National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myeloid Growth Factors

Version 2.2013

NCCN.org

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2013 of the NCCN Guidelines for Myeloid Growth Factors from Version 1.2013 include:

MGF-E 1 of 2

- **Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery**
  - **1st bullet: "tbo-filgrastim" was added as a category 1 recommendation. A corresponding footnote was added: "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."**
  - **5th bullet was revised: "Subcutaneous route is preferred for all ~~3~~ *4* agents."**
- **Footnote "3" was modified by adding: "There is category 1 evidence to support filgrastim, *tbo-filgrastim*, or pegfilgrastim for the prevention of febrile neutropenia."**

MGF-F

- **A new page regarding myeloid growth factors in mobilization and post stem cell transplant was added to the guidelines.**

MS-1

- **The discussion section was updated to reflect the changes in the algorithm.**

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Myeloid Growth Factors

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Discussion

Updates in Version 1.2013 of the NCCN Guidelines for Myeloid Growth Factors from Version 1.2012 include:

MGF-1

- Footnote "f" was modified: "The confounding effects of chemotherapy dose and schedule, ~~additional~~ radiation, and CSFs use on the excess risk of leukemia..."

MGF-2

- Febrile neutropenia, prior use of CSFs
  - Secondary prophylaxis was modified: "Consider *chemotherapy* dose reduction or change in treatment regimen."

MGF-A 1 of 4

- Regimens with a High Risk for Febrile Neutropenia
  - Acute Lymphoblastic Leukemia (ALL), "ALL induction regimens (See NCCN Guidelines for ALL)" was added.
  - Soft Tissue Sarcoma, "ifosfamide/doxorubicin" was added with a corresponding reference.
  - Breast Cancer, "AT (doxorubicin, paclitaxel); AT (doxorubicin, docetaxel)" was removed as it is no longer recommended in the Guidelines for Breast Cancer.
  - Multiple Myeloma, "modified HyperCVAD" was removed since it is no longer recommended in the Guidelines for Multiple Myeloma.
- The following bullet was removed: "Pegfilgrastim has not been documented to have benefit in regimens given under a 2-week duration." (Also for MGF-A 2 of 4.)
- The following note was removed and added to each reference page: "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." (Also for MGF-A 2 of 4.)
- Footnote was removed: "When using G-CSFs with bleomycin-containing regimens, there may be an increased risk for pulmonary toxicity. (See Discussion for further details.)" This information is on MGF-C. (Also for MGF-A 2 of 4.)

MGF-A 2 of 4

- Regimens with an Intermediate Risk for Febrile Neutropenia
  - Cervical Cancer, "paclitaxel/cisplatin" was added with a corresponding reference.
  - Multiple Myeloma, "DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide and "DT-PACE + bortezomib (VTD-PACE)" were added with corresponding references.
  - Pancreatic Cancer, "FOLFIRINOX" was added with a corresponding footnote and references, "A small retrospective trial had a 17% risk of FN in neoadjuvant setting and a randomized trial had a 5.4% in metastatic setting. While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features."
  - Breast Cancer, "epirubicin; epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil; vinblastine" was removed as it is no longer recommended in the Guidelines for Breast Cancer.

MGF-C

- The toxicity risks for pegfilgrastim were removed and combined with filgrastim as "Filgrastim and derivative products including pegfilgrastim."
  - Warnings,
    - Allergic reactions, 3rd bullet was modified as "Cardiovascular: hypotension, tachycardia, *anaphylaxis*."
    - "Bleomycin-containing regimens: pulmonary toxicity" was added and a footnote regarding bleomycin-containing regimens was removed.
    - Sickle cell crises was modified by adding: "(only in patients with sickle cell disease)."
  - Adverse reactions, bullet was modified: "~~Medullary~~ Bone pain."
- Footnotes
  - The footnotes with links to the prescribing information were replaced with footnote 1: "See full prescribing information for specific product information."
  - Footnote "2" was added: "Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim and pegfilgrastim."
  - Footnote "3" was extensively revised: "*The toxicities listed are from the prescribing information and are based on studies from different patient populations. For filgrastrim and derivative products, the toxicities are based on non-myeloid malignancies. For sargramostim, the t*oxicities 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.*"

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Updates in Version 1.2013 of the NCCN Myeloid Growth Factors Guidelines from Version 1.2012 include:

MGF-E 1 of 2

- **Filgrastim**
  - **2nd sub-bullet was modified: "Start ~~24-72 h~~ *the next day up to 3-4 days* after completion of chemotherapy and treat through post-nadir recovery~~. Administration of growth factor on the same day as chemotherapy is not recommended~~."**
- **Pegfilgrastim**
  - **Sub-bullet was removed: "Start 24-72 h after completion of chemotherapy. Administration of growth factor on the same day as chemotherapy is not recommended."**
  - **Sub-bullets 2 through 4 were added:**
    - **The majority of trials administered pegfilgrastim the day after chemotherapy (category 1).**
    - **Administration of pegfilgrastim up to 3-4 days after chemotherapy is also reasonable based on trials with filgrastim.**
    - **Limited data suggest that same-day administration of pegfilgrastim may be considered in certain circumstances.**
      - **Related references were added to MGF-E 2 of 2.**
  - **Sub-bullets 6 and 7 were modified:**
    - ***There are phase* II studies *that* demonstrate efficacy for chemotherapy regimens given every 2 wks.**
    - **There are insufficient data to support ~~dose and schedule~~ *use* for weekly *chemotherapy* regimens ~~or chemotherapy schedules less than 2 wks~~; *therefore, use of pegfilgrastim* cannot be recommended.**
- **Sargramostim**
  - **2nd sub-bullet was modified: "Start ~~24-72 h~~ *the next day up to 3-4 days* after completion of chemotherapy and treat through post-nadir recovery. ~~Administration of growth factor on the same day as chemotherapy is not recommended~~."**
- **The following bullets were removed from the page:**
  - **"There are no data to support alternative dosing schedules in intermediate and high-risk patients."**
  - **"The safety data appear to be similar between filgrastim and pegfilgrastim." This information is on MGF-C.**
- **Footnote**
  - **Footnote "2" was modified by adding: "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."**

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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,e]

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

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

CSFs= Colony-stimulating factors

[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 Myelodysplastic Syndromes, and in Acute Myeloid Leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia.

[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 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; these include type of chemotherapy regimen (See MGF-A) and patient risk factors including a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity (See MGF-B).

[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.)

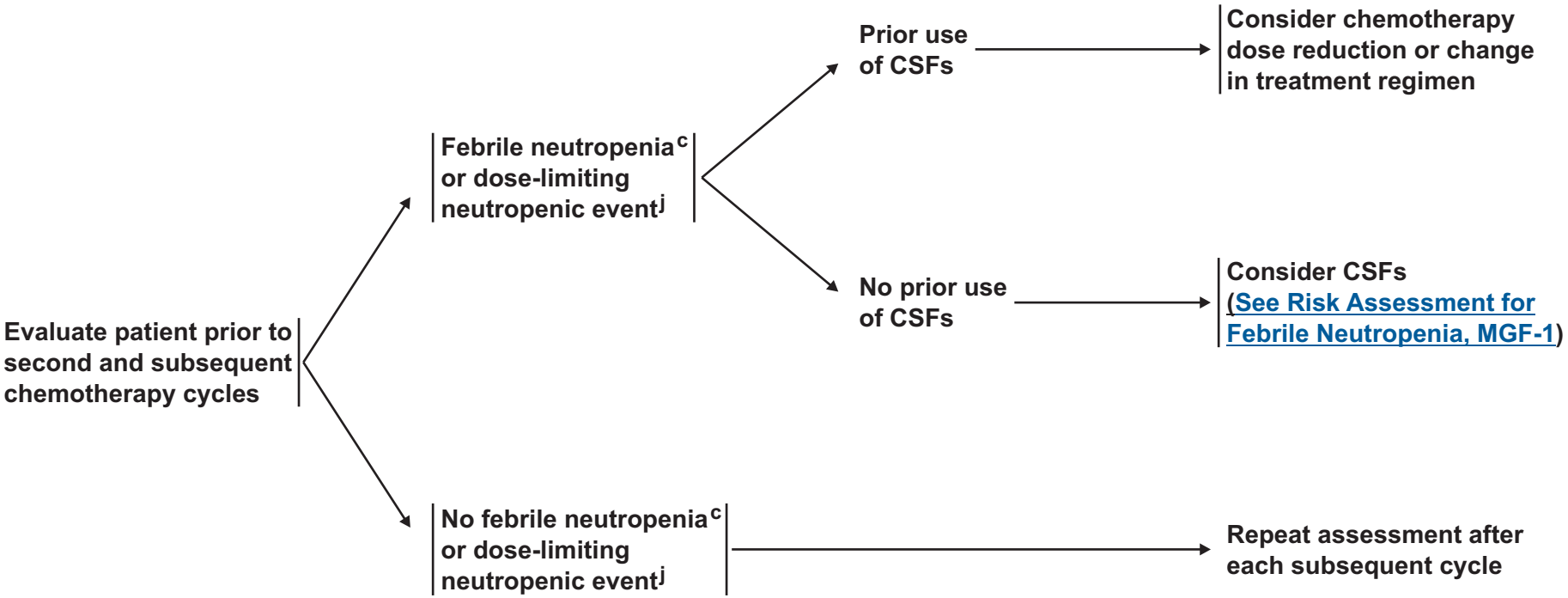
[h] Only consider CSFs if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

[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 10-20%, CSFs are reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

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

EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



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

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

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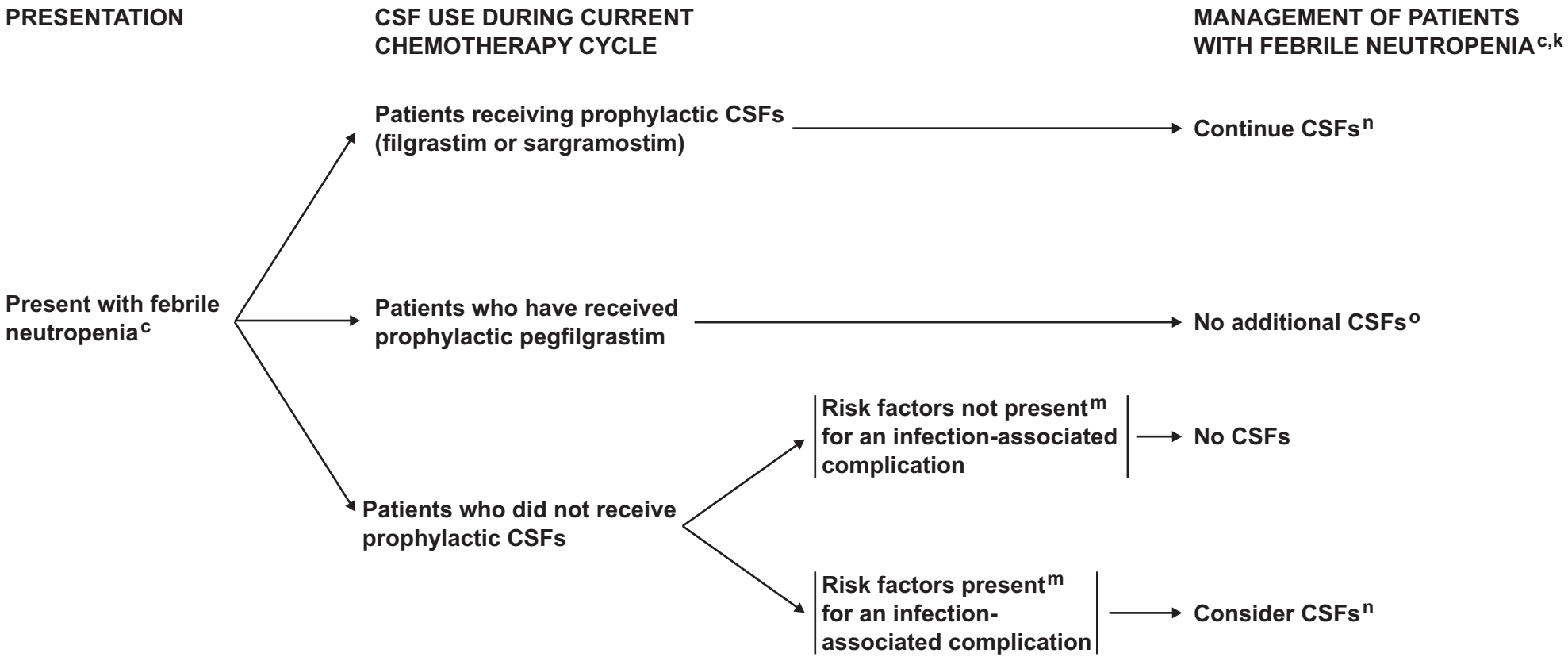
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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 <1,000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[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.

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

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

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

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

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

Breast Cancer
- 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) (DLBCL, PTCL, 2nd line, salvage)[10]
- RICE * (rituximab, ifosfamide, carboplatin, etoposide)[11]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab[12,13]
- MINE (mesna, ifosfamide, novantrone, etoposide) DLBCL, PTCL, 2nd line, refractory)[14]
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd line)[15]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (DLBCL, PTCL, 2nd line, recurrent)[16]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[17,18]

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

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

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

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

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

Occult Primary - Adenocarcinoma
- Gemcitabine/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] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

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

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

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

Note: All recommendations are category 2A unless otherwise indicated.
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CHEMOTHERAPY REGIMEN REFERENCES

Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

[1] Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol 20924. J Clin Oncol 2001;19:2638-2646.

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

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

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

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

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

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

[8] Wierda W, Faderl S, O'Brien S, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR) is active for relapsed and refractory patients with CLL [abstract]. Blood 2004; 104:Abstract 340.

[9] Wierda W, O'Brien S, Ferrajoli A, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR), an active frontline regimen for high-risk patients with CLL [abstract]. Blood 2007;110: Abstract 628.

[10] Hertzberg MS, Crombie C, Benson W, et al. Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. Ann Oncol 2006;Suppl 4:25-30.

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

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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 Guidelines for Senior Adult Oncology)**
- **Previous chemotherapy or radiation therapy**
- **Preexisting neutropenia or bone marrow involvement with tumor**
- **Preexisting conditions**
  - **Neutropenia**
  - **Infection/open wounds**
  - **Recent surgery**
- **Poor performance status**
- **Poor renal function**
- **Liver dysfunction, most notably elevated bilirubin**

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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 non-myeloid malignancies. For sargramostim, the toxicities are based primarily on studies from leukemia and transplant patients and the listed toxicities may reflect intravenous route of administration and may differ from those of subcutaneous administration.
[4] See Discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.
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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 to use CSFs in the treatment of febrile neutropenia is controversial. See Discussion for further details.

[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;24:3187-3205.

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

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

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

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

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

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

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

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

[3] There is category 1 evidence to support filgrastim, tbo-filgrastim, or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence for a category 1 recommendation for sargramostim in this setting. Sargramostim is indicated for use following induction chemotherapy in older adult patients with AML. Sargramostim is also indicated for mobilization of hematopoietic progenitor cells and acceleration of myeloid recovery in patients receiving 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.

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

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

References for pegfilgrastim

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Summary of 4 prospective trials.

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

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Prospective randomized trial favored next-day administration.

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Prospective randomized trial favored next-day administration.

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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/day 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 about 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/day X 4 days, then plerixafor 240 mcg/kg/day (dose adjusted for GFR <50 mL/min, maximum dose 40 mg/day, maximum 4 days) by subcutaneous injection the evening of day 4 prior to collection beginning the next morning (day 5):**
  - **For patients who were heavily pre-treated[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/day by subcutaneous injection, start collection on day 4 or 5.[9-11]**
- **Use of plerixafor in normal donors is under study.**
- **Allogeneic donors for granulocyte transfusion: one dose of G-CSF 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8-24 hours prior to collection.[12]**

Supportive care

- **Post autologous stem cell or cord blood transplant: G-CSF dose 5 mcg/kg/day. 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/day until ANC >1.5 x 10^9/L times 3 days.[19-21]**

See References, MGF-F (2 of 2)

†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.

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST STEM CELL TRANSPLANT

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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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 demonstrated that prophylactic use of colony-stimulating factors (CSF) 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[3] showed that about 25% to 40% of treatment-naive 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 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 U.S. Food and Drug Administration (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 (AML) 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 Guidelines for Myeloid Growth factors 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 Guidelines for Myelodysplastic Syndromes and the NCCN Guidelines for Acute Myeloid Leukemia.

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-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 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 risk of FN (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 over 12,000 patients undergoing chemotherapy with or without G-CSF support. With an average follow-up of 5 years, G-CSF was associated with a 3.40% and 0.90 reduction in absolute and relative risk for all-cause mortality, respectively, although this comes with an increase in risk for AML and myelodysplastic syndromes (MDS) (see below). The degree of benefit correlated with chemotherapy dose intensity.

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%.[25] Economic analyses of CSFs have yielded mixed results, depending on the context of usage.[26-30] 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.

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 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, 2.15–7.52; $P < .001$).[23]

There have also been reports of rare cases of splenic rupture with G-CSF usage, 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 there have been suggestions of potentially increased risk of AML/MDS with G-CSF administration from 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. It is not possible from this meta-analysis to determine whether the risk of AML/MDS is secondary to G-CSF or related to the higher total doses of chemotherapy. As discussed above, overall mortality was nevertheless decreased.

There has been controversy surrounding the use of G-CSFs for patients with Hodgkin's 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 on 141 patients.[38] In a systematic review of case reports by Azoulay and colleagues,[39] 70 cases of G-CSF-related pulmonary toxicity were identified in cancer patients with neutropenia. Thirty-six patients had received bleomycin, but the majority of these were NHL patients who 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 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, 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). 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 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-naive patients are considered by the panel as being at "high risk". It is emphasized that the type of chemotherapy regimen is only one component of the risk assessment and needs to be combined with patient risk factors for an estimation of the overall risk of FN.

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

Evens et al[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 discussion of risks and benefits with the patient.

Patient Risk Factors for Developing FN

Patient risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk (reviewed by Lyman et al[41]). 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. Even a low-risk regimen does not necessarily preclude the use of CSFs in a patient with high-risk factors.

Higher age, notably over 65 years, is the most important risk factor for developing severe neutropenia (see NCCN Guidelines for Senior Adult Oncology).[42-47] 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. Most of these have been confirmed as independent risk factors for neutropenic complications in a risk model developed by Lyman and colleagues that was validated in a study population of 3,760 cancer patients beginning chemotherapy.[48]

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 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 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 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 ($P < .001$). 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 placebo group had a 6% rate of FN 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 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.

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% 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 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 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 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.

Dosing and Administration

Currently used or approved myeloid growth factors (MGFs) for the prophylaxis of FN and maintenance of scheduled dose delivery include filgrastim, tbo-filgrastim, pegfilgrastim, and sargramostim, preferably

given subcutaneously. While data from randomized studies support the use of filgrastim, tbo-filgrastim, and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on its use following induction therapy for AML and in various stem cell transplantation settings. Therefore, when choosing among MGFs, filgrastim, tbo-filgrastim, and pegfilgrastim are considered category 1 recommendations, while sargramostim is considered a category 2B recommendation. NCCN 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 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 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.

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 into health care practice.[54]

In August 2012, the FDA announced the approval of tbo-filgrastim, describing it as “a leukocyte growth factor indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.” Approval was based on 3 randomized clinical trials involving 680 cancer patients. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.[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 NHL 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 demonstrated 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.

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. Since 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 practice “same-day” pegfilgrastim or administration of pegfilgrastim on a day during which patients receive chemotherapy. This is done 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 safety and efficacy of pegfilgrastim administered within 24 hours after chemotherapy.[62,63] Burris and colleagues[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 towards longer duration of severe neutropenia for the same-day group.[65,66] The third study in lung cancer patients 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 length. 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] There are insufficient data to support dose and schedule of weekly regimens and these cannot be recommended.

Sargramostim

There is insufficient evidence from randomized trials to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. Sargramostim is indicated for use following induction chemotherapy in older adult patients with AML.[75-77] Administration should start the next day up to 3 to 4 days after completion of chemotherapy and treat through post-nadir recovery.

Therapeutic Use of MGFs

Compared to prophylactic use, there is less evidence supporting therapeutic use of MGFs for FN as an adjunct to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials [78], Clark and colleagues reported a shorter length of hospitalization (HR, 0.63; 95% CI, 0.49–0.82; P = .0006), 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] also found no difference in mortality, but they were unable to assess other clinical benefits. Of note, Berghmans' analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF or placebo.[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, since pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional CSF.[81] 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 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 due to 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 chemo-mobilization 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 rise of the white blood count when the CD34+ cells are circulating. More recently, addition of the CXCR4 inhibitor plerixafor to chemo-mobilization has been shown to accelerate 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 demonstrated that pegfilgrastim resulted in a better PBSC yield than filgrastim, requiring less use of rescue plerixafor,[92] but there have not been any randomized trials.

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 (GVHD) in the recipient, but studies have demonstrated 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 under study.

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 post-transplant setting. G-CSF administration after high-dose chemotherapy and autologous PBSC transplantation has been shown to expedite neutrophil recovery in prospective randomized trials.[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 two 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 demonstrated 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

The NCCN Guidelines for Myeloid Growth Factors 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 on a randomized control 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/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 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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