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NCCN

Myeloid Growth Factors

Clinical Practice Guidelines in Oncology

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Abstract

Febrile neutropenia, a common side effect of myelosuppressive chemotherapy in patients with cancer, can result in prolonged hospitalization and broad-spectrum antibiotic use, often prompting treatment delays or dose reductions of drug regimens. Prophylactic use of myeloid growth factors (mainly the colony-stimulating factors filgrastim and pegfilgrastim) in patients of heightened risk can reduce the severity and duration of febrile neutropenia. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myeloid Growth Factors provide recommendations on the use of these agents mainly in the oncology setting based on clinical evidence and expert consensus. This version includes revisions surrounding the issue of timing of pegfilgrastim administration. It also includes new sections on tbo-filgrastim, a recently approved agent that is biologically similar to filgrastim, and the role of myeloid growth factors in the hematopoietic cell transplant setting (*JNCCN* 2013;11:1266–1290)

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.

Overview

Neutropenia (<500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h) and resulting febrile neutropenia (FN; ≥38.3°C orally or ≥38.0°C over 1 h) can be induced by myelosuppressive chemotherapy. FN, in turn, is a major dose-limiting toxicity of chemotherapy, often requiring prolonged hospitalization and broad-spectrum antibiotic use (reviewed by Lyman and Kuderer[1]). These can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome. Studies have shown that prophylactic use of colony-

Please Note

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Disclosures for the NCCN Myeloid Growth Factors Panel

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.

Individual disclosures for the NCCN Myeloid Growth Factors Panel members can be found on page 1290. (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.

stimulating factors (CSFs) can reduce the risk, severity, and duration of FN, but the cost has prevented routine use for all patients receiving myelosuppressive chemotherapy. Selective use of CSFs in patients at increased risk for neutropenic complications may, however, enhance the cost-effectiveness.

The risk of FN is usually based on the treatment regimen and delivered dose intensity. A survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin's lymphoma (NHL) has shown, however, that the rates of myelosuppression and delivered dose intensity are underreported.[2] When reported, the rates of myelosuppression with the same and similar regimens varied greatly, making it difficult to determine the actual risk for neutropenic complications associated with common chemotherapy regimens.[2] Differences in the reported rates of neutropenic complications may relate to differences in study patient populations and the delivered dose intensity. Treatment dose intensity was reported with even less consistency, making it very difficult to interpret differences in reported rates of toxicity or treatment efficacy.

A review by Dale[3] showed that approximately 25% to 40% of treatment-naïve patients develop FN with common chemotherapy regimens. Occurrence of FN may delay subsequent chemotherapy courses or result in dose reduction that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. In addition, correlations have

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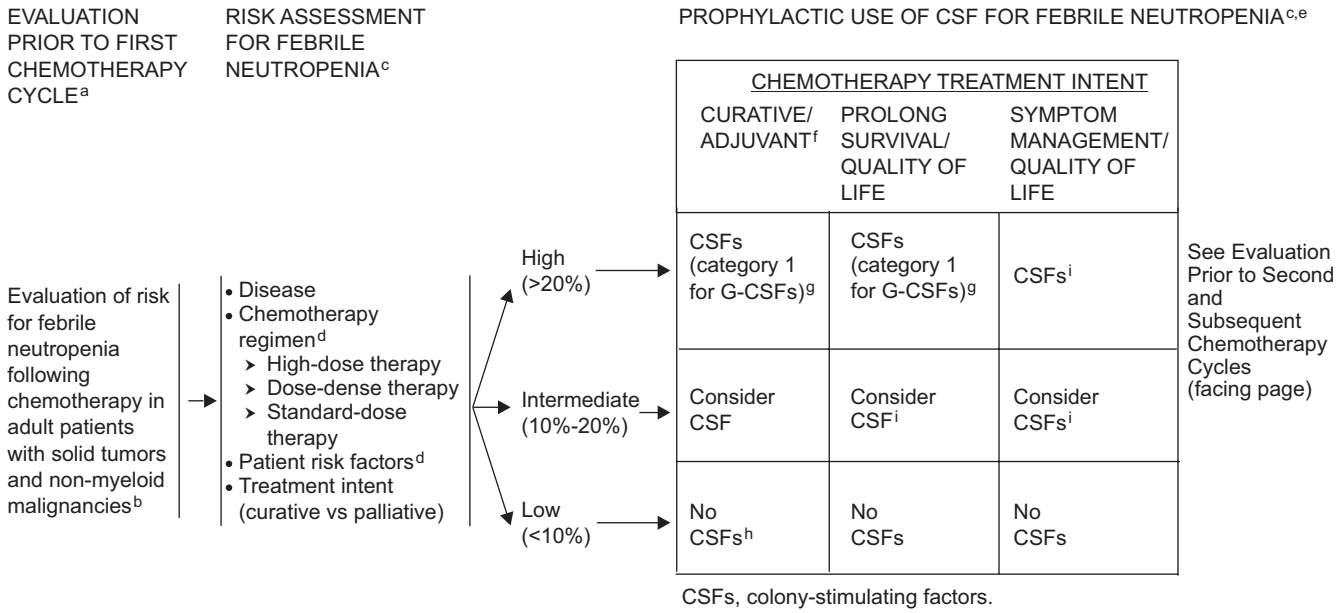


CSFs, colony-stimulating factors.

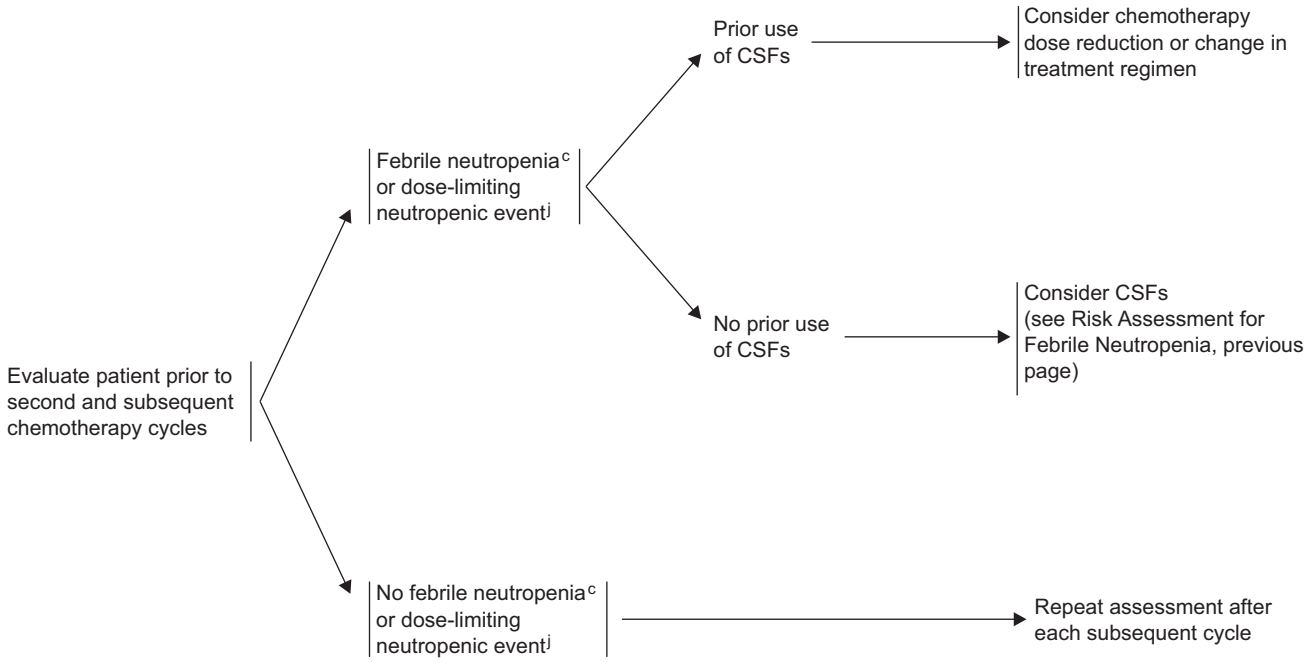
*To view the most recent version of these guidelines, visit NCCN.org.

[a]The NCCN Myeloid Growth Factors Guidelines were formulated in reference to adult patients.
[b]For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for MDS,* and in acute myeloid leukemia (AML), see the NCCN Guidelines for AML.*
[c]Febrile neutropenia is defined as single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.*
[d]There are many factors that need to be evaluated to determine a patient's risk categorization, including type of chemotherapy regimen (see MGF-A) and patient risk factors, such as a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity (see MGF-B).
[e]See Toxicity Risks with Growth Factors (MGF-C).
[f]The confounding effects of chemotherapy dose and schedule, radiation, and CSFs use on the excess risk of leukemia and MDS in patients treated with these agents and modalities are currently being evaluated. See Discussion for further details.
[g]There is category 1 evidence for G-CSFs for a reduction of risk of febrile neutropenia, hospitalization, and intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSFs for a reduction in infection-related mortality during the course of treatment. (See Discussion for further details.)
[h]Only consider CSFs if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.
[i]The use of CSFs in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is 10% to 20%, CSFs are reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less-myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

Myeloid Growth Factors, Version 2.2013

EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS

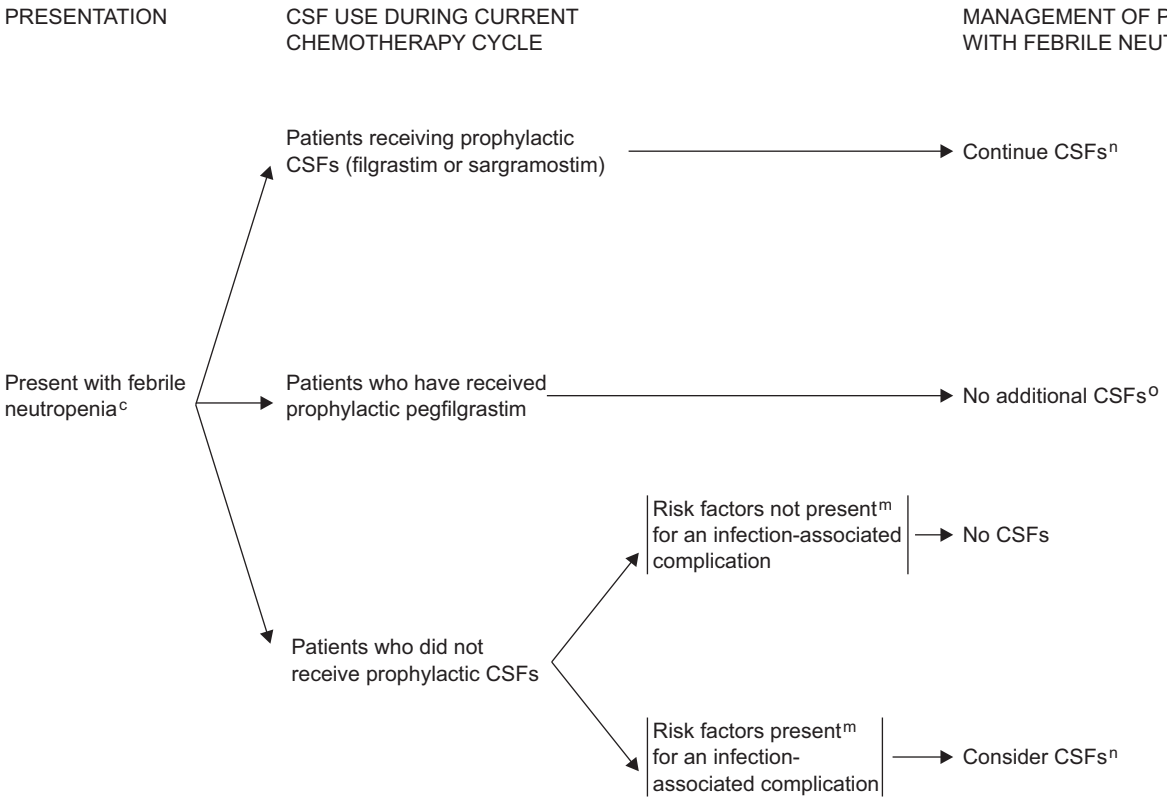


[c]Febrile neutropenia is defined as, single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit NCCN.org).

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

MGF-2

THERAPEUTIC USE OF CSF 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 <1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit NCCN.org).

[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 CSFs in the therapeutic setting is controversial. See Discussion for further details.

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

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

[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 suggests that additional CSFs will not be beneficial.

Myeloid Growth Factors, Version 2.2013

Examples of Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia (>20%)

- The type of chemotherapy regimen is only one component of the risk assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-B)
- This list is not comprehensive; there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (ie, treatment-naive vs heavily pretreated patients). (See MGF-1)

Acute Lymphoblastic Leukemia (ALL)
- ALL induction regimens (see NCCN Guidelines for ALL; to view the most recent version of these guidelines, visit NCCN.org)

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
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory)[8,9]
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma [DLBCL], peripheral T-cell lymphomas [PTCLs], 2nd line, salvage)[10]
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)[11]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab[12,13]
- MINE (mesna, ifosfamide, novantrone, etoposide) DLBCL, PTCLs, 2nd line, refractory)[14]
- DHAP (dexamethasone, cisplatin, cytarabine) (PTCLs, DLBCL, 2nd line)[15]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (DLBCL, PTCLs, 2nd line, recurrent)[16]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[17,18]

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

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine[20]
- Decitabine[21]

Ovarian Cancer
- Topotecan[22]
- Paclitaxel[23]
- Docetaxel[24]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[25]
- Doxorubicin[26]
- Ifosfamide/doxorubicin[27]

Small Cell Lung Cancer
- Topotecan[28]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[29]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[30,31]
- TIP (paclitaxel, ifosfamide, cisplatin)[32]

*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)

Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia (10%-20%)

- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile
- Neutropenia (MGF-B)
- This list is not comprehensive; there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel[33]

Breast Cancer
- Docetaxel every 21 days[34]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[35]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)[36]
- AC + sequential docetaxel + trastuzumab (adjuvant)[37]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[38]
- Paclitaxel every 21 days (metastatic or relapsed)[39]

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

Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[45]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[46]
- Epirubicin/cisplatin/5-fluorouracil[47]
- Epirubicin/cisplatin/capecitabine[47]

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

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

Non-Hodgkin's Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt lymphoma, recurrent)[52]
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, DLBCL, recurrent)[52]
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)[53]
- GDP (gemcitabine, dexamethasone, cisplatin) (DLBCL, PTCL, 2nd line)[54]
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (DLBCL, 2nd line)[54]
- FMR (fludarabine, mitoxantrone, rituximab)[55]
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[56,57] including regimens with pegylated liposomal doxorubicin[58,59] or mitoxantrone[60] substituted for doxorubicin

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

Ovarian Cancer
- Carboplatin/docetaxel[66]

Pancreatic Cancer
- FOLFIRINOX†

Prostate Cancer
- Cabazitaxel‡,[67]

Small Cell Lung Cancer
- Etoposide/carboplatin[68]

Testicular Cancer
- Etoposide/cisplatin[69]

Uterine Sarcoma
- Docetaxel (advanced or metastatic)[70]

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

†A small retrospective trial had a 17% risk of FN in neoadjuvant setting[71] and a randomized trial had a 5.4% in metastatic setting.[72] Although G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

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

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

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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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 2.2013

PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

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

- Older patient, notably patients age ≥65 years (See NCCN Guidelines for Senior Adult Oncology; to view the most recent version of these guidelines, visit NCCN.org)
- Previous chemotherapy or radiation therapy
- Preexisting neutropenia or bone marrow involvement with tumor
- Preexisting conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

TOXICITY RISKS WITH GROWTH FACTORS

Filgrastim and derivative products including pegfilgrastim[1,2,3]

- Warnings
  - Allergic reactions
    - Skin: rash, urticaria, facial edema
    - Respiratory: wheezing, dyspnea
    - Cardiovascular: hypotension, tachycardia, anaphylaxis
  - Bleomycin-containing regimens: pulmonary toxicity[4]
  - Splenic rupture
  - Acute respiratory distress syndrome
  - Alveolar hemorrhage and hemoptysis
  - Sickle cell crises (only in patients with sickle cell disease)
  - MDS and AML (see Discussion for details)
- Precautions
  - Cutaneous vasculitis
  - Immunogenicity
- Adverse reactions
  - Bone pain

Sargramostim[1,3]

- Warnings
  - Fluid retention: edema, capillary leak syndrome, pleural and/or pericardial effusion
  - Respiratory symptoms: sequestration of granulocytes in pulmonary circulation, dyspnea
  - Cardiovascular symptoms: occasional transient supraventricular arrhythmia; use with caution in patients with preexisting cardiac disease
  - Renal and hepatic dysfunction: elevation of serum creatinine or bilirubin and hepatic enzymes; monitor patients who display renal or hepatic dysfunction prior to initiation of treatment
- Adverse events occurring in >10% of patients receiving sargramostim in controlled clinical trials and reported in a higher frequency than placebo
  - AML: fever, skin reactions, metabolic disturbances, nausea, vomiting, weight loss, edema, anorexia
  - Autologous bone marrow transplant or peripheral blood progenitor cell transplant: asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder
  - Allogeneic bone marrow transplant or peripheral blood progenitor cell transplant: abdominal pain, chills, chest pain, diarrhea, nausea, vomiting, hematemesis, dysphagia, GI hemorrhage, pruritus, bone pain, arthralgia, eye hemorrhage, hypertension, tachycardia, bilirubinemia, hyperglycemia, increased creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high BUN, and high cholesterol

[1] See full prescribing information for specific product information.
[2] Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim and pegfilgrastim.
[3] 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 nonmyeloid 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.
[4] See Discussion for details.

MGF-B

MGF-C

PATIENT RISK FACTORS FOR POOR CLINICAL OUTCOMES OR FOR DEVELOPING INFECTION-ASSOCIATED COMPLICATIONS[1,2]

Patient risk factors include:

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

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MGF-D

Myeloid Growth Factors, Version 2.2013

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

- Filgrastim or tbo-filgrastim[1] (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until postnadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start the next day up to 3-4 days after completion of chemotherapy and treat through postnadir recovery.

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

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

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

- Prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.
- Subcutaneous route is preferred for all 4 agents.
- Prophylactic antibiotics are not routinely recommended for standard-dose chemotherapy. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit NCCN.org).

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Retrospective study supports same-day administration.

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

Belani CP, Ramalingam S, Al-Janadi A, et al. A randomized double-blind phase II study to evaluate same-day vs next-day administration of pegfilgrastim with carboplatin and docetaxel in patients with NSCLC [abstract]. J Clin Oncol 2006;24(Suppl 18S):Abstract 7110.
Prospective randomized trial showing no difference between same-day and next-day administration.

Kaufman PA, Paroly W, Rinaldi D, et al. Randomized double blind phase 2 study evaluating same-day vs next-day administration of pegfilgrastim with docetaxel, doxorubicin and cyclophosphamide (TAC) in women with early stage and advanced breast cancer SABCS [abstract]. Breast Cancer Res Treat 2004;88:Abstract 1054.
Prospective randomized trial favored next-day administration.

Saven A, Schwartzberg L, Kaywin P, et al. Randomized, double-blind, phase 2 study evaluating same day vs next day administration of pegfilgrastim with RCHOP in non-Hodgkins lymphoma [abstract]. J Clin Oncol 2006;24:Abstract 7570.
Prospective randomized trial favored next-day administration.

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

[2] For references for pegfilgrastim, see MGF-E 2 of 2.

[3] There is category 1 evidence to support filgrastim, tbo-filgrastim, or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence for a category 1 recommendation for sargramostim in this setting. Sargramostim is indicated for use after induction chemotherapy in older adult patients with AML. Sargramostim is also indicated for mobilization of hematopoietic progenitor cells and acceleration of myeloid recovery in patients receiving bone marrow transplantation (BMT), and for patients who have undergone BMT in whom engraftment is delayed or has failed. Studies are ongoing in other areas.

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST STEM CELL TRANSPLANT

Mobilization of hematopoietic progenitor cells in autologous setting

- Single-agent growth factor: G-CSF dose range 10-32 mcg/kg/d by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5.[1]
- Combination of similar doses of G-CSF after chemotherapy (eg, cyclophosphamide,[2] ICE,[3] DHAP,[3] VDT-PACE,[4] and others) with the goal of mobilization during count recovery. G-CSF is started approximately 24 hours after completion of chemotherapy.

Combination of G-CSF with plerixafor (for selected patients with non-Hodgkin's lymphoma or multiple myeloma)

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

Mobilization of allogeneic donors

- Allogeneic stem cell donors: G-CSF, 10 mcg/kg/d by subcutaneous injection, start collection on day 4 or 5.[9-11]
- Use of plerixafor in normal donors is under study.
- Allogeneic donors for granulocyte transfusion: one dose of G-CSF, 5 mcg/kg subcutaneously with dexamethasone, 10 mg PO 8-24 hours before collection.[12]

Supportive care

- Post autologous stem cell or cord blood transplant: G-CS, 5 mcg/kg/d. Begin day +5 post transplant until recovery of ANC (eg, >1.5 x 10^9/L times 2 days).[13,†]

Role of pegfilgrastim in mobilization and post transplant

- Limited data suggest that pegfilgrastim may be equivalent to G-CSF in this setting.[14,15]

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

- Mobilization as single agent[16,17,‡]
- Mobilization in combination: G-CSF, 7.5 mcg/kg each morning, GM-CSF, 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.[18]
- Post autologous stem cell transplant or for delayed hematopoietic engraftment after transplant: 250 mcg/m^2/d until ANC >1.5 x 10^9/L times 3 days.[19-21]

†G-CSF accelerates neutrophil recovery but has not impacted survival. See Discussion for details.

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

See References, MGF-F (2 of 2)

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST STEM CELL TRANSPLANT (cont.)

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Text continued from p. 1267

been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.[4]

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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myeloid Growth Factors (MGF) is focused on the use of CSFs in the cancer setting. Specifically, the guidelines address adult patients with solid tumors and nonmyeloid malignancies. Growth factors in the treatment of myeloid malignancies are discussed in the NCCN Guidelines for Myelodysplastic Syndromes (MDS) and the NCCN Guidelines for Acute Myeloid Leukemia (AML). To view the most recent versions of these guidelines, visit NCCN.org.

Benefits and Risks of MGFs

The prophylactic use of G-CSFs has been shown to reduce the incidence, length, and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, and NHL.[5–16] G-CSFs also improved delivery of full chemotherapy dose intensity at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival.[5,7,9,12–15,17,18] However, in node-positive breast cancer[19] and aggressive lymphoma,[20] dose-dense regimens supported by G-CSFs improved disease-free and/or overall survival compared with conventional chemotherapy.

Meta-analyses have confirmed the efficacy of prophylactic CSFs in decreasing rates of infection[21,22] and the risk of neutropenia.[21,22] In a meta-analysis of 17 randomized trials of prophylactic G-CSFs including 3493 adult patients with solid tumor and lymphoma,[23] G-CSF as primary prophylaxis reduces the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; $P<.001$) and improves relative dose intensity of the chemotherapy delivered (average difference between study arms, 8.4%; $P=.001$). For the first time, this analysis also reported a substantial reduction in risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; $P=.018$) and all early deaths during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; $P=.002$). The survival advantage is confirmed in a recent systematic review by Lyman et al[24] of 25 randomized controlled trials involving 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 3.40% and 0.90 reduction in absolute and relative risk for all-cause mortality, respectively, although this comes with an increase in risk for AML and MDS (see later discussion). The degree of benefit correlated with chemotherapy dose intensity.

Over 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 CSFs have yielded mixed results, depending on the context of use.[26–30] However, the policy of this panel is to look primarily at issues of therapeutic efficacy and clinical benefit, rather than cost. The indication for prophylactic CSF use depends on the risk of FN or other neutropenic events that can potentially compromise treatment.

To date, the main consistently observed toxicity associated with G-CSF therapy was mild to moderate bone pain.[31,32] This is usually effectively controlled by nonnarcotic analgesics. The meta-analysis by Kuderer et al[23] confirmed a heightened risk of musculoskeletal pain associated with CSF (RR, 4.03; 95% CI, 2.15–7.52; $P<.001$).

Rare cases of splenic rupture with G-CSF use have also been reported, some of which were fatal.[33] These cases occurred in patients and healthy donors in the stem cell transplantation setting. Some patients develop allergic reactions in the skin, the respiratory system, or the cardiovascular system (filgrastim only). Other warnings from the prescribing information include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.[31,32,34] Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease, but not for patients with sickle cell trait.[35–37] Similar toxicities are expected for filgrastim and pegfilgrastim, although not all toxicities have been reported with each preparation.

Although a potentially increased risk of AML/MDS with G-CSF administration has been suggested by epidemiologic studies, this was not observed in individual randomized trials.[33] The recent analysis by Lyman et al[24] reported an increase in absolute and relative risk of AML/MDS of 0.41% and 1.92, respectively, related to G-CSF. Whether the risk of AML/MDS is secondary to G-CSF or related to the higher total doses of chemotherapy cannot be determined from this meta-analysis. Overall mortality was nevertheless decreased.

Controversy has surrounded 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.[38] In a systematic review of case reports by Azoulay et al,[39] 70 cases of G-CSF-related pulmonary toxicity were identified in patients with cancer with neutropenia; 36 patients had received bleomycin, but most of these had NHL and had also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). This toxicity potential is unclear for BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), although bleomycin is given every 3 weeks in this regimen as opposed to every 2 weeks in ABVD. Clinicians should be alert to signs and symptoms of this complication for both regimens. An increase in bleomycin pulmonary toxicity has not been reported with G-CSF use in bleomycin-containing testicular cancer chemotherapy regimens.[18]

Prophylactic Use of MGFs

Risk Assessment

The guidelines begin with an evaluation of risk for chemotherapy-induced FN before the first cycle. The risk assessment involves varied components, including the disease type, chemotherapeutic regimen (high-dose, dose-dense or standard-dose therapy), patient risk factors, and treatment intent. Three categories based on the intent of chemotherapy have been designated by the NCCN panel, including curative/adjuvant therapy, treatment directed toward prolonging survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to an overall high-risk group (>20% risk of FN), an intermediate-risk group (10%–20% risk), and a low-risk group (<10% risk). Notably, no consensus nomogram for risk assessment currently exists. Although the NCCN panel outlines criteria to aid in assessment, independent clinical judgment should be exercised based on the patient's situation. When determining the appropriate use of CSFs, in addition to assessing patient and treatment-related risk, consideration should be given to the intent of cancer treatment. For example, one criterion that identifies a high-risk patient is a previous neutropenic complication in the immediate previous cycle with no plan to reduce the dose intensity.

Chemotherapy Regimens and Risk of FN

The development of FN is a common dose-limiting toxicity of many single agents and combination chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy regimens that have an incidence of FN greater than 20% in clinical trials in chemotherapy-naïve patients are considered by the panel to be at high risk. It is emphasized that the type of chemotherapy regimen is only one component of the risk assessment, and must be combined with patient risk factors for an estimation of the overall risk of FN.

The algorithm includes lists of common chemotherapy regimens associated with a high risk (>20%) or intermediate risk (10%–20%) of FN development. These lists are not comprehensive but are meant to serve as examples only, because the exact risk will depend on the agent, dose, and the treatment setting. Some regimens, such as the RICE and CHOP-14 regimen for non-Hodgkin's lymphoma, have only been tested with growth factor support.

Evens et al[40] showed that standard chemotherapy for Hodgkin's lymphoma (ABVD) can be safely administered at full dose without G-CSF support. However, this requires treatment with ABVD in some patients at the time of neutropenia. Until further evidence from larger prospective studies becomes available, prophylactic G-CSF use with ABVD can be considered after the risks and benefits are discussed with the patient.

Patient Risk Factors for Developing FN

Patient risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk (reviewed by Lyman et al[41]). Patient factors may elevate the overall risk to a high-risk category, wherein prophylactic CSFs are more routinely recommended. For example, many regimens for breast and lung cancer are associated with an intermediate risk of neutropenic complications, and it is important to identify which of these patients would be considered at high risk. Even a low-risk regimen does not necessarily preclude the use of CSFs in a patient with high-risk factors.

Higher age, notably older than 65 years, is the most important risk factor for developing severe neutropenia (see NCCN Guidelines for Senior Adult Oncology).[42–47] Other risk factors include previous chemotherapy or radiotherapy; preexisting neutropenia or tumor involvement in the bone marrow; poor performance status; comorbidities, including renal or liver dysfunction; 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[48] that was validated in a study population of 3760 patients with cancer beginning chemotherapy.

Patients at High Risk of FN: NCCN panel discussions have focused on defining a risk level of FN that would warrant routine use of prophylactic growth factors. The guidelines recommended prophylactic CSF if the risk of FN was 20% or greater. The most recent update of the ASCO guidelines and the European Organisation for Research and Treatment of Cancer (EORTC) both adopted the 20% threshold for considering routine prophylactic treatment.[49,50]

These consistent recommendations are based on the results of several large randomized trials that have documented that the risk of FN can be significantly reduced by primary prophylaxis when the risk of FN without prophylaxis is 20%. For example, Vogel et al[8] reported on the results of a double-blind, randomized, placebo-controlled multicenter study to show whether first and subsequent cycle prophylactic CSF support with pegfilgrastim would significantly reduce FN in a regimen that had previously been associated with an expected FN incidence of 20%. This is the largest randomized study of prophylactic growth factor support that has been performed. Women with breast cancer received docetaxel at 100 mg/m^2 every 3 weeks. A total of 465 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 end point. The placebo group had an overall incidence of FN of 17%. By contrast, the pegfilgrastim group had a 1% incidence. The incidence of hospitalization was reduced from 14% to 1%, and the use of intravenous anti-infectives was reduced from 10% to 2%, with all of these differences statistically significant (P<.001). In cycle 1, there was an 11% rate of FN in the first cycle for the placebo group versus less than 1% in the pegfilgrastim group. For cycles 2 through 4, the rate of FN was 6% in the placebo group compared with 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.[6] In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN, compared with 9 patients (10%) in the antibiotics plus FN group (P=.01). In cycles 2 to 5, the incidences of FN were similar in both groups (17% vs 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis is effective in reducing FN and infections in patients with small cell lung cancer with the first cycle of chemotherapy. Furthermore, this strategy could be considered for other patients with cancer with a similar risk of FN.

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

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

Patients at Intermediate Risk of FN: The NCCN panel defines intermediate risk as a 10% to 20% probability of developing FN or a neutropenic event that would compromise treatment. In all 3 categories of treatment intent, the panel recommends individualized consideration of CSF use based on physician-patient discussion of the risk/benefit ratio of the likelihood of developing FN, the potential consequences of a neutropenic event, and the implications of reduced chemotherapy dose delivery. When the intent of chemotherapy is designed to prolong survival or for symp-

tom management, the use of CSF is a difficult decision and requires careful discussion between the physician and patient. If patient risk factors determine the risk, CSF is reasonable. If the risk is from the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

Patients at Low Risk of FN: For low-risk patients, as defined by risk less than 10%, routine use of CSFs is not considered cost-effective, and alternative treatment options are appropriate.[25,49,51,52] However, CSFs may be considered if the patient is receiving curative or adjuvant treatment and is at significant risk for serious medical consequences of FN, including death.

Evaluation of Subsequent Chemotherapy Cycles

After the first cycle, patient evaluation should be performed 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 cycle of treatment with the same dose and schedule planned for the current cycle, this patient is now in the high-risk group.

If the patient experiences such an episode despite receiving CSF, the panel recommends a chemotherapy dose reduction or change in treatment regimen, unless it will affect 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

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

Filgrastim

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

Tbo-filgrastim

As patents for oncology biologics begin to expire, the United States is developing an abbreviated regulatory pathway for the approval of similar follow-on formulations, termed *biosimilars*.[53] The NCCN Biosimilars Work Group published a white paper identifying the challenges in the incorporation of these agents in health care practice.[54]

In August of 2012, the FDA announced the approval of tbo-filgrastim, described as "a leukocyte growth factor indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia." Approval was based on 3 randomized clinical trials involving 680 cancer patients. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.[55] 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 non-Hodgkin's lymphoma receiving chemotherapy also reported similar efficacy of tbo-filgrastim and filgrastim.[56,57] 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 incidence of FN, irrespective of the myelotoxicity of the chemotherapy regimen.[58] Studies in healthy subjects showed similar pharmacokinetic and pharmacodynamic profiles.[59,60]

Although tbo-filgrastim is available in the European Union as a biosimilar to filgrastim,[50] it was approved by the FDA in an original biologic license application because the biosimilar approval process has not yet been finalized in the United States.

Pegfilgrastim

Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient per chemotherapy cycle.

The NCCN panel discussed 2 issues that have emerged regarding the use of pegfilgrastim. The first is the timing of administration after chemotherapy. Because most clinical studies administer the agent the day after chemotherapy completion, this is a category 1 recommendation.[32] Based on trials of filgrastim, panelists agreed that giving pegfilgrastim up to 3 to 4 days after chemotherapy is also reasonable. In addition, panelists pointed out that some institutions practise "same-day" pegfilgrastim, or administration of pegfilgrastim on a day in which patients receive chemotherapy, for logistical reasons and to minimize burdens on long-distance patients.[61] The NCCN panel agreed that this strategy may be considered under certain circumstances. Retrospective studies in patients with gynecologic malignancies demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours after chemotherapy.[62,63] Burris et al[64] reviewed data available in abstract form from 3 randomized phase II studies comparing same-day and next-day pegfilgrastim. Two of the studies, conducted in patients with breast cancer and lymphoma, showed a statistically insignificant trend toward longer duration of severe neutropenia for the same-day group.[65,66] The third study, in patients with lung cancer, had an unexpected low rate of severe neutropenia (only 2 patients per group).[67]

The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle lengths. Use of pegfilgrastim after chemotherapy given every 3 weeks is a category 1 recommendation based on phase III clinical trials.[8,68] Phase II studies demonstrated the efficacy of pegfilgrastim for chemotherapy regimens administered every 14 days.[69–74] Insufficient data support dose and schedule of weekly regimens, and therefore these cannot be recommended.

Sargramostim

Insufficient evidence from randomized trials supports a category 1 recommendation for sargramostim in nonmyeloid malignancies. Sargramostim is indicated for use after induction chemotherapy in older adult patients with AML.[75–77] Administration should start the next day or up to 3 to 4 days after completion of chemotherapy, and treatment should continue through postnadir recovery.

Therapeutic Use of MGFs

Compared with their prophylactic use, the therapeutic use of MGFs for FN as an adjunctive to antibiotics has less supporting evidence. In a Cochrane meta-analysis including 1518 patients from 13 trials, Clark et al[78] reported a shorter length of hospitalization (hazard ratio [HR], 0.63; 95% CI, 0.49–0.82; P=.0006) and shorter time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; P<.00001), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al[79] again found no difference in mortality, but they were unable to assess other clinical benefits. Notably, Berghmans' analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF or placebo.[80] The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median, 2 vs 3 days; P=.0004), antibiotic therapy (median, 5 vs 6 days; P=.013), and hospital stay (median, 5 vs 7 days; P=.015).

Patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, because pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional CSF.[81] Also, because a lack of evidence currently exists supporting the therapeutic use of pegfilgrastim, only filgrastim or sargramostim should be administered in the therapeutic setting. For patients who have not received prophylactic CSFs, the NCCN panel recommends an evaluation for risk factors for infection-related complications or poor clinical outcome, including old age (>65 years); sepsis syndrome; severe (ANC<100/l) or anticipated prolonged (>10 days) neutropenia; pneumonia; invasive fungal infection or other clinically documented infections; hospitalization; and prior episode of FN. If risk factors are present, CSFs should be considered.

MGFs in the Hematopoietic Cell Transplant Setting

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

Mobilization of peripheral blood stem cells (PBSCs) by G-CSF has largely replaced bone marrow collection for autologous transplantation because of ease of collection, avoidance of general anesthesia, and more rapid recovery of blood counts.[82] Most data are focused on filgrastim, although studies suggest that single-dose pegfilgrastim has similar efficacy.[83] G-CSF can be administered as a single agent[84] or as part of a chemomobilization regimen,[85–87] starting on the day after completion of chemotherapy. Apheresis usually commences on the fourth or fifth day of G-CSF initiation when it is used as a single agent. After mobilization with chemotherapy plus growth factor, leukapheresis commences after a rise of the white blood count when the CD34+ cells are circulating. More recently, addition of the CXCR4 inhibitor plerixafor to chemomobilization has been shown to accelerate an increase in PBSC count.[88–91] This may be used as a rescue strategy when PBSC yield is poor, or when the CD34+ cell count does not reach the target level. One retrospective analysis showed that pegfilgrastim resulted in a better PBSC yield than filgrastim, requiring less use of rescue plerixafor,[92] but no randomized trials have been conducted.

G-CSF is also used to mobilize PBSCs in the allogeneic setting. Initially, there were concerns about normal donor toxicity and risk of graft-versus-host disease in the recipient, but studies have shown G-CSF to be well tolerated by donors, without an effect on long-term survival.[93–95] The use of plerixafor in normal donors is currently being studied.

Studies using GM-CSF as a single mobilization agent or in sequential combination with G-CSF reported good yields of PBSC in normal donors.[96–98]

Growth Factors as part of Supportive Care After Transplant

Consensus is lacking on the use of growth factors in the posttransplant setting. G-CSF administration after high-dose chemotherapy and autologous PBSC transplantation has been shown to expedite neutrophil recovery in prospective randomized trials.[99–103] 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,[104] concluded that the 2 are at least equally effective.[105]

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.[106] However, it has been used routinely after cord blood transplant, which has been associated with delayed recovery of blood counts.

GM-CSF has been shown to promote hematopoietic recovery after autologous bone marrow transplantation or delayed autologous engraftment.[107,108] It has also been used for mobilization, but G-CSF use has been favored for this purpose.

Severe Chronic Neutropenia

These NCCN Guidelines are focused on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia that requires G-CSF therapy is briefly discussed in this section. G-CSF is established as an effective treatment for cyclic, congenital, and idiopathic neutropenia (types of severe chronic neutropenia) based on a randomized controlled trial involving 123 patients.[109] In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers, and infections. Subsequent observation studies show that patients with idiopathic and cyclic neutropenia generally respond to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF (1–3 mcg/kg/d). Patients with congenital neutropenia generally require somewhat higher doses (3–10 mcg/kg/d). All patients should have doses adjusted to maintain a blood neutrophil level in the normal or low normal range. Acute adverse effects include bone pain, arthralgias, and myalgias, which usually diminish in the first few weeks of treatment. The greatest concern is that patients diagnosed with severe congenital neutropenia, but not all patients with chronic neutropenia, are at risk of developing myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, as reflected by the requirement of higher doses of G-CSF, seem to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following these patients carefully. Currently, the only alternative therapy is hematopoietic stem cell transplantation. For further reading on chronic neutropenia, refer to the Web site developed by The Severe Chronic Neutropenia International Registry: http://depts.washington.edu/registry/index.html.

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