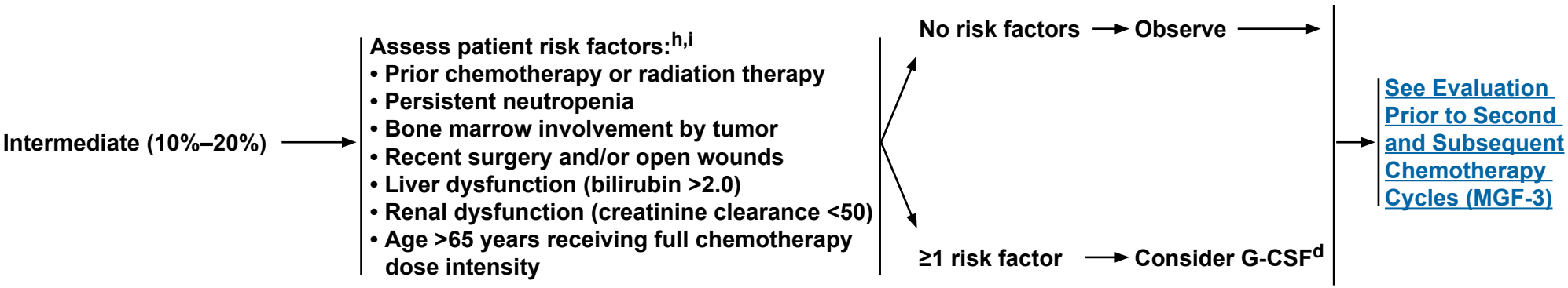
[d]G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[e]See Toxicity Risks with Myeloid Growth Factors (MGF-E).

[f]For 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.

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

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**




[c]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 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[d]G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[h]Other possible patient risk factors for febrile neutropenia may include poor performance status or HIV infection (in particular, patients with low CD4 counts).The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory cancer patients receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoetic cell transplant. (Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90:190-199)

[i]Other factors may warrant the use of G-CSF (eg, chronic immunosuppression in the post-transplant setting, including organ transplant).

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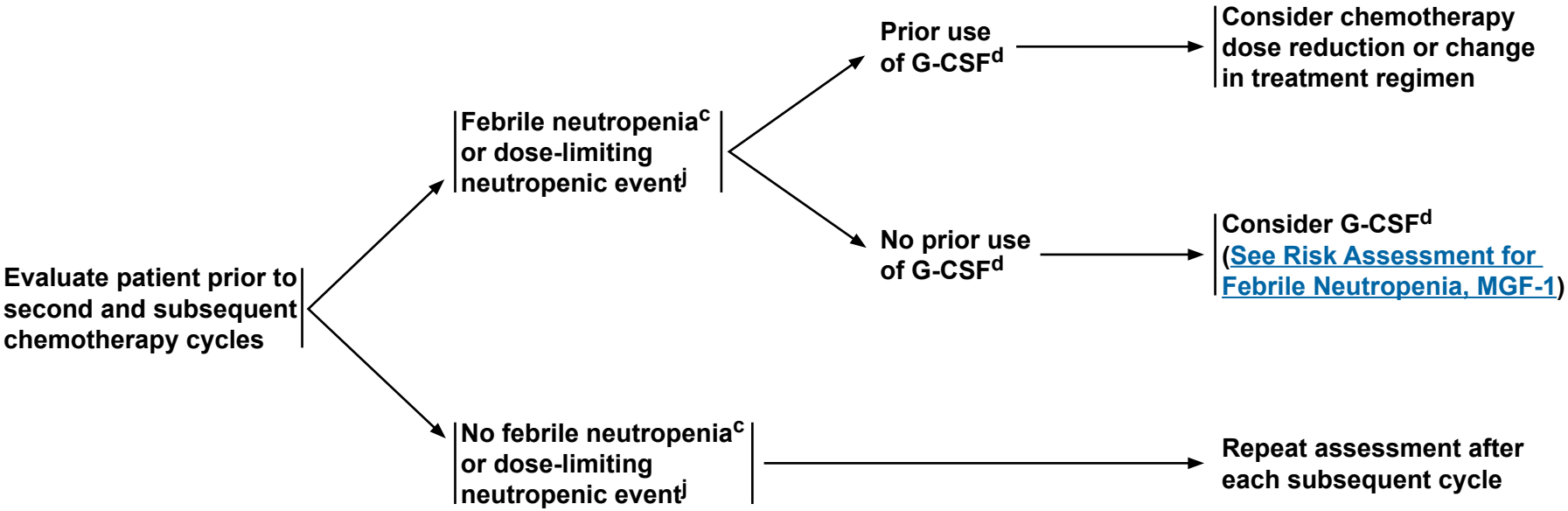
## EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

## SECONDARY PROPHYLAXIS




[c]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 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[d]G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[j]Dose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy.

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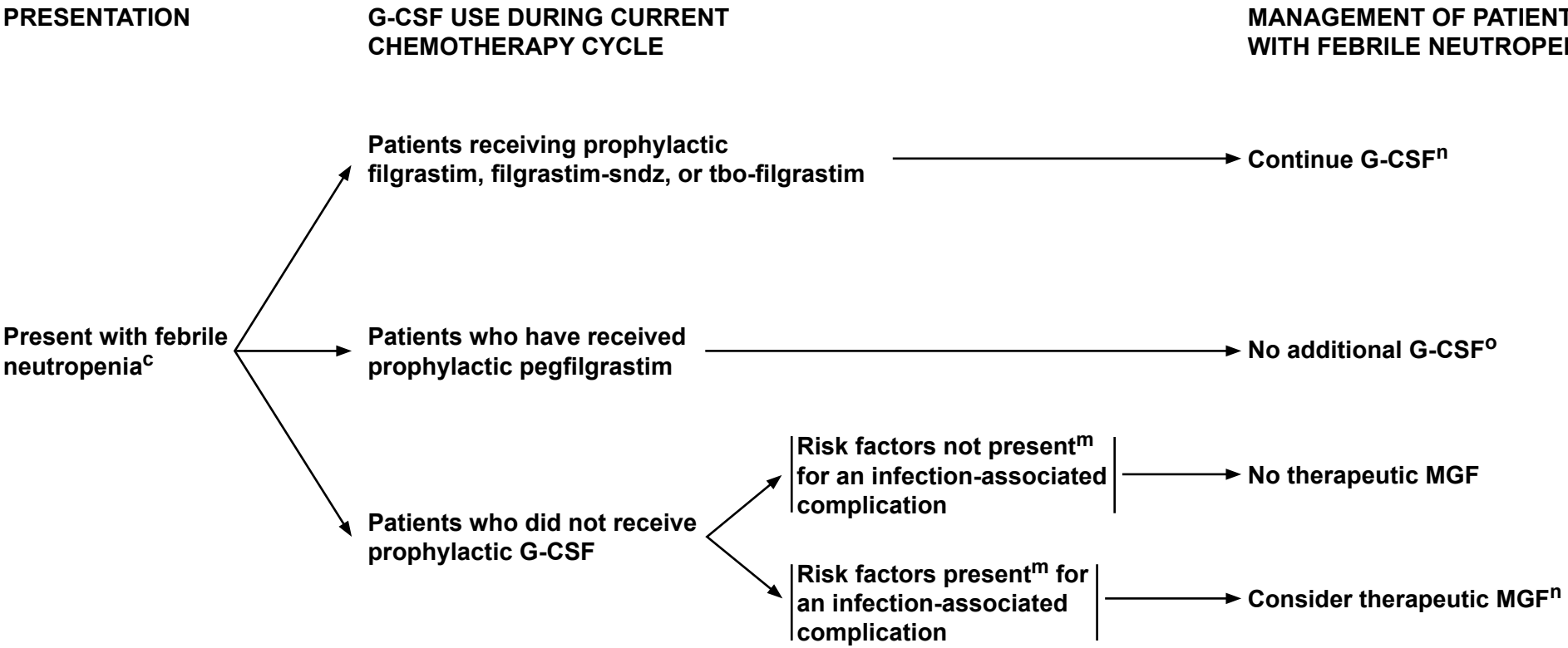
## THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGF) FOR FEBRILE NEUTROPENIA[c,k,l]




[c]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 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

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

[l]The decision to use MGF in the therapeutic setting is controversial. See Discussion for further details.

[m]See Possible Indications for the Initiation of Therapeutic MGF for Management of Febrile Neutropenia (MGF-C).

[n]See Discussion for further details. Tbo-filgrastim and pegfilgrastim have only been studied for prophylactic use. Filgrastim, filgrastim-sndz, or sargramostim may be used therapeutically with initial dosing and discontinued at time of neutrophil recovery (See MGF-C).

[o]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 suggest that additional G-CSF may not be beneficial; but in patients with prolonged neutropenia additional G-CSF may be considered.

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## 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 type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. 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**
- Docetaxel + trastuzumab (metastatic or relapsed)[2]
- 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**
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma [DLBCL], peripheral T-cell lymphomas [PTCL], 2nd line)[8]
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)[9]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab[10,11]
- MINE (mesna, ifosfamide, novantrone, etoposide) (DLBCL, 2nd line, refractory)[12]
- DHAP (dexamethasone, cisplatin, cytarabine) (PTCL, DLBCL, 2nd line)[13]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (DLBCL, PTCL, 2nd line, recurrent)[14]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[15,16]

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

**Ovarian Cancer**
- Topotecan[18]
- Paclitaxel[19]
- Docetaxel[20]

**Soft Tissue Sarcoma**
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[21]
- Doxorubicin[22]
- Ifosfamide/doxorubicin[23]

**Small Cell Lung Cancer**
- Topotecan[24]

**Testicular Cancer**
- VeIP (vinblastine, ifosfamide, cisplatin)[25]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[26,27]
- TIP (paclitaxel, ifosfamide, cisplatin)[28]

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

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 4)

See Chemotherapy Regimen References, MGF-A (3 of 4)

**Note: All recommendations are category 2A unless otherwise indicated.**
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## 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 type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-2).
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)

**Occult Primary - Adenocarcinoma**
- Gemcitabine/docetaxel[29]

**Breast Cancer**
- Docetaxel every 21 days[30]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[31]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)[32]
- AC + sequential docetaxel + trastuzumab (adjuvant)[33]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[34]
- Paclitaxel every 21 days (metastatic or relapsed)[35]
- TC[a] (docetaxel, cyclophosphamide)[36]

**Cervical Cancer**
- Cisplatin/topotecan (recurrent or metastatic)[37,38,39]
- Paclitaxel/cisplatin[39]
- Topotecan (recurrent or metastatic)[40]
- Irinotecan (recurrent or metastatic)[41]

**Colorectal Cancer**
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[42]

**Esophageal and Gastric Cancers**
- Irinotecan/cisplatin[43]
- Epirubicin/cisplatin/5-fluorouracil[44]
- Epirubicin/cisplatin/capecitabine[44]

**Multiple Myeloma**
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[45]
- DT-PACE + bortezomib (VTD-PACE)[46]

**Non-Hodgkin's Lymphomas**
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt lymphoma, recurrent, other NHL subtypes)[47]
- EPOCH + IT chemotherapy (AIDS-related NHL, DLBCL, recurrent)[47]
- GDP (gemcitabine, dexamethasone, cisplatin) (DLBCL, PTCL, 2nd line)[48]
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (DLBCL, 2nd line, Burkitt lymphoma, other NHL subtypes)[48]
- FMR (fludarabine, mitoxantrone, rituximab)[49]
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[50,51] including regimens with pegylated liposomal doxorubicin[52,53] or mitoxantrone[54] substituted for doxorubicin

**Non-Small Cell Lung Cancer**
- Cisplatin/paclitaxel (advanced/metastatic)[55]
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)[56]
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)[55,57]
- Cisplatin/etoposide (adjuvant, advanced/metastatic)[58]
- Carboplatin/paclitaxel[b] (adjuvant, advanced/metastatic)[59]
- Docetaxel (advanced/metastatic)[57]

**Ovarian Cancer**
- Carboplatin/docetaxel[60]

**Pancreatic Cancer**
- FOLFIRINOX[c]

**Prostate Cancer**
- Cabazitaxel[d,61]

**Small Cell Lung Cancer**
- Etoposide/carboplatin[62]

**Testicular Cancer**
- Etoposide/cisplatin[63]

**Uterine Sarcoma**
- Docetaxel (advanced or metastatic)[64]

[a]Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.
[b]If carboplatin dose is AUC >6 and/or patient is of Japanese ancestry.
[c]A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[65] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSF was administered to 42.5% of patients who received FOLFIRINOX).[66] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.
[d]The published results for cabazitaxel have an 8% rate of febrile neutropenia but neutropenic deaths were reported. Primary prophylaxis with G-CSFs should be considered in patients with high-risk clinical features.

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)

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## CHEMOTHERAPY REGIMEN REFERENCES

**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.**

[1]Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638-2646.

[2]Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005;23:4265-4274.

[3]Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-1439.

[4]Martin M, Lluch A, Segui MA, et al. Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study [abstract]. Proc Amer Soc Clin Oncol 2004;23:Abstract 620.

[5]Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.

[6]Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;348:2386-2395.

[7]Nanus DM, Garino A, Milowsky MI, et al. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. Cancer 2004;101:1545-1551.

[8]Hertzberg MS, Crombie C, Benson W, et al. Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. Ann Oncol 2006;Suppl 4:iv25-30.

[9]Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-3688.

[10]Blayney DW, LeBlanc ML, Grogan T, et al. Dose-intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone may improve survival in intermediate- and high-grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003;21:2466-2473.

[11]Watanabe T, Tobinai K, Shibata T, et al. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. J Clin Oncol 2011;29:3990-3998.

[12]Rodriguez MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol 1995;6:609-611.

[13]Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

[14]Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: A 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

[15]Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.

[16]Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023.

[17]Eton O, Legha S, Bedikian A, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: Results from a phase III randomized trial. J Clin Oncol 2002;20:2045-2052.

[18]Swisher EM, et al. Topotecan in platinum- and paclitaxel-resistant ovarian cancer. Gynecol Oncol 1997;66:480-486.

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**Note: All recommendations are category 2A unless otherwise indicated.**
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## G-CSF FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- **Filgrastim (category 1), tbo-filgrastim[a] (category 1), or filgrastim-sndz[b] (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 or up to 3–4 days after completion of chemotherapy and treat through post-nadir recovery.**

- **Pegfilgrastim (category 1)[1-8]**
  - **One dose of 6 mg per cycle of treatment.**
    - ◊ **The majority of trials administered pegfilgrastim the day after chemotherapy (category 1).**
    - ◊ **Beginning pegfilgrastim the day after chemotherapy is preferred. Although same-day administration of pegfilgrastim can be considered in certain circumstances, the results are mixed and better options now exist.[c,1-8]**
    - ◊ **Administration of pegfilgrastim up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.**
  - **There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).**
  - **There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 weeks.**
  - **There are insufficient data to support use for weekly chemotherapy regimens; therefore, use of pegfilgrastim cannot be recommended.**

- **Prophylactic use of G-CSF in patients given concurrent chemotherapy and radiation is not recommended.**
- **Subcutaneous route is preferred for all G-CSF listed above.**
- **Prophylactic antibiotics are not routinely recommended for standard-dose chemotherapy. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

References on next page

See Toxicity Risks with Myeloid Growth Factors (MGF-E)

[a]Tbo-filgrastim is a human G-CSF approved by the FDA through an original biologic license application. All of these G-CSF are 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.

[b]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.

[c]An FDA-approved delivery device is available that can be applied the same day as chemotherapy and set to deliver the full dose of pegfilgrastim the following day. This may be an option for patients who cannot return to the clinic for next-day administration of pegfilgrastim.[8]

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## G-CSF FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

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**Prospective randomized trial favored next-day administration.**

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## MYELOID GROWTH FACTORS FOR THERAPEUTIC USE

**Possible Indications for the Initiation of Therapeutic MGF for Management of Febrile Neutropenia[a,b]**

- **Sepsis syndrome**
- **Age >65 years**
- **Absolute neutrophil count [ANC] <100/mcL**
- **Neutropenia expected to be more than 10 days in duration**
- **Pneumonia or other clinically documented infections**
- **Invasive fungal infection**
- **Hospitalization at the time of fever**
- **Prior episode of febrile neutropenia**

**MGF for Therapeutic Use and Maintenance of Scheduled Dose Delivery:[c]**

- **Filgrastim or filgrastim-sndz[d]**
  - **Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits).**
  - **Continue until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.**
- **Sargramostim**
  - **Used in clinical trials at a dose of 250 mcg/m$^2$/d (rounding to the nearest vial size by institution-defined weight limits).**
  - **Continue until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.**

See Toxicity Risks with Myeloid Growth Factors (MGF-E)

[a]The decision to use or not to use MGF in the treatment of febrile neutropenia is controversial. See Discussion for further details.
[b]Smith TJ, Khatcheressian J, Lyman G, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-3205.
[c]Tbo-filgrastim and pegfilgrastim have only been studied for prophylactic use. See Discussion for further details.
[d]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.

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## MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

### Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

- **Single-agent growth factor:**[1-3]
  - **Filgrastim or filgrastim-sndz[a] or tbo-filgrastim**
    - ◊ **Dose: 10–32 mcg/kg/d by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5 and continue until leukapheresis.**
- **Combination chemotherapy followed by filgrastim/filgrastim-sndz[a]/tbo-filgrastim with the goal of mobilization during count recovery.**[4-6]
  - **Filgrastim/filgrastim-sndz[a]/tbo-filgrastim is started about 24 hours after completion of chemotherapy.**
- **Concurrent filgrastim/filgrastim-sndz[a] + sargramostim (category 2B)**
  - **Filgrastim/filgrastim-sndz[a] 7.5 mcg/kg each morning, sargramostim 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.**[7]
- **Filgrastim/filgrastim-sndz[a]/tbo-filgrastim + plerixafor (for selected patients with non-Hodgkin's lymphoma or multiple myeloma)**[8-10]
  - **Plerixafor is indicated for:**
    - ◊ **Patients who were heavily pre-treated**[11] **or had prior treatment with >10 cycles of cytotoxic chemotherapy, or those who have failed prior collection attempts or exhibit risk factors for being poor mobilizers due to more than 6 cycles of lenalidomide or fludarabine, or radiation to the pelvis.**
    - ◊ **As "just in time" or "rescue" in the case of suboptimal peripheral CD34+ count.**[12-14]
  - **Dosing:**
    - ◊ **Filgrastim/filgrastim-sndz[a]/tbo-filgrastim dose: 10 mcg/kg/d x 4 days. On the evening of day 4, start plerixafor by subcutaneous injection 11 hours prior to day 5 collection (the next morning).**
    - ◊ **Plerixafor dose: 0.24 mg/kg/d for patients weighing >83 kg; 20 mg (fixed dose), or 0.24 mg/kg/d for patients weighing ≤83 kg, maximum 4 doses (if creatinine clearance >50 mL/min, maximum dose 40 mg/d)**

Continued on next page

See References, MGF-D (3 of 3)

See Toxicity Risks with Myeloid Growth Factors (MGF-E)

[a]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.

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## MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

### Mobilization of Allogeneic Donors

- **Allogeneic hematopoietic cell donors:**
  - **Filgrastim (preferred) or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)**
    - ◊ **Dose: 10 mcg/kg/d by subcutaneous injection, start collection on day 4 or 5.[15-17]**
  - **Plerixafor (category 2B): Use in normal donors is under study.[18,19]**
- **For granulocyte transfusion:**
  - **Filgrastim or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)**
    - ◊ **Single dose: 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8–24 hours prior to collection.[20]**

### Supportive Care Options

- **Filgrastim[b,21] or filgrastim-sndz[a] or tbo-filgrastim**
  - **Post autologous hematopoietic cell or cord blood transplant**
  - **5 mcg/kg/d. Begin day +5 post transplant until recovery of ANC (eg, >1.5 x $10^9$/L x 2 d).[c]**
- **Sargramostim[22-24]**
  - **Post autologous hematopoietic cell transplant or delayed hematopoietic engraftment after transplant**
  - **250 mcg/$m^2$/d until ANC >1.5 x $10^9$/L x 3 d.**
- **Pegfilgrastim[25]**
  - **Post autologous hematopoietic cell transplant**

See References, MGF-D (3 of 3)

See Toxicity Risks with Myeloid Growth Factors (MGF-E)

[a]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.
[b]Filgrastim accelerates neutrophil recovery but has not impacted survival. See Discussion for details.
[c]For additional dosing information refer to the package insert: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=97cc73cc-b5b7-458a-a933-77b00523e193. (Accessed March 14, 2016.)

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## MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT
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**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## TOXICITY RISKS WITH MYELOID GROWTH FACTORS

**Filgrastim and derivative products including pegfilgrastim[a,b,c]**

- **Warnings**
  - **Allergic reactions**
    - ◊ **Skin: rash, urticaria, facial edema**
    - ◊ **Respiratory: wheezing, dyspnea**
    - ◊ **Cardiovascular: hypotension, tachycardia, anaphylaxis**
  - **Bleomycin-containing regimens: pulmonary toxicity[d]**
  - **Splenic rupture**
  - **Acute respiratory distress syndrome**
  - **Alveolar hemorrhage and hemoptysis**
  - **Sickle cell crises (only in patients with sickle cell disease)**
  - **MDS and AML[e]**
- **Precautions**
  - **Cutaneous vasculitis**
  - **Immunogenicity**
- **Adverse reactions**
  - **Bone pain**

**Sargramostim[a,c]**

- **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 blood urea nitrogen (BUN), and high cholesterol**

[a]See full prescribing information for specific product information.
[b]Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim and pegfilgrastim.
[c]The toxicities listed are from the prescribing information and are based on studies from different patient populations. For filgrastrim 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.
[d]See Discussion for details.
[e]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.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer 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

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 patients with cancer 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 duration 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]). Occurrences of severe neutropenia or FN 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 related to 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] Due to individual patient risk factors, 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. Thus, 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. 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, these guidelines 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 term "MGF" will be utilized when the data are supported by studies for both G-CSF and GM-CSF.

Filgrastim, filgrastim-sndz, 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 their FDA approval to use in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. Tbo-filgrastim was approved by the FDA in an original biologic license application in August 2012[10,11] and therefore has a more restricted indication.[12] Filgrastim-sndz was approved as a biosimilar allowing it to gain approval for the broader indications of the originator product filgrastim (see *Biosimilars*). Additional indications for filgrastim and filgrastim-sndz include treatment for patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy, patients with cancer receiving bone marrow transplant, patients undergoing peripheral blood progenitor cell collection (PBPC)

and therapy, and patients with severe chronic neutropenia. Filgrastim is also approved by the FDA for the treatment of patients acutely exposed to myelosuppressive doses of radiation.[13] While the European guidelines also include lenograstim as a recommended G-CSF in solid tumors and non-myeloid malignancies,[14] it is not approved for use in the United States and is therefore not addressed in these guidelines.

The only GM-CSF that is FDA-approved is sargramostim, although some clinical trials have used the GM-CSF molgramostim. Molgramostim is not recommended by the panel due to the increased adverse events compared to sargramostim[15] as well as the lack of FDA approval. Sargramostim is limited to use following induction therapy for AML and in various hematopoietic 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 versus GM-CSFs.

The NCCN Guidelines for Myeloid Growth Factors are 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 MGFs. Growth factors in the treatment of hematologic malignancies are discussed in the NCCN Guidelines for Myelodysplastic Syndromes, the NCCN Guidelines for Multiple Myeloma, and the NCCN Guidelines for Acute Myeloid Leukemia.

## Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Myeloid Growth Factors, an electronic search of the PubMed database was performed to obtain key literature published between November 1, 2014, and December 22, 2015**,** using the following search terms: myeloid growth factors and cancer; colony stimulating factor and cancer; pegfilgrastim and cancer; filgrastim and cancer; tbo-filgrastim and cancer; and sargramostim and cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[16]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 45 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

## Benefits and Risks of MGFs

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

Studies showed that the prophylactic use of MGFs 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.[17-33] Additionally, the benefit of GM-CSF therapy was seen in the treatment of myeloid malignancies.[34] MGFs improved the delivery of full dose-intensity chemotherapy on schedule, although this has not been shown to lead to better response or higher overall survival (OS) in most studies.[17,19,21,24-27,31,35,36] However, in node-positive breast cancer[31,37] and aggressive lymphoma,[33,38,39] dose-dense regimens supported by MGFs improved disease-free survival and/or OS compared to conventional chemotherapy.

Meta-analyses confirmed the efficacy of prophylactic MGFs in decreasing rates of infection and risk of neutropenia.[40-43] The meta-analysis from Clark et al[42] included 13 studies, in which 6 studies involved treatment of patients with G-CSF; 6 studies involved treatment of 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; $P$ = .10), the infection-related mortality had a borderline significant benefit with the use of MGFs (OR, 0.51; 95% CI, 0.26–1.00; $P$ = .05). 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 MGFs.

In a systematic review of 17 randomized trials of prophylactic G-CSFs, including 3493 adult patients with solid tumors and lymphoma, 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 the relative dose intensity of the chemotherapy delivered with an average difference between study arms of 8.4% ($P$ = .001).[44] 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, 0.60; 95% CI, 0.43–0.83; $P$ = .002). The survival advantage was confirmed in a systematic review by Lyman et al[45] of 25 randomized controlled trials that involved more than 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 risk and RR 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.

Several randomized trials have also demonstrated improved outcomes with the prophylactic use of tbo-filgrastim for the prevention of FN. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.[46] 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.[47,48] 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.[49] Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.[50,51]

In addition to improved outcome, MGFs have associated toxicity risks that have been reported (see *Toxicity Risks with Myeloid Growth Factors* in the algorithm). Similar toxicities to filgrastim are expected for pegfilgrastim and filgrastim biosimilars, although not all toxicities have been reported with each preparation. To date, the main consistently

observed toxicity associated with G-CSF therapy is mild to moderate bone pain in 10% to 30% of patients.[52-58] This is usually effectively controlled by non-narcotic analgesics.[52,53] The meta-analysis by Kuderer et al[59] confirmed a heightened risk of musculoskeletal pain associated with MGFs (RR, 4.03; 95% CI, 2.15–7.52; $P < .001$).[44]

There have also been reports of rare cases of splenic rupture with G-CSF usage, some of which were fatal.[60] These cases occurred in patients and healthy donors in the hematopoietic cell transplantation setting. Some patients develop allergic reactions involving 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.[52,53,61] Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease, but not for patients with sickle cell trait.[62-64] Worsening of amyloidosis following G-CSF administration has been reported; however, this is based on two case reports in patients who were already prone to life-threatening complications.[65,66]

Pulmonary toxicity has been reported following the use of G-CSFs for patients with Hodgkin lymphoma undergoing bleomycin-containing chemotherapy, especially ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). An increased risk of bleomycin pulmonary toxicity has been reported with G-CSF use for this disease in a retrospective study of 141 patients.[67] In a systematic review of case reports by Azoulay and colleagues,[68] 70 cases of G-CSF–related pulmonary toxicity were identified in neutropenic patients with cancer. Thirty-six patients had received bleomycin, but the majority of patients with NHL had also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). The toxicity potential for patients following the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen is more unclear, although bleomycin is given every 3 weeks in this regimen as opposed to every 2 weeks in ABVD. Conversely, an increase in bleomycin pulmonary toxicity has not been reported with G-CSF use in bleomycin-containing testicular cancer chemotherapy regimens.[36] Due to the controversy of G-CSF use during bleomycin-containing chemotherapy, clinicians should be highly alert to signs and symptoms of this complication. The routine use of G-CSF is not recommended in conjunction with the most common chemotherapy regimens for classical Hodgkin lymphoma (ABVD and Stanford V). Furthermore, two studies have shown that ABVD can be safely administered at full dose without G-CSF support.[69,70] However, due to the high incidence of toxicity and treatment delays, G-CSF support is recommended for patients with Hodgkin lymphoma treated with the escalated BEACOPP regimen.

Adverse events have also 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.[71] 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.[72]

Though uncommon, significant side effects have been reported for GM-CSF. Less than 1% of patients will develop blood clots.[73-75] Though blood clots rarely lead to pulmonary embolism or stroke, these life-threating conditions are possible. There have been reports in clinical trials of capillary leak syndrome,[76-78] a condition in which fluids move from the vascular system into the interstitial space resulting in hypotension and reduced blood flow to internal organs.[73] While this is

more common with GM-CSF, it has also been reported to occur with G-CSF therapy.[79,80]

Although there have been suggestions of a potentially increased risk for AML/MDS with MGF administration from epidemiologic studies, this was not observed in individual randomized trials.[60,81-83] The meta-analysis by Lyman et al[45] reported an increase in absolute risk and RR for 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 for 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.[83] One caveat of the study was that it could not exclude the possibility that the 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.

The recommendations in the NCCN Myeloid Growth Factors Guidelines are based on therapeutic efficacy and clinical benefit of treatment. However, in addition to evaluating the clinical benefits and risks of MGF 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%.[84] Economic analyses of MGFs have yielded mixed results, depending on the context of usage.[85-89] While the addition of MGFs 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.

## Biosimilars

A biosimilar is a biological product that is highly similar to the FDA-approved reference product with the exception of minor differences in clinically inactive components and no differences regarding efficacy, safety, and purity between the biosimilar and the reference product. Biosimilars have the same amino acid sequence; however, they may differ at the protein level due to the nature and complexity of biologic products. Differences may be seen in the three-dimensional structure, the glycosylation sites, the isoform profiles, and the level of protein aggregation.[90,91] Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biological activity, efficacy, and safety.[92] If overall safety and efficacy remain unaffected, biosimilars may be approved for the same indications. Biosimilars can be substituted for the originator product. If the biosimilar is also designated as interchangeable, alternating or switching between the two products is acceptable and is not expected to result in a greater risk to the patient's safety or a diminished efficacy. However, if the biosimilar is not deemed interchangeable, switching between biosimilars and originator products is not recommended during treatment.

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim. The FDA has given a nonproprietary name to this biologic by attaching a 4-letter suffix to the product name. Data have shown filgrastim-sndz to have identical protein structure, mass, size, charge, and hydrophobicity to the originator product.[93] Pharmacokinetic and pharmacodynamic modeling further confirmed that the mechanism of action is the same and occurs through the binding of the G-CSF receptor.[94] Clinical data leading to the approval of filgrastim-sndz were predominately based on data from healthy volunteers and data in patients with cancer in the context of the prevention of chemotherapy-induced neutropenia.

Although a potential concern regarding immunogenicity exists regarding biosimilars, immunogenicity is anticipated to be low to nonexistent in filgrastim biosimilars based on the nature of filgrastim as an unglycosylated protein and the lack of immunogenicity seen with the reference product. Filgrastim-sndz was evaluated in limited clinical studies of healthy volunteers or cancer patients with the incidence of antibodies binding to filgrastim of 3% (11 out of 333 patients).[95] Further analysis of the 11 patients showed no evidence of neutralizing antibodies. The data suggest that there is no increase in risk of immunogenic adverse events or reduction of efficacy; however, it is recommended that patients remain on the same product throughout treatment.[96]

The FDA approved filgrastim-sndz for the following indications: 1) to decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; 2) to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy of patients with AML; 3) to reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation; 4) to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and 5) to reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.[95]

Filgrastim-sndz has been approved as a biosimilar but has not been sought approval as an interchangeable biologic. Therefore, whether treatment is started with the reference product or the biosimilar, the patient should remain on the same product throughout treatment whenever possible. The process by which biosimilars are approved makes it unlikely that phase III trials involving filgrastim-sndz will be initiated; therefore, data must be extrapolated to the indications for which a biosimilar has been approved, and clinicians must make decisions on the appropriate incorporation of biosimilars by relying on fewer comprehensive studies and more on clinical experience and judgment. Furthermore, the nature of biosimilars reflects variation in manufacturing that could result in differences in efficacy and safety that may require longer study evaluation. Continued postmarketing safety and surveillance are invaluable strategies to monitor these drugs moving forward.

## Prophylactic Use of MGFs

### Risk Assessment

The guidelines begin with an evaluation of risk for chemotherapy-induced FN prior to the first cycle of chemotherapy. The risk assessment includes disease type, chemotherapy regimen (high-dose, dose-dense, or standard-dose therapy), patient risk factors, and treatment intent (curative/adjuvant vs. palliative). 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) (see *Evaluation, Risk Assessment, and Prophylactic Use* in the algorithm). 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 (see *Additional Evaluation of Patient Risk Factors for Prophylactic Use* in the algorithm).

### Chemotherapy Regimens and Risk for FN

The development of FN is a common dose-limiting toxicity of many single-agent and combination chemotherapy regimens that is directly related to the intensity of the 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 FN risk.

The algorithm lists 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 and Risk for Febrile Neutropenia* in the algorithm). 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 regimens for NHL, have only been tested with growth factor support.

### 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[97]). Patient factors may elevate the overall risk to a high-risk category, where prophylactic MGFs 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 patients would be considered high risk. Even a low-risk regimen does not necessarily preclude the use of MGFs in a patient with high-risk factors.

The most important risk factor for developing severe neutropenia is higher age, notably over 65 years, in patients who receive full chemotherapy dose intensity (see NCCN Guidelines for Older Adult Oncology).[98-103] Other risk factors include prior 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 *Additional Evaluation of Patient Risk Factors for Prophylactic Use* in the algorithm). 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 patients with cancer beginning chemotherapy treatment.[104]

### 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 MGF 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.[105,106]

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[20] reported on the results of a double-blind, randomized, placebo-controlled, multicenter study to demonstrate whether first and subsequent cycle prophylactic MGF support with pegfilgrastim would significantly reduce FN in a regimen that had previously been associated with an expected FN incidence of 20%.[20] 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 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 rate of less than 1% in the pegfilgrastim group.

A second trial reported the results of 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF.[18] In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with 9 patients (10%) in the antibiotics plus G-CSF 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 when given with the first cycle of chemotherapy. Furthermore, this strategy could be considered for other patients with cancer who have 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 MGF is recommended for any patient considered at high risk, regardless of the treatment intent.

### 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. The panel recommends individualized consideration of MGFs 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 MGF is a difficult decision and requires careful discussion between the physician and patient. If the increased risk for FN is a result of patient risk factors, MGF 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 MGF is not recommended as alternative treatment options are appropriate and more cost-effective.[84,105,107,108] However, MGF may be considered if the patient is receiving curative or adjuvant treatment and is at a 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 treatment cycle, 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 MGF, 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.

### Dosing and Administration

Filgrastim, filgrastim-sndz, tbo-filgrastim, pegfilgrastim, and sargramostim are FDA-approved options for the prophylactic treatment of FN. While data from randomized studies support the use of filgrastim, filgrastim-sndz, 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 hematopoietic cell transplantation settings. The subcutaneous administration of filgrastim, filgrastim-sndz, tbo-filgrastim, or pegfilgrastim is a category 1 recommendation for the prophylactic treatment of FN. Sargramostim is no longer recommended in this setting. The NCCN Panel does not routinely recommend prophylactic antibiotics for standard-dose chemotherapy. In addition, prophylactic use of MGF in patients given concurrent chemotherapy and radiation has not been evaluated and is therefore not recommended.

#### *Filgrastim, Tbo-filgrastim, Filgrastim-sndz*

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.

#### *Pegfilgrastim*

Clinical trials both in support of and against same-day pegfilgrastim have been published. The original rationale for not giving same-day MGF was the potential for increased neutropenia resulting from MGF stimulation of myeloid progenitors at the time of cytotoxic chemotherapy.[109-111] In a direct comparison, Kaufman et al[112] administered either same-day or next-day pegfilgrastim in women with breast cancer receiving docetaxel, doxorubicin, and cyclophosphamide. FN was observed in 33% of patients treated in the same-day group compared with only 11% of patients treated in the next-day group.[112] 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.[113] 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. However, the study recommends administration of pegfilgrastim 24 hours after chemotherapy.

Vance et al[114] 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.[115] This study of 159 patients spanned 15 different tumor types and 50 different chemotherapy regimens.[115] A double-blind phase 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.[116] 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.[117] 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.[116] More recent retrospective studies in patients with gynecologic malignancies demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours of chemotherapy.[118,119]

Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient per chemotherapy cycle (category 1). Since most clinical studies administer the agent the day after chemotherapy completion, next-day administration is preferred.[53] Based on trials of filgrastim, panelists agreed that giving pegfilgrastim up to 3 to 4 days after chemotherapy is also reasonable. In addition, panelists recognized that some institutions have administered “same-day” pegfilgrastim, defined as administration of pegfilgrastim on the day during which patients receive chemotherapy. This was done for logistical reasons and to minimize burdens on long-distance patients.[120] However, the recent FDA approval of a delivery device that can be applied the same day as chemotherapy and set to deliver the full dose of pegfilgrastim the following day is an alternative to same-day administration for patients who cannot return to the clinic for next-day administration of pegfilgrastim.[121]

The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle length. Based on phase III clinical trials,[20,122] 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.[123-128] There are insufficient data to support the dose and schedule for weekly regimens; therefore, these cannot be recommended.

## Therapeutic Use of MGFs

Compared to prophylactic use, there is less evidence supporting the therapeutic use of MGFs for FN as an adjunct to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials,[42] Clark and colleagues[42] 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 OS with therapeutic MGF. An earlier meta-analysis by Berghmans et al[129] also found no difference in mortality, but they were unable to assess other clinical benefits. Conversely, in 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, 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).[130]

The NCCN Panel recommends that patients with FN who received prophylactic G-CSF should continue with the same G-CSF. However, since pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional MGF.[131] For patients who have not received prophylactic MGFs, 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, MGFs should be considered. Filgrastim, filgrastim-sndz, or sargramostim may be administered in the therapeutic setting. Tbo-filgrastim and pegfilgrastim have only been studied for prophylactic use.

### Dosing and Administration

If G-CSF was not given prophylactically, filgrastim, filgrastim-sndz, and sargramostim are the recommended MGFs for the therapeutic treatment of FN in selected high-risk patients as outlined above (also see *Therapeutic Use of Myeloid Growth Factors (MGF) for Febrile Neutropenia* in the algorithm). Filgrastim or filgrastim-sndz 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$^2$/d (rounding to the nearest vial size by institution-defined weight limits). Treatment should continue through post-nadir recovery. If G-CSF was given prophylactically, the same G-CSF should be continued in the therapeutic setting.

## Mobilization and Post Hematopoietic Cell Transplant

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

### Mobilization with Growth Factors in the Autologous Setting

Mobilization of PBPCs 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.[132] Most data are focused on filgrastim,[133-137] although studies suggest that single-dose pegfilgrastim has similar efficacy.[138]

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 PBPC count.[134,135,139-143] This may be used as a rescue strategy when PBPC yield is poor, or when the CD34+ cell count does not reach the target level.[140-142] Plerixafor is indicated for patients who were heavily pre-treated[143] or had prior treatment with greater than 10 cycles of cytotoxic chemotherapy, or those who have had failed prior collection attempts that failed or who exhibit risk factors for being poor mobilizers due to more than 6 cycles of lenalidomide or fludarabine, or radiation to the pelvis. One retrospective analysis demonstrated that pegfilgrastim resulted in a better PBPC yield than filgrastim, requiring less use of rescue plerixafor,[144] but there have not been any randomized trials that address the effect of plerixafor when used in combination with pegfilgrastim.

While filgrastim-sndz has been accepted as an equivalent treatment option to filgrastim for patients with FN, there is discussion among medical professions regarding equivalency in hematopoietic cell mobilization or in patients with chronic neutropenia.[145] There are data to support the use of filgrastim-sndz in the autologous hematopoietic cell transplant setting.[146-151] However, the panel acknowledges the limitations of these studies regarding long-term outcomes and the potential impact of the different manufacturing processes. Therefore, while it is reasonable to substitute with filgrastim-sndz, clinicians should be alert to any complications presented in the literature or in their patients. Accurate and timely disclosure of any variation in expected outcome with the biosimilar compared to the originator filgrastim will be of paramount importance.

The NCCN Panel recommends administration of filgrastim, filgrastim-sndz, or tbo-filgrastim as a single agent[133] or as part of a chemo-mobilization regimen,[152-154] starting on the day after completion of chemotherapy (category 2A). Several regimens are effective in chemo-mobilization of hematopoietic progenitors, including cyclophosphamide,[153] ICE,[154] DHAP,[154] VTD-PACE,[152] and others. Studies using GM-CSF as a single mobilization agent or in sequential combination with G-CSF reported good yields of PBPC in normal donors.[155-157] Although both MGFs have been used for mobilization, G-CSF has been favored for this purpose.[158] The use of concurrent filgrastim or filgrastim-sndz and sargramostim is a category 2B recommendation. For select patients with NHL or multiple myeloma, filgrastim, filgrastim-sndz, or tbo-filgrastim can be given followed by plerixafor.

### Mobilization with Growth Factors in the Allogeneic Setting

Initially, there were concerns about mobilization in the allogeneic setting due to normal donor toxicity and the risk for 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.[134-136] The use of plerixafor in normal donors is currently under study.[159,160] Tbo-filgrastim has also been shown to mobilize PBPC 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.[161-163] Studies of filgrastim-sndz have been predominately in the settings of autologous PBPC mobilization and in support of count recovery after transplant, whereas data are sparse in the allogeneic setting. The smaller studies in allogeneic progenitor cell donors have suggested that there are no short-term safety issues;[164-166] however, the long-term data are not yet available. A single retrospective study of filgrastim-sndz in comparison to filgrastim for mobilization in normal donors reported that 3 out of 18 donors mobilization in the filgrastim-sndz group failed without any mobilization failures in the filgrastim group.[167] Neutrophil and platelet count recovery after allogeneic transplant were similar in both arms. The World Marrow Donor Association recommends against the use of filgrastim biosimilars in unrelated donors based on extrapolation from autologous transplant data.[168]

The NCCN Panel recommends single-agent filgrastim (category 2A, preferred), filgrastim-sndz (category 2B), or tbo-filgrastim (category 2B) for allogeneic hematopoietic cell mobilization and for granulocyte transfusion. The addition of plerixafor in selection patients is a category 2B recommendation.

### 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 PBPC transplantation has been shown to expedite neutrophil recovery in prospective randomized trials.[169-173] 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,[174] concluded that the two are at least equally effective.[175]

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.[176] 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 PBPC grafts.[177]

GM-CSF has been demonstrated to promote hematopoietic recovery after autologous hematopoietic cell transplantation or delayed autologous engraftment.[178,179] GM-CSF therapy has been shown to improve treatment outcome in patients with hematologic malignancies who previously had graft failure following bone marrow transplant.[180] 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.[178]

The NCCN Panel recommends consideration of MGFs in the supportive care setting post-autologous hematopoietic cell transplant. Filgrastim, filgrastim-sndz, tbo-filgrastim, pegfilgrastim, and sargramostim (all category 2A) can be considered in the supportive care setting.

### Dosing and Administration

For dosing information, see *Myeloid Growth Factors in Mobilization and Post Hematopoietic Cell Transplant* in the algorithm.

## 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 controlled trial involving 123 patients.[181] 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/d). Congenital neutropenia patients generally require higher doses (3–10 mcg/kg/d). All patients should have doses adjusted to maintain a blood neutrophil level in the normal or low-normal range. Acute adverse effects include bone pain, arthralgias, and myalgias, which usually diminish in the first few weeks of treatment. The greatest concern is that patients with 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 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.

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