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Myeloid Growth Factors, Version 2.2017

Clinical Practice Guidelines in Oncology

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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 <500 neutrophils/mcL or an ANC of <1,000 neutrophils/mcL and a predicted decline ≤500 neutrophils/mcL over the next 48 hours. Neutropenia can

Abstract

Myeloid growth factors (MGFs) are given as supportive care to patients receiving myelosuppressive chemotherapy to reduce the incidence of neutropenia. This selection from the NCCN Guidelines for MGFs focuses on the evaluation of regimen- and patient-specific risk factors for the development of febrile neutropenia (FN), the prophylactic use of MGFs for the prevention of chemotherapy-induced FN, and assessing the risks and benefits of MGF use in clinical practice.

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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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Myeloid Growth Factors are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

Disclosures for the NCCN Myeloid Growth Factors

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

IIndividual disclosures for the NCCN Myeloid Growth Factors Panel members can be found on page 1541. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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.[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[2] showed that approximately 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.

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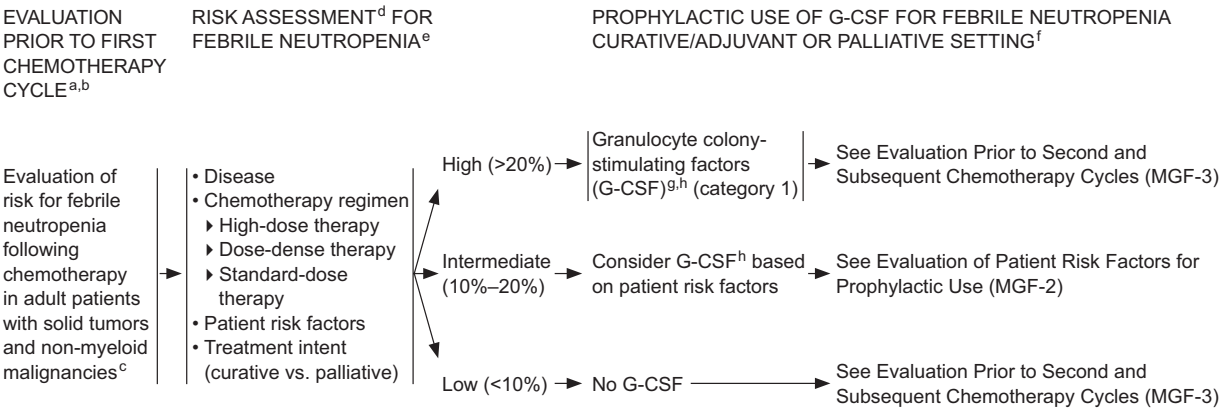

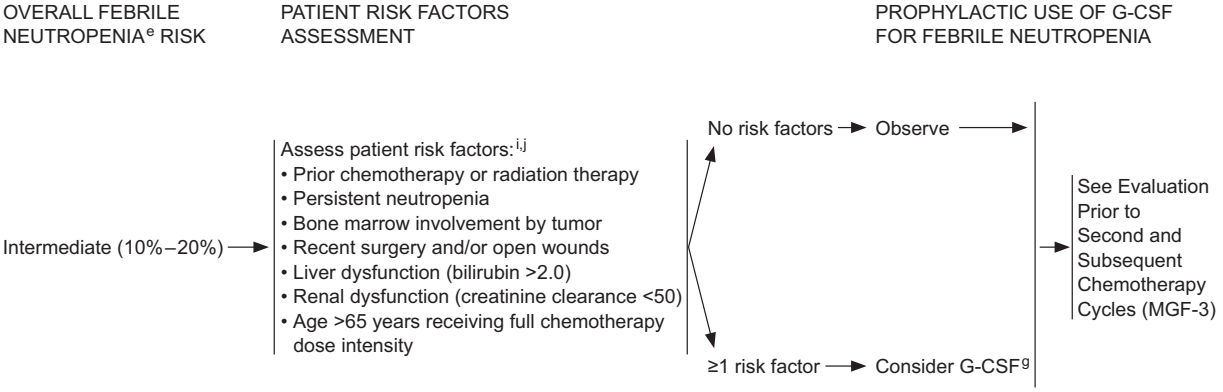

*Available at NCCN.org.

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

[b]Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with MGF as clinically indicated, unless precluded by trial specifications.

[c]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*.

[d]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).

[e]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*.

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

[g]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]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).

[i]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)

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

MGF-1
MGF-2

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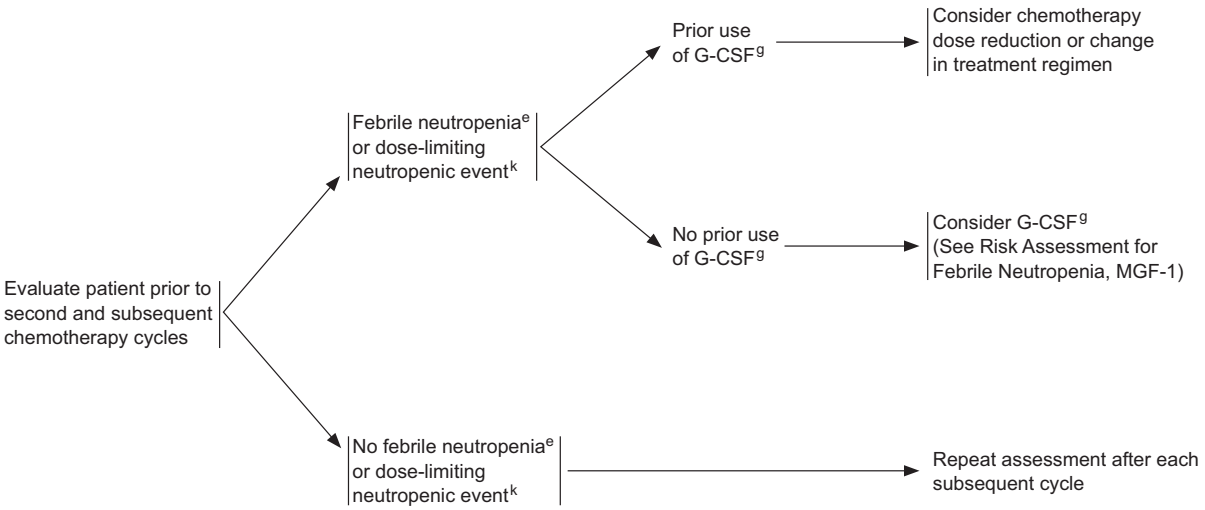
EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS

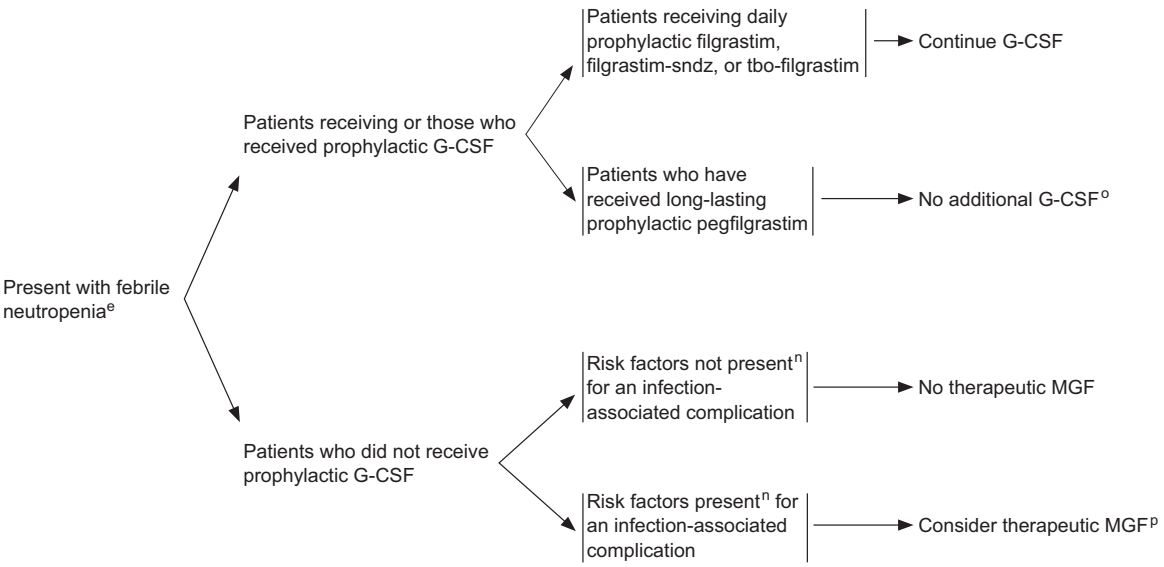


[e]Febrile neutropenia is defined as single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[g]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).

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

THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGF) FOR FEBRILE NEUTROPENIA[e,l,m]



[e]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 (available at NCCN.org).

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

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

[n]See Possible Indications for the Initiation of Therapeutic MGF for Management of Febrile Neutropenia see MGF-C, available online, in these guidelines, at NCCN.org).

[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.

[p]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, available online, in these guidelines, at NCCN.org).

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EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- *This list is not comprehensive*; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for treatment by cancer site are considered when updating this list of examples.
- 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)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL, available at NCCN.org)

Bladder Cancer
- Dose-dense MVAC[b] (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Breast Cancer
- Dose-dense AC followed by T[b] (doxorubicin, cyclophosphamide, paclitaxel)[2]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[3]
- TC[a,c] (docetaxel, cyclophosphamide)[4]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[5]

Hodgkin Lymphoma
- Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[7]

Kidney Cancer
- Doxorubicin/gemcitabine[8]

Non-Hodgkin's Lymphomas
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[9]
- ICE (ifosfamide, carboplatin, etoposide)[a,10,11]
- Dose-dense CHOP-14[a,b] (cyclophosphamide, doxorubicin, vincristine, prednisone)[12,13]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[14]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[15]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[16]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[17,18]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[19]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[20] ± bortezomib (VTD-PACE)[21]

Ovarian Cancer
- Topotecan[a,22]
- Docetaxel[23]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[24]
- Doxorubicin[a,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]

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

See References, MGF-A (3 of 4)

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for treatment by cancer site (available at NCCN.org).

[b]In general, dose-dense regimens require growth factor support for chemotherapy administration.

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

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH AN INTERMEDIATE RISK FOR FEBRILE NEUTROPENIA (10%–20%)[a]

- *This list is not comprehensive*; there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for treatment by cancer site are considered when updating this list of examples.
- 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[32]

Breast Cancer
- Docetaxel[a,33,34]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil)[35]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,36]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[a,37]
- Paclitaxel every 21 days[a,38]

Cervical Cancer
- Cisplatin/topotecan[39,40,41]
- Paclitaxel/cisplatin[a,41]
- Topotecan[42]
- Irinotecan[43]

Colorectal Cancer
- FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[44]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,45]
- Epirubicin/cisplatin/5-fluorouracil[46]
- Epirubicin/cisplatin/capecitabine[46]

Non-Hodgkin's Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,47]
- CHOPa (cyclophosphamide, doxorubicin, vincristine, prednisone)[48,49] including regimens with pegylated liposomal doxorubicin[50,51]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[52]
- Cisplatin/vinorelbine[53]
- Cisplatin/docetaxel[52,54]
- Cisplatin/etoposide[55]
- Carboplatin/paclitaxel[a,d,56]
- Docetaxel[54]

Ovarian Cancer
- Carboplatin/docetaxel[57]

Pancreatic Cancer
- FOLFIRINOX[e]
- Prostate Cancer
- Cabazitaxel[f,58]

Small Cell Lung Cancer
- Etoposide/carboplatin[59]

Testicular Cancer
- Etoposide/cisplatin[60]

Uterine Sarcoma
- Docetaxel[61]

See References, MGF-A (4 of 4)

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for treatment by cancer site (available at NCCN.org).

[d]If carboplatin dose is AUC >6 and/or patient is of Japanese ancestry.

[e]A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[62] 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).[63] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

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

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.

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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.

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Myeloid Growth Factors, Version 2.2017

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.[c]
- Pegfilgrastim (category 1)
  - One dose of 6 mg per cycle of treatment.
    - Based on clinical trial data, pegfilgrastim should be administered the day after chemotherapy (category 1).
    - For patients who cannot return to the clinic for next-day administration, alternative options exist.[d]
    - 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 cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.
- 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.
- For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial) see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available at NCCN.org).

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]Studies suggest that shorter durations of G-CSFs may be less efficacious. (Weycker D, Li X, Tzivelekis S, et al. Burden of chemotherapy-induced febrile neutropenia hospitalizations in US clinical practice, by use and patterns of prophylaxis with colony-stimulating factor. Support Care Cancer 2017;25:439-447.)

[d]An FDA-approved delivery device is available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application). (Yang BB, Morrow PK, Wu X, et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 2015;75:1199-1206.)

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[d]
  - 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 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.

[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.

MGF-E

Cont. from page 1521.

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. These NCCN Guidelines focus on the 2 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 used 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 FDA for the prevention of chemotherapy-induced neutropenia. Both tbo-filgrastim and pegfilgrastim are restricted in their FDA approval for use in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs. Tbo-filgrastim was approved by the FDA in an original biologic license application in August 2012,[5,6] and therefore has a more restricted indication.[7] Filgrastim-sndz was approved as a biosimilar, allowing it to gain approval for the broader indications of the originator product filgrastim. 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. 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 (PBPC) collection 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.[8] Although the European guidelines also include lenograstim as a recommended G-CSF in solid tumors and nonmyeloid malignancies,[9] it is not approved for use in the United States and is therefore not addressed in the NCCN 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 NCCN Panel due to the increased adverse events compared with sargramostim[10] and 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.

These NCCN Guidelines focus on the use of MGFs in the cancer setting, primarily addressing the use of MGFs in adult patients with solid tumors and nonmyeloid malignancies. The NCCN Panel convenes annually to update their recommendations for the use of MGFs, which are based on a review of recently published clinical trials that have led to significant improvements in treatment or have yielded new information regarding biologic factors that may have prognostic importance. This portion of the NCCN Guidelines discusses recommendations outlined for the evaluation of regimen- and patient-specific risk factors for the development of FN, the prophylactic use of MGFs for the prevention of chemotherapy-induced FN, and assessing the risks and benefits of MGF use in clinical practice. For the complete version of these Guidelines, visit NCCN.org.

Evaluating Regimen- and Patient-Specific Risk Factors for Developing FN

Risk Assessment

The risk for chemotherapy-induced FN should be evaluated before the first cycle of chemotherapy. Risk assessment includes disease type, chemotherapy regimen, patient risk factors, and treatment intent. 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. The NCCN Panel recommends that independent clinical judgment be exercised in the assessment of a patient's FN risk. The panel also recommends that patients receiving cytotoxic chemotherapy as part of a clinical trial be evaluated for prophylactic use of MGFs based on both regimen-specific and patient-specific risk factors, unless precluded by trial specifications.

Chemotherapy Regimens and Risk for FN

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

men. Clinical trial data of chemotherapy regimens that have an FN incidence >20% in chemotherapy-naive patients are considered by the NCCN Panel as high risk. It should be noted that the addition of monoclonal antibodies to chemotherapy regimens has the potential to increase FN risk. Of particular concern is rituximab, an anti-CD20 monoclonal antibody used in the treatment of CD20+ hematologic malignancies, which is known to have an independent potential to cause severe neutropenia. It has been associated with prolonged, delayed-onset neutropenia both with or without chemotherapy.[11] 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. 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.

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.[12] Patient factors may elevate the overall risk to a high-risk category, wherein 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 >65 years, in patients who receive full chemotherapy dose intensity.[13–18] Other risk factors include prior chemotherapy or radiotherapy, preexisting neutropenia or tumor involvement in the bone marrow, poor performance status, comorbidities including renal or liver dysfunction, HIV infection, and preexisting conditions such as neutropenia and infection. Most of these have been confirmed as independent risk factors for neutropenic complications in a risk model developed by Lyman et al[19] that was validated in a study population of 3,760 patients with cancer beginning chemotherapy treatment.

High FN Risk

The NCCN Guidelines recommend prophylactic use of MGFs if the risk of FN is >20%. The most recent update of the ASCO guidelines and the EORTC both adopted the 20% threshold for considering routine prophylactic treatment.[20,21]

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 et al[22] 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%. This is the largest randomized study of prophylactic growth factor support that has been performed. In this double-blind study designed with FN as the primary end point, women with breast cancer receiving docetaxel at 100 mg/m^2 every 3 weeks were randomized to either placebo injection (n=465) or pegfilgrastim (n=463), each administered 24 hours after chemotherapy. The placebo group had a 17% overall incidence of FN, whereas the pegfilgrastim group had a 1% incidence. In the pegfilgrastim group, the incidence of hospitalization was 1% versus 14% for the placebo group, and the use of intravenous anti-infectives was reduced from 2% versus 10%, with all of these differences being statistically significant (P<.001). In cycle 1, there was an 11% rate of FN for the placebo group versus <1% in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN with a rate of <1% in the pegfilgrastim group.

A second trial reported the results for 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF.[23] 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.

Intermediate FN Risk

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 to prolong survival or for symptom management, the use of MGF is a difficult decision and requires careful discussion between 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.

Low FN Risk

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.[20,24–26] 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.

Risk Evaluation for Subsequent Chemotherapy Cycles

After the first cycle of chemotherapy, patient evaluation should be performed before each subsequent cycle to determine the risk categorization and treatment intent. If the patient experienced a previous episode of FN or a dose-limiting neutropenic event (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 moves to 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.

Prophylactic Use of MGFs

Filgrastim, filgrastim-sndz, tbo-filgrastim, pegfilgrastim, and sargramostim are FDA-approved options for the prophylactic treatment of FN. Although 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 after 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, and 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 postnadir ANC recovers to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. The NCCN Panel recommends treatment of patients through postnadir recovery because studies have shown that shorter durations of G-CSF treatment are less efficacious.[27]

Pegfilgrastim

Clinical trials both in support of and against same-day pegfilgrastim have been published. The origi-

nal 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.[28–30] In a direct comparison, Kaufman et al[31] 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.[31] A similar trend was seen in a prospective randomized double-blind trial of patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like therapy for NHL wherein same-day pegfilgrastim was associated with enhanced myelosuppression and no reduction in leukopenia was seen.[32] 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 noninferiority margin. However, the study recommends administration of pegfilgrastim 24 hours after chemotherapy.

In a retrospective review of same-day pegfilgrastim in patients with breast cancer receiving dose-dense doxorubicin, Vance and Carpenter[33] observed no increased neutropenia. Another retrospective study from a community-based oncology practice showed similar incidence of myelosuppressive adverse events when comparing the 2 groups.[34] This study of 159 patients spanned 15 different tumor types and 50 different chemotherapy regimens.[34] 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 those receiving next-day pegfilgrastim treatment.[35] 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 from not only a safety perspective but also a logistical one, wherein next-day pegfilgrastim would have compromised the weekly chemotherapy schedule.[36] 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.[35] Other retrospective studies in patients with gynecologic malignancies have also demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours of chemotherapy.[37,38]

Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient per chemotherapy cycle (category 1 recommendation). Because most clinical studies administer the agent the day after chemotherapy completion, next-day administration is preferred.[39] 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 same day patients receive chemotherapy, for logistical reasons and to minimize burdens on long-distance patients.[40] However, the recent FDA-approved 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.[41]

The NCCN Panel also set criteria for the use of pegfilgrastim in chemotherapy regimens of different cycle length. Based on phase III clinical trials,[22,42] 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.[43–48] Data are insufficient to support the dose and schedule for weekly regimens; therefore, pegfilgrastim should not be used.

Risks and Benefits of MGF Use

MGFs are incorporated into chemotherapy regimens to prevent the development of FN and improve the care of patients. Studies have shown 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.[22,23,49–63] Additionally, the benefit of GM-CSF therapy was seen in the treatment of myeloid malignancies.[64] 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 in most studies.[49–51,54–57,61,65,66] However, in node-positive breast cancer[61,67] and aggressive lymphoma,[63,68,69] dose-dense regimens sup-

ported by MGFs improved disease-free and/or overall survival compared with conventional chemotherapy.

Meta-analyses confirmed the efficacy of prophylactic MGFs in decreasing rates of infection and risk of neutropenia.[70–73] The meta-analysis from Clark et al[72] included 13 studies, of which 6 involved treatment of patients with G-CSF, 6 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, 1,518 patients were evaluated for overall mortality, infection-related mortality, length of hospitalization, and time to neutrophil recovery. Although 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 including 3,493 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).[74] 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 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[75] 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% reduction in absolute risk and a RR of 0.90 for all-cause mortality, 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 either tbo-filgrastim, filgrastim, or placebo.[76] 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,[77,78] and toxicities were also similar. A meta-analysis of the 3 trials concluded tbo-filgrastim to be noninferior to filgrastim for the reduced incidence of FN, irrespective of the myelotoxicity of the chemotherapy regimen.[79] Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.[80,81]

MGFs also have associated toxicity risks that have been reported in various studies. 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.[82–88] This is usually effectively controlled by non-narcotic analgesics.[82,83] The meta-analysis by Kuderer et al[89] confirmed a heightened risk of musculoskeletal pain associated with MGFs (RR, 4.03; 95% CI, 2.15–7.52; *P*<.001).[74]

There have also been reports of rare cases of splenic rupture with G-CSF use, some of which were fatal.[90–95] These cases occurred in patients with underlying hematopoietic disorders, patients with solid tumors, and healthy donors of PBPC. The exact mechanism of G-CSF–induced splenic rupture is unknown, but is thought to involve intrasplenic accumulation of circulating granulocytes and myeloid precursors.[92] Although G-CSF–induced splenic rupture is rare, it is potentially life-threatening. Therefore, physicians should monitor patients closely for signs of splenic rupture, including abdominal pain (especially in the upper left quadrant), nausea, vomiting, and progressively worsening anemia, in order to prevent a fatal outcome. Prospective studies on health status, baseline spleen size, and CBC count may be required to identify risk factors for rupture in individual patients.[94]

Additionally, some patients develop allergic reactions involving the skin, respiratory system, or cardiovascular system (filgrastim only). Other warnings from the prescribing information include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.[82,83,96] Sickle cell crisis, sometimes fatal,

has been reported in patients with sickle cell disease, but not those with sickle cell trait.[97–99] Worsening of amyloidosis after G-CSF administration has been reported; however, this is based on 2 case reports in patients who were already prone to life-threatening complications.[100,101]

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.[102] In a systematic review of case reports by Azoulay et al,[103] 70 cases of G-CSF–related pulmonary toxicity were identified in patients with cancer and neutropenia. Thirty-six patients had received bleomycin, but most with NHL had also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). The toxicity potential for patients after BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) 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-induced pulmonary toxicity has not been reported with G-CSF use in bleomycin-containing chemotherapy regimens for testicular cancer.[66] Due to the controversy regarding G-CSF use during bleomycin-containing chemotherapy, clinicians should be highly alert to signs and symptoms of pulmonary toxicity. The routine use of G-CSF is not recommended in conjunction with the most common chemotherapy regimens for classical Hodgkin lymphoma (ie, ABVD and Stanford V). Furthermore, 2 studies have shown that ABVD can be safely administered at full dose without G-CSF support.[104,105] 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 after administration of GM-CSF. Adverse reactions were seen in 65% of these patients, although they were not severe and were reversible. These reactions included mild myalgias, facial flushing, low-grade fever, headache, bone discomfort, nausea, and dyspnea.[106] A side-effect profile of GM-CSF, completed several years later, reported a lower rate of 20% to 30% of patients experiencing mild-to-moderate adverse events, and attributed this decline to improved dosing and delivery.[107]

Although uncommon, severe side effects have been reported for GM-CSF; <1% of patients will develop blood clots.[108–110] Although blood clots rarely lead to pulmonary embolism or stroke, these life-threating conditions are possible. There have also been reports in clinical trials of capillary leak syndrome,[111–113] a condition in which fluids move from the vascular system into the interstitial space, resulting in hypotension and reduced blood flow to internal organs.[108] Although this more commonly occurs with GM-CSF, it has also been reported with G-CSF therapy.[114,115]

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.[90,116–118] The meta-analysis by Lyman et al[75] reported an increase in absolute risk of 0.41% and an RR of 1.92 for the development of AML/MDS 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 earlier, overall mortality was nevertheless decreased. These data mirror an earlier report based on the SEER database that showed an elevated risk for development of AML/MDS in patients receiving either G-CSF or GM-CSF therapy.[118] 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 these NCCN 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. During the past decade, the costs of inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.[25] Economic analyses of MGFs have yielded mixed results, depending on the context of use.[119–123] Although the addition of MGFs to treatment regimens inevitably

increases the drug cost, it may actually equate to substantial savings compared with the cost of hospitalization and subsequent treatment of neutropenia.

Summary

MGFs can be used in the supportive care of patients receiving myelosuppressive chemotherapy to prevent severe complications, such as FN and associated infections, and improve overall quality of life. Prophylactic use of MGFs has been shown to reduce the risk, severity, and duration of chemotherapy-related FN in a variety of cancers. The risk of developing FN is related to the treatment regimen and delivered dose intensity as well as individual patient risk factors, such as increased age (>65 years), comorbidities including renal or liver dysfunction, and preexisting infections. Because development of FN can prompt dose reductions or treatment delays, use of MGFs can help ensure the delivery of full dose-intensity chemotherapy on schedule, resulting in improved clinical outcome. However, associated costs have prevented their routine use in all patients receiving myelosuppressive chemotherapy. In addition to the clinical benefits of their prophylactic use, MGFs also have associated toxicities, including bone pain, splenic rupture, allergic reactions, and pulmonary complications. Therefore, selective use of MGFs in patients at increased risk for neutropenic complications may enhance both the safety and cost-effectiveness of these agents.

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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty:
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[b]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:
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