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Myeloid Growth Factors

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See NCCN Categories of Evidence and Consensus

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Summary of the Guidelines updates

Summary of the changes in the 1.2010 version of the Myeloid Growth Factors Guidelines from the 1.2009 version include:

MGF-2

- Footnote l, "Dose-limiting neutropenic event could be a nadir count or day of treatment count that may otherwise impact planned dose of chemotherapy."

MGF-3

- Footnote 'p' was modified as, "There are no studies which have addressed therapeutic use of *filgrastim* for febrile neutropenia *in patients who have already received prophylactic pegfilgrastim*."

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- Regimens at high risk of febrile neutropenia, the following were added:
  - "HyperCVAD" for treatment of multiple myeloma.
  - "Antithymocyte globulin, rabbit/cyclosporine" for treatment of myelodysplastic syndrome.
  - "Doxorubicin/gemcitabine" for treatment of kidney cancer.

MGF-B

- First bullet, "Older patient, notably patients age 65 and older" was modified by adding a link, "See NCCN Senior Adult Oncology Guidelines".

MGF-C

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

MGF-D

- Footnote 4, "Toxicity data are based primarily on studies from leukemia and transplant patients" is new to the page.

MGF-E

- "Prior episode of febrile neutropenia" was added as a patient risk factor for poor clinical outcome or for developing infection-associated complications.

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Myeloid Growth Factors

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EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE[a]

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

RISK ASSESSMENT FOR FEBRILE NEUTROPENIA[c]

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

PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,f,g]

	CHEMOTHERAPY TREATMENT INTENT		
	CURATIVE/ ADJUVANT[h]	PROLONG SURVIVAL/ QUALITY OF LIFE	SYMPTOM MANAGEMENT/ QUALITY OF LIFE
High[e] (> 20%)	CSF (category 1 for G-CSF)[i]	CSF (category 1 for G-CSF)[i]	CSF[k]
Intermediate (10 - 20%)	Consider CSF	Consider CSF[k]	Consider CSF[k]
Low (< 10%)	No CSF[j]	No CSF	No CSF

CSF= Colony stimulating factors

See Evaluation Prior to Second or Subsequent Chemotherapy Cycles (MGF-2)

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

[b] For use of growth factors in Myelodysplastic Syndromes, see the NCCN Myelodysplastic Guidelines. For use of growth factors in Acute Myeloid Leukemia, see the NCCN Acute Myeloid Leukemia Guidelines.

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

[d] There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (See Disease Settings and Examples of Chemotherapy Regimens and Risk of Febrile Neutropenia MGF-A) and patient risk factors (See Patient Risk Factors for Developing Febrile Neutropenia MGF-B).

[e] One criterion that places a patient at high risk is a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity.

[f] This table applies to prophylaxis for the first cycle of chemotherapy for solid tumors and non-myeloid malignancies. See Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-C).

[g] See Toxicity Risks With Growth Factors (MGF-D).

[h] The confounding effects of anthracycline and alkylating agent dose, radiation dose and field size, and colony stimulating factors use on the slight excess risk of leukemia and MDS in patients treated with these agents and modalities are currently unquantified. The associated risk of leukemia and MDS has been suggested by epidemiologic studies, but has not been observed in the available prospective randomized studies.

[i] There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, 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 further detail.)

[j] Only consider CSF if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

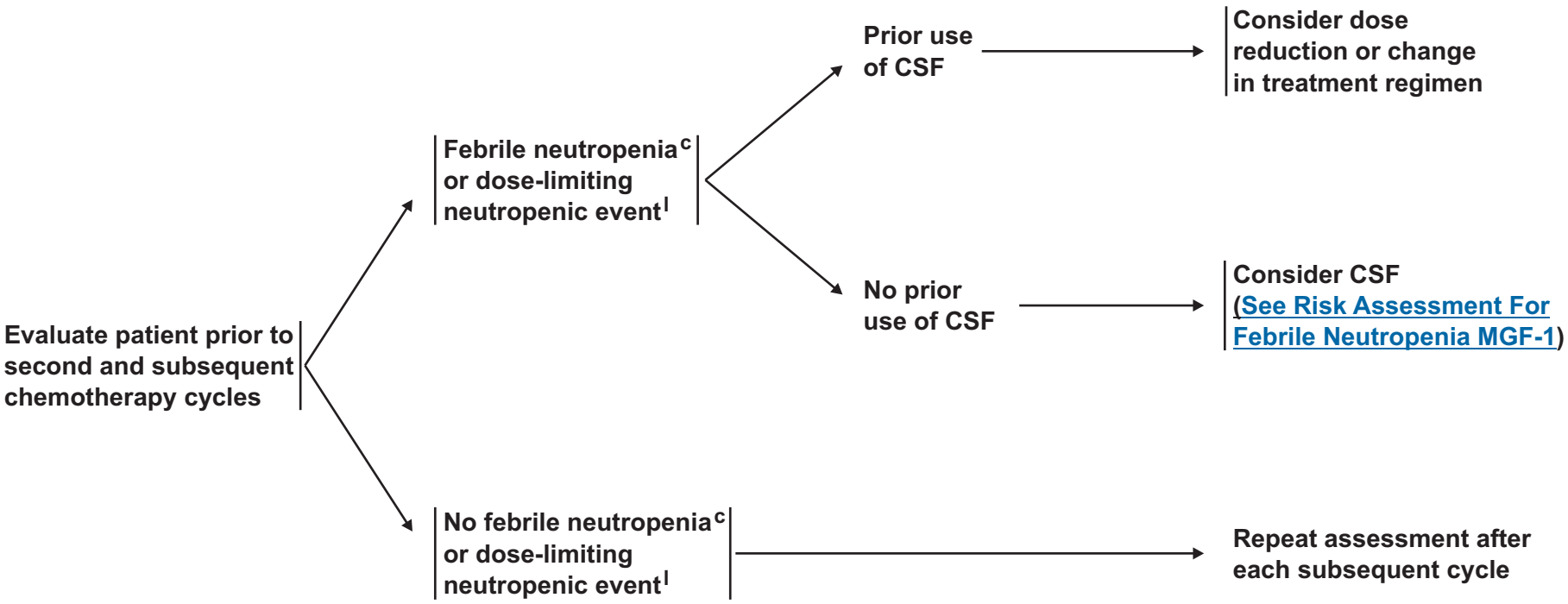
[k] The use of CSF in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is10 -20%, CSF is reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

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EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES



SECONDARY PROPHYLAXIS

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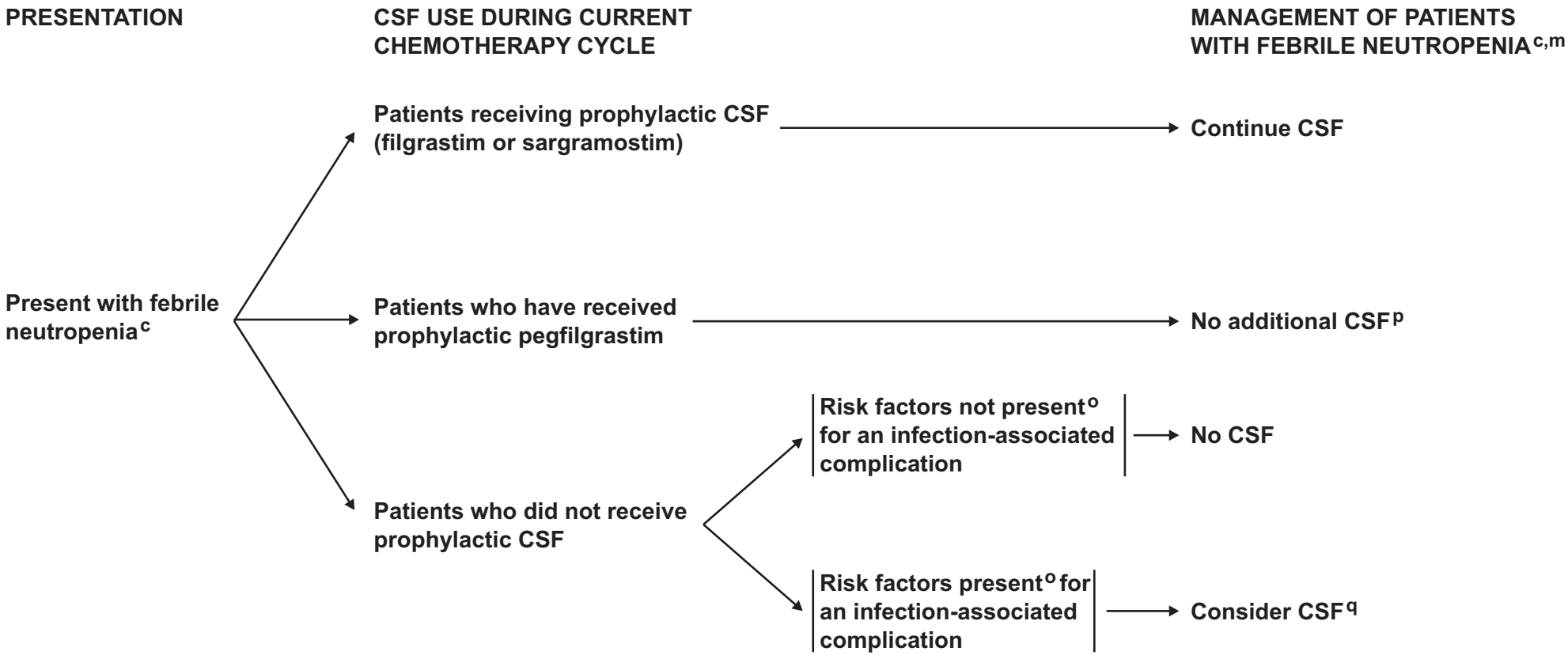
[l]Dose-limiting neutropenic event could be a nadir count or day of treatment count that may otherwise impact planned dose of chemotherapy.

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THERAPEUTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,m,n]



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

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

[n] The decision to use CSF in the therapeutic setting is controversial. See discussion for further detail.

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

[p] There are no studies which 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 CSF will not be beneficial.

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

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Myeloid Growth Factors

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

- *This list is not comprehensive*, there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia MGF-B)
- Pegfilgrastim has not been documented to have benefit in regimens given under a 2 week duration.
- 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.

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)[1]

Breast Cancer
- Docetaxel + trastuzumab (metastatic or relapsed)[2]
- Dose dense AC → T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)[3]
- AT (doxorubicin, paclitaxel) (metastatic or relapsed)[4]
- AT (doxorubicin, docetaxel) (metastatic or relapsed)[5]
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)[6]

Esophageal and Gastric Cancer
- Docetaxel/cisplatin/fluorouracil[7]

Kidney Cancer
- Doxorubicin/gemcitabine[8]

Non-Hodgkin's Lymphoma
- ICE (ifosfamide, carboplatin, etoposide) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphomas, 2nd line, salvage)[9]
- RICE * (rituximab, ifosfamide, carboplatin, etoposide)[10]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone)[11]
- MINE (mesna, ifosfamide, novantrone and etoposide) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphomas, 2nd line, refractory)[12]
- DHAP (dexamethasone, cisplatin, cytarabine) (Peripheral T-cell Lymphomas, Diffuse Large B-Cell Lymphoma, 2nd line)[13]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphoma, 2nd line, recurrent)[14]
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[15]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[16,17]

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)[18]
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)[18]

Multiple Myeloma
- Modified HyperCVAD[19]

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

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

Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[25]
- Doxorubicin[26]

Small Cell Lung Cancer
- Topotecan[27]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[28]
- VIP (etoposide,ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[29]

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

See Chemotherapy Regimen References MGF-A (3 of 5)

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

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

- ***This list is not comprehensive***, there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia MGF-B)
- Pegfilgrastim has not been documented to have benefit in regimens given under a 2 week duration.
- Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

Occult Primary-Adenocarcinoma
- Gemcitabine, docetaxel[30]

Breast Cancer
- Docetaxel every 21 days [31]
- Epirubicin (adjuvant)[32]
- Epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil (adjuvant)[32]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[32]
- AC (doxorubicin, cyclophosphamide)+ sequential docetaxel (adjuvant) (taxane portion only)[33]
- AC + sequential docetaxel + trastuzumab (adjuvant)[34]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel [35]
- Paclitaxel every 21 days (metastatic or relapsed)[36]
- Vinblastine (metastatic or relapsed)[37]

Cervical Cancer
- Cisplatin + topotecan (recurrent or metastatic)[38]
- Topotecan (recurrent or metastatic)[39]
- Irinotecan (recurrent or metastatic)[40]

Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[41]

Esophageal and Gastric Cancer
- Irinotecan/cisplatin[42]
- Epirubicin/cisplatin/5-fluorouracil[43]
- Epirubicin/cisplatin/capecitabine[43]

Hodgkin Lymphoma
- ABVD† (doxorubicin, bleomycin, vinblastine, dacarbazine)[44]
- Stanford V† (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)[45]

Non-Hodgkin's Lymphoma
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt's lymphoma, recurrent)[46]
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, Diffuse Large B-Cell Lymphoma, recurrent)[46]
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)[47]
- GDP (gemcitabine, dexamethasone, cisplatin) (Peripheral T-cell Lymphomas, Diffuse Large B-Cell Lymphoma, 2nd line)[48]
- GDP (gemcitabine, dexamethasone, cisplatin) + Rituximab (Diffuse Large B-Cell Lymphoma, 2nd line)[48]
- FM (fludarabine, mitoxantrone)[49]
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[50,51]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel (adjuvant, advanced/metastatic)[52]
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)[53]
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)[52,54]
- Cisplatin/irinotecan (advanced/metastatic)[55]
- Cisplatin/etoposide (adjuvant, advanced/metastatic)[56]
- Carboplatin/paclitaxel (adjuvant, advanced/metastatic)[55]
- Docetaxel (advanced/metastatic)[54]

Ovarian Cancer
- Carboplatin/docetaxel[57]

Small Cell Lung Cancer
- Etoposide/carboplatin[58]

Testicular Cancer
- Etoposide/cisplatin[59]

Uterine Cancer
- Docetaxel (uterine sarcoma, advanced or metastatic)[60]

† There is one retrospective review that suggests pulmonary toxicity maybe increased using G-CSF in bleomycin containing regimens. (See discussion for further detail.)

See Chemotherapy Regimen References MGF-A (4 of 5)

See Disease Settings and Chemotherapy Regimens with a High Risk of Febrile Neutropenia MGF-A (1 of 5)

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PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

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

- **Older patient, notably patients age 65 and older (See NCCN Senior Adult Oncology Guidelines)**
- **Previous chemotherapy or radiation therapy**
- **Pre-existing 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**

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

- **Filgrastim (category 1)**
  - **Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.**
  - **Start 24-72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.**
- **Pegfilgrastim (category 1) (For prophylactic use only)**
  - **One dose of 6 mg per cycle of treatment.**
  - **Start 24-72 h after completion of chemotherapy. Administration of growth factor on same day as chemotherapy is not recommended.[1]**
  - **There is evidence to support use for chemotherapy regimens given every 3 wks (category 1).**
  - **Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 wks.**
  - **There are insufficient data to support dose and schedule of weekly regimens or chemotherapy schedules less than 2 weeks and these cannot be recommended.**
- **Sargramostim[2] (category 2B)**
  - **Used in clinical trials at a dose of 250 mcg/m^2/day (rounding to the nearest vial size by institution-defined weight limits).**
  - **Start 24-72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.**

- **Prophylactic use of CSF in patients given concurrent chemotherapy and radiation is not recommended.**
- **Subcutaneous route is preferred for all 3 agents.**
- **There are no data to support alternative dosing schedules in intermediate and high risk patients.**
- **The safety data appears to be similar between filgrastim and pegfilgrastim.**
- **Prophylactic antibiotics are not routinely recommended for standard dose chemotherapy, see NCCN Prevention and Treatment of Cancer-Related Infections Guidelines.**

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

[2] There is category 1 evidence to support filgrastim or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence for a category 1 recommendation for sargramostim in this setting. Sargramostim is indicated for use following induction chemotherapy in older adult patients with AML. Studies are ongoing in other areas.

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TOXICITY RISKS WITH GROWTH FACTORS

Filgrastim[1]

- Warnings
  - Allergic reactions
    - Skin: rash, urticaria, facial edema
    - Respiratory: wheezing, dyspnea
    - Cardiovascular: hypotension, tachycardia
  - Splenic rupture
  - Adult respiratory distress syndrome
  - Precipitate sickle cell disease crisis
- Adverse reactions
  - Medullary bone pain (>10%)
- Precautions
  - Cutaneous vasculitis

Pegfilgrastim[2]

- Warnings
  - Splenic rupture
  - Adult respiratory distress syndrome
  - Allergic reactions
    - Skin: rash, urticaria
    - Respiratory: anaphylaxis
  - Precipitate sickle cell disease crisis
- Adverse reactions
  - Bone pain

Sargramostim[3,4]

- 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 reactions with autologous bone marrow transplant or peripheral blood progenitor cell transplant
  - Asthenia, diarrhea, rash
- Adverse reactions with allogeneic bone marrow transplant or peripheral blood progenitor cell transplant
  - Abdominal pain, chest pain, diarrhea, nausea, vomiting, GI hemorrhage, pruritus, bone pain, eye hemorrhage, hyperglycemia, hypomagnesemia, pharyngitis, insomnia, anxiety, high BUN, high cholesterol

[1] View filgrastim prescribing information.
[2] View pegfilgrastim prescribing information.
[3] View sargramostim prescribing information.
[4] Toxicity data are based primarily on studies from leukemia and transplant patients.

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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**

[1]The decision to use or not use CSF in the treatment of febrile neutropenia is controversial. See discussion for further detail.

[2]Smith TJ, Khatcheressian J, Lyman G, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006; 24:1-11.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

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

The risk of FN is usually based on the treatment regimen and delivered dose intensity. A survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin's lymphoma (NHL) has shown, however, that the rates of myelosuppression and delivered dose intensity are underreported.[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 as well as the delivered dose intensity. Treatment dose intensity was reported with even less consistency, making it very difficult to interpret differences in reported rates of toxicity or treatment efficacy.

A review by Dale et al showed that about 25-40% of treatment-naive patients develop FN with common chemotherapy regimens.[3] Occurrence of FN may delay subsequent chemotherapy courses or result in dose reduction that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. In addition, correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.[4]

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

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Myeloid Growth Factors

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

Benefits and Risks of CSFs

The prophylactic use of G-CSFs has been shown to reduce the incidence, length and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, and non-Hodgkin's lymphoma.[5-16] G-CSFs also improved delivery of full dose intensity of chemotherapy at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival.[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 to conventional chemotherapy.

Meta-analyses have confirmed the efficacy of prophylactic CSFs in decreasing rates of infection,[21,22] and risk of neutropenia.[21,22] In a recent meta-analysis of seventeen randomized trials of prophylactic G-CSFs including 3493 adult patients with solid tumor and lymphoma,[23] G-CSF as primary prophylaxis reduces risk of FN (RR = 0.54; 95% CI, 0.43 to 0.67; P < 0.001) and improves relative dose-intensity of the chemotherapy delivered (average difference between study arms 8.4%; P = 0.001). For the first time, this analysis also reports a substantial reduction in risk of infection-related mortality (RR = 0.55; 95% CI, 0.33 to 0.90; P = 0.018) and all early deaths during chemotherapy (RR = 0.60; 95% CI, 0.43 to 0.83; P = 0.002).

Over the last decade, the costs of inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.[24] Economic analyses of CSFs have yielded mixed results, depending on the context of usage. [25-29] However, the policy of the NCCN Myeloid Growth Factors guidelines panel is to look primarily at issues of therapeutic efficacy and clinical benefit, rather than cost. The indication for prophylactic CSF use depends on the risk of FN or other neutropenic events that can potentially compromise treatment.

Toxicity risks associated with G-CSFs and GM-CSF, as outlined in the prescribing information, are listed on MGF-D. To date, the main consistently observed toxicity associated with G-CSF therapy was mild to moderate bone pain.[30] This is usually effectively controlled by non-narcotic analgesics. The meta-analysis by Kuderer et al confirmed a heightened risk of musculoskeletal pain associated with CSF (RR = 4.03; 95% CI, 2.15 to 7.52; P < 0.001).[23] In a retrospective review, a heightened rate of bleomycin pulmonary toxicity has been linked to G-CSF use in Hodgkin's lymphoma patients receiving bleomycin-containing therapy.[31] This has not been seen with G-CSF use in bleomycin-containing testicular cancer chemotherapy regimens.[18]

There have also been reports of rare cases of splenic rupture with G-CSF usage, some of which were fatal.[30] These cases occurred in patients and healthy donors in the stem cell transplantation setting. Some patients develop allergic reactions in the skin, the respiratory system, or the cardiovascular system (filgrastim only). Although there have been suggestions of potentially increased risk of acute leukemia with G-CSF administration from epidemiological studies, they are confounded by differences in the chemotherapy dose delivered. The Research on Adverse Drug Events and Reports (RADAR) group concluded that long-term safety data is still lacking to confirm such a relationship. [32]

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Prophylactic Use of CSFs

Risk Assessment

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

Patients at High Risk of FN

NCCN panel discussions have focused on defining a risk level of FN that would warrant routine use of prophylactic growth factors. The guidelines recommended prophylactic CSF if the risk of FN was 20% or greater. The most recent update of the ASCO guidelines and the European Organisation for Research and Treatment of Cancer (EORTC) both adopted the 20% threshold for considering routine prophylactic treatment.[33,34]

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

A second trial reported the results of 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF.[6] In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with nine patients (10%) in the antibiotics plus FN group ($P = 0.01$). In cycles 2 to 5, the incidences of FN were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis is effective in reducing FN and infections in patients with small cell lung cancer with the first cycle of chemotherapy.

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Furthermore, this strategy could be considered for other cancer patients with a similar risk of FN.

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

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

Patients at Intermediate Risk of FN

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

Patients at Low Risk of FN

For low-risk patients, as defined by a <10% risk, routine use of CSFs is not considered cost-effective and alternative treatment options are appropriate.[24,34-36] 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 (MGF-2)

After the first cycle, patient evaluation should be performed prior to each subsequent cycle to determine the risk categorization and treatment intent. If the patient experienced a previous episode of FN or a dose-limiting neutropenic event (a nadir or a day-of-treatment count impacting the planned dose of chemotherapy) during the previous cycle of treatment with the same dose and schedule planned for the current cycle, this patient is now in the high risk group.

If the patient experiences such an episode despite receiving CSF, the panel recommends a chemotherapy dose reduction or change in treatment regimen unless there is an impact on patient survival. If the patient does not develop FN or a dose-limiting neutropenic event and is thought to be benefiting from chemotherapy, the previous assessment should be repeated after each subsequent cycle.

Chemotherapy Regimens and Risk of FN (MGF-A)

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

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There has been controversy surrounding the use of G-CSFs for patients with Hodgkin's lymphoma undergoing bleomycin-containing chemotherapy. An increased risk of bleomycin pulmonary toxicity has been reported with G-CSF use for this disease in a retrospective study on 141 patients.[31] In a systematic review of case reports by Azoulay and colleagues,[37] 70 cases of G-CSF-related pulmonary toxicity was identified in cancer patients with neutropenia. 36 patients had received bleomycin, but the majority of these were non-Hodgkin's lymphoma patients who have also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). Of note, this possible risk of increased pulmonary toxicity was not seen with bleomycin-containing testicular cancer chemotherapy.[18]

Evens et al[38] showed that standard chemotherapy for Hodgkin's lymphoma (ABVD) can be safely administered at full dose without G-CSF support. However, this requires treatment with ABVD in some patients at the time of neutropenia. Until further evidence from larger prospective studies becomes available, prophylactic G-CSF use with ABVD can be considered after discussion of risks and benefits with the patient.

Patient Risk Factors for Developing FN (MGF-B)

As previously mentioned, patient risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk (reviewed by Lyman et al [39]). Patient factors may elevate the overall risk to a high risk category, where prophylactic CSFs are more routinely recommended. For example, many regimens for breast and lung cancer are associated with an intermediate risk of neutropenic complications, and it is important to identify which of these patients would be considered at high risk. Higher age, notably over 65 years, is the most important risk factor for developing severe neutropenia (see NCCN Senior Adult Oncology Guidelines).[40-45] Other risk factors include previous chemotherapy or radiotherapy, pre-existing neutropenia or tumor involvement in the bone marrow, poor performance status, comorbidities including renal or liver dysfunction, and pre-existing conditions such as neutropenia and infection.

Therapeutic Use of CSFs (MGF-3)

Compared to prophylactic use, there is less evidence supporting therapeutic use of CSFs for FN as an adjunctive to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials [46], Clark and colleagues reported a shorter length of hospitalization (HR = 0.63; 95% CI, 0.49 to 0.82; P = 0.0006), shorter time to neutrophil recovery (HR = 0.32; 95% CI, 0.23 to 0.46; P < 0.00001), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al [47] again found no difference in mortality, but they were unable to assess other clinical benefits. Of note, Berghmans' analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF or placebo.[48] The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days, P = 0.0004), antibiotic therapy (median 5 vs. 6 days, P = 0.013) and hospital stay (median 5 vs. 7 days, P = 0.015).

Patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, since pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional CSF.[49] Also, as there is currently a lack of evidence for 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. These include: old age (> 65 years), sepsis syndrome, severe (ANC < 100/mcl) or anticipated

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prolonged (> 10 days) neutropenia, pneumonia, invasive fungal infection or other clinically-documented infections, hospitalization, and prior episode of FN. If risk factors are present, CSFs should be considered.

Dosing and Administration

Currently used myeloid growth factors for the prophylaxis of FN and maintenance of scheduled dose delivery include filgrastim, pegfilgrastim and sargramostim. While data from randomized studies support the use of filgrastim and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on its use following induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. Therefore, when choosing among myeloid growth factors, filgrastim and pegfilgrastim are considered category 1 recommendations, while sargramostin is considered a category 2B recommendation.

Initial doses of filgrastim are initiated beginning within 1-3 days after completion of chemotherapy in a daily dose of 5 mcg/kg until post-nadir ANC recovery is to normal or near-normal ANC levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. There is also evidence to support use of pegfilgrastim 24 hours after completion of chemotherapy given every 3 weeks in one dose of 6 mg per cycle of treatment.[8,50] There are insufficient data to support dose and schedule of weekly regimens or schedules less than 2 weeks and these cannot be recommended. Same day administration of filgrastim or pegfilgrastim (within 24 hours of chemotherapy) is not recommended. Phase II studies of pegfilgrastim administration the same day as chemotherapy versus administration the day after chemotherapy have demonstrated increased incidence of FN and/or adverse events in breast cancer and lymphoma.[51-53] Same day pegfilgrastim showed comparable benefit in one study of a regimen with low risk neutropenia, but in this setting pegfilgrastim would not be routinely indicated.[54] There is insufficient evidence from randomized trials to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. Sargramostim is indicated for use following induction chemotherapy in older adult patients with AML.[55] Again, administration of sargramostim on the same day as chemotherapy is not recommended. The subcutaneous route is preferred for all three agents. There are no data to support alternative dosing schedules in intermediate and high risk patients. The NCCN Myeloid Growth Factors panel members do not routinely recommend use of prophylactic antibiotics in these settings. In addition, prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.

Severe Chronic Neutropenia

The NCCN Myeloid Growth Factors Guidelines is focused on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia that requires G-CSF therapy is briefly discussed below. G-CSF is established as an effective treatment for cyclic, congenital and idiopathic neutropenia (types of severe chronic neutropenia), based a randomized control trial involving 123 patients.[56] In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers and infections. Subsequent observation studies show that patients with idiopathic and cyclic neutropenia generally respond to low-dose daily, alternate-day or thrice-per-week subcutaneous G-CSF (1-3 mcg/kg/day). Congenital neutropenia patients generally require somewhat higher doses (3-10 mcg/kg./day). All patients should have doses adjusted to maintain a blood neutrophil level in the normal or low normal range. Acute adverse effects include bone pain, arthralgias and myalgias which usually diminish in the first few weeks of treatment. The greatest concern is that patients with the diagnosis of severe congenital neutropenia, but not all patients with chronic neutropenia, are at risk of evolving to myelodysplasia and leukemia, with or without

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G-CSF treatment. More severely affected patients, as reflected by the requirement of higher doses of G-CSF, appear to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following these patients carefully. Currently the only alternative therapy is hematopoietic stem cell transplantation. For further reading on chronic neutropenia, refer to the web site developed by The Severe Chronic Neutropenia International Registry. http://depts.washington.edu/registry/index.html

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