National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myeloid Growth Factors

Version 1.2018 — March 2, 2018

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NCCN Guidelines Version 1.2018
Myeloid Growth Factors

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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 indicated.

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2018 of the NCCN Guidelines for Myeloid Growth Factors from Version 2.2017 include:

MGF-1

- **Heading added: "Overall Febrile Neutropenia Risk"**
- **Footnote "c" revised: "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*; and in chronic myeloid leukemia (CML) see the NCCN Guidelines for Chronic Myeloid Leukemia."***

MGF-A (2 of 4)

- **"CMF classic (cyclophosphamide, methotrexate, fluorouracil)" has been removed from the list of examples of breast cancer regimens with an intermediate risk of febrile neutropenia.**

MGF-A (4 of 4)

- **The following reference has been removed: "Poole CJ, Earl HM, Dunn JA, et al. NEAT (National Epirubicin Adjuvant Trial) and SCTBG BR9601 (Scottish Cancer Trials Breast Group) phase III adjuvant breast trials show a significant relapse-free and overall survival advantage for sequential ECMF [abstract]. Proc Am Soc Clin Oncol 2003;22:Abstract 13."**

MGF-B

- **Under pegfilgrastim dosing, the second sub-bullet has been revised: "For patients who cannot return to the clinic for next-day administration, ~~alternative options exist~~ *there is an FDA-approved delivery device available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application)*."**
- **Footnote "d" has been added: "Neutrophil counts should be monitored, as indicated, appropriate to the setting."**
- **Footnote "e" has been added: "Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Cancer Care 2017;25:2619-2629."**
- **Footnote "f" revised: "~~An FDA-approved delivery device is available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application).~~ Rarely, there is a failure to inject that requires further medical attention."**

Continued

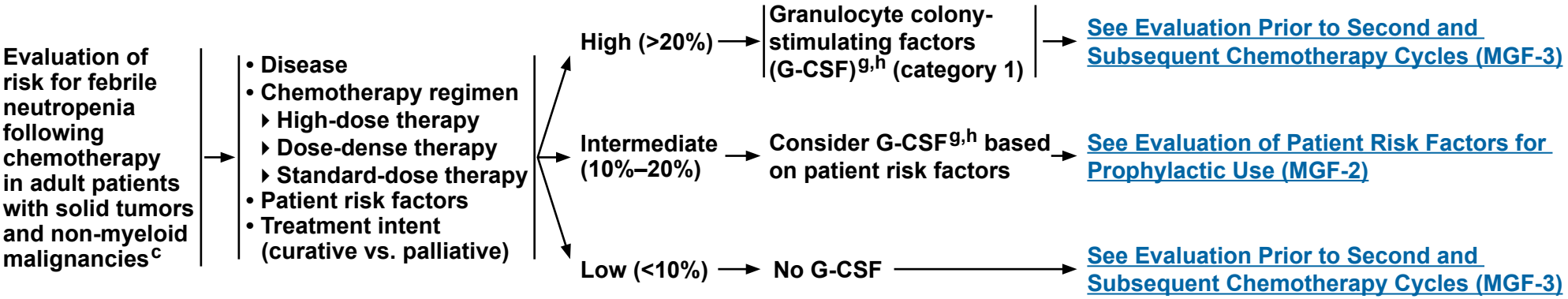
Updates in Version 1.2018 of the NCCN Guidelines for Myeloid Growth Factors from Version 2.2017 include:

MGF-D (1 of 4)
- First line added: "Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and incorporation of plerixafor with either approach."
- Mobilization of Hematopoietic Progenitor Cells in Autologous Setting
  - Second bullet revised and reference added: "Combination chemotherapy followed by filgrastim/filgrastim-sndz/tbo-filgrastim with the goal of mobilization during count recovery *that may result in higher collection yields with fewer days of apheresis but increased rate of hospitalizations for neutropenic fever. This approach may also reduce burden of residual tumor."* (Chao N, Grima D, Carrum G, et al. Chemo-mobilization provides superior mobilization and collection in autologous stem cell transplants but with less predictability and at a higher cost [abstract] Blood 2011;118: Abstract 4048.)
  - Under fourth bullet, prior indications for plerixafor have been replaced with the following bullets:
    - ◊ Plerixafor is FDA approved in combination with G-CSF for the purpose of mobilizing autologous hematopoietic stem cells to the peripheral blood in patients with non-Hodgkin lymphoma and multiple myeloma.
    - ◊ Existing literature suggests that a preemptive "just in time" strategy of adding it for patients who do not mount a sufficient CD34+ cell count is highly successful.
    - ◊ There is limited data on parameters for predicting poor mobilization and which patients may benefit from upfront use of plerixafor. Risk factors that have been associated with poor mobilization include older age, extensive prior therapy, prior radiation to marrow containing regions, or multiple cycles of certain agents such as fludarabine or lenalidomide. See Discussion.
  - Dosing for MGF and plerixafor has been updated.

MGF-D (2 of 4)
- Under Supportive Care Options:
  - First sub-bullet revised under filgrastim or filgrastim-sndz or tbo-filgrastim: "Post-autologous hematopoietic cell*, haploidentical transplant,* or cord blood transplant."
  - Sargramostim removed from the supportive care options.

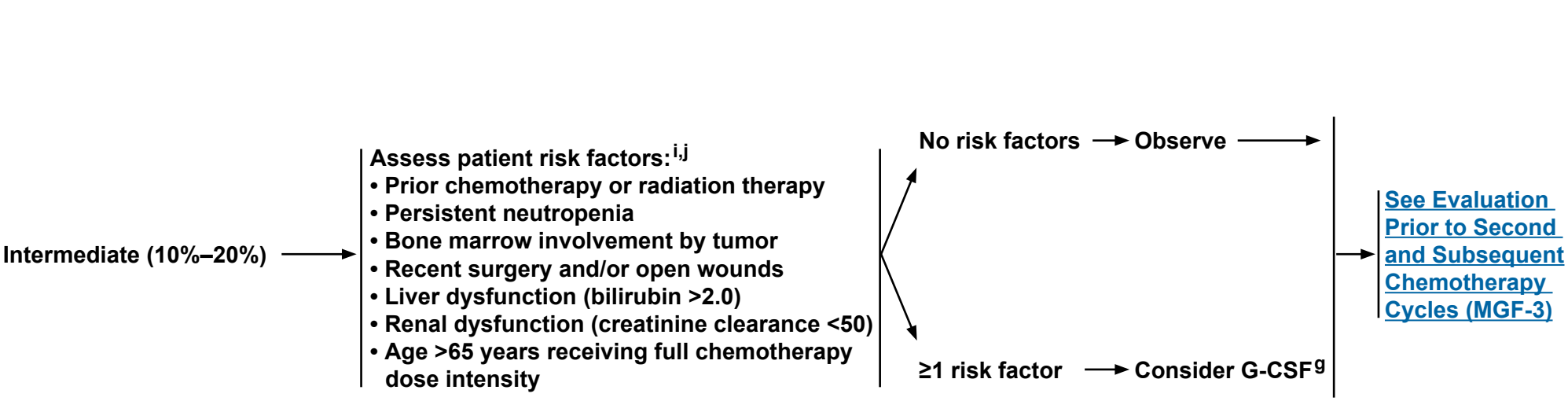
MGF-D (3 of 4) and **(4 of 4)**
- References have been updated.

MS-1
- The Discussion section has been updated to reflect the changes in the algorithm.



[a]The NCCN Guidelines for Myeloid Growth Factors were formulated in reference to adult patients.
[b]Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with MGF as clinically indicated, unless precluded by trial specifications.
[c]For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes; in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia; and in chronic myeloid leukemia (CML) see the NCCN Guidelines for Chronic Myeloid Leukemia.
[d]There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (See MGF-A) and patient risk factors (See MGF-2).
[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[f]See Toxicity Risks with Myeloid Growth Factors (MGF-E).
[g]G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).
[h]There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, and intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSF for a reduction in infection-related mortality during the course of treatment (see Discussion for details).

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



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

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

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

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

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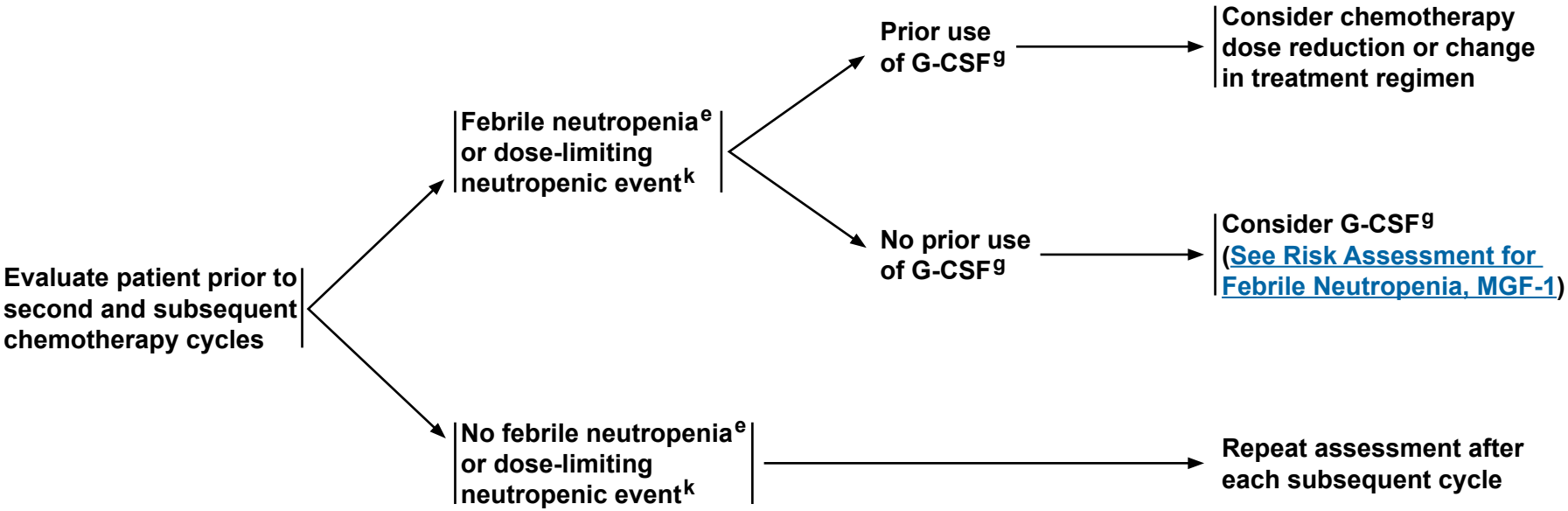
EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



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

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

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

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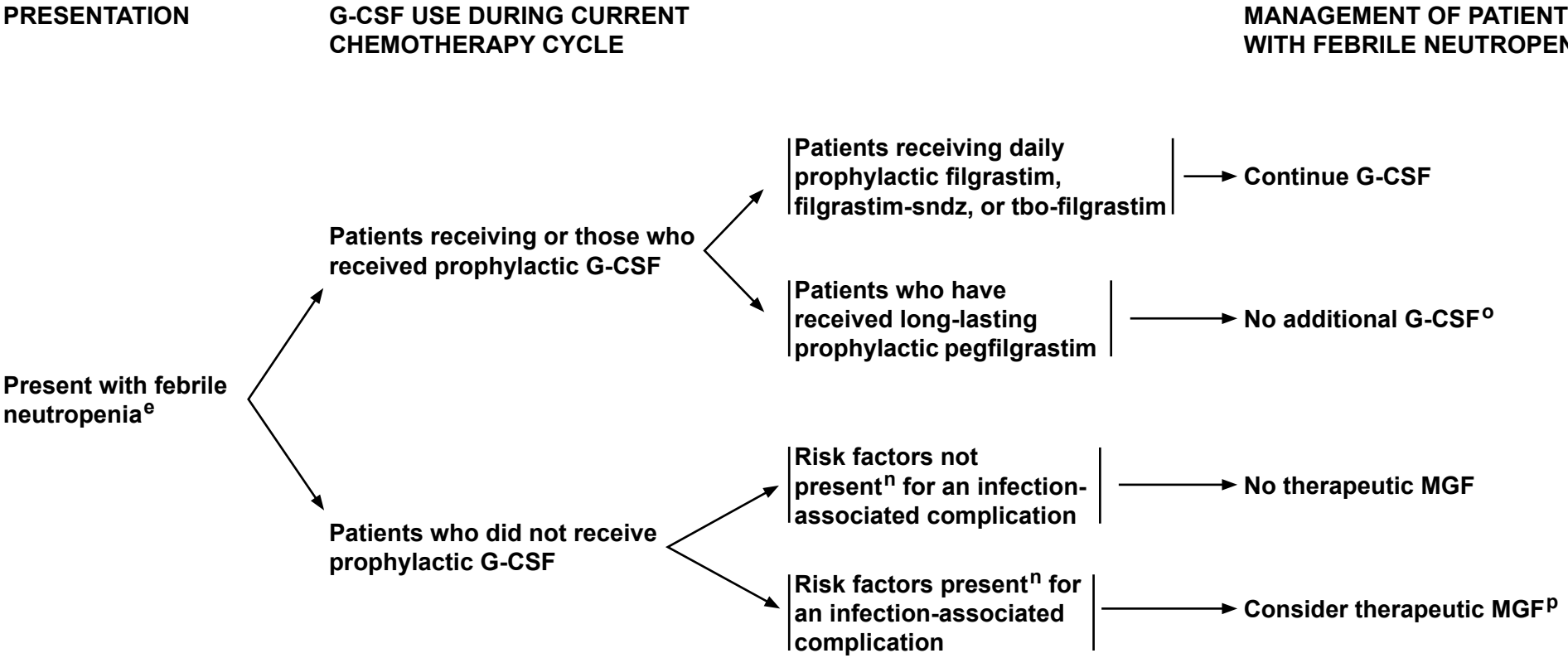
THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGF) FOR FEBRILE NEUTROPENIA[e,l,m]



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

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

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

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

[o]There are no studies that have addressed therapeutic use of filgrastim for febrile neutropenia in patients who have already received prophylactic pegfilgrastim. However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggest that additional G-CSF may not be beneficial; but in patients with prolonged neutropenia additional G-CSF may be considered.

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

Note: All recommendations are category 2A unless otherwise indicated.
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EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for treatment by cancer site are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

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

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

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

Kidney Cancer
- Doxorubicin/gemcitabine[8]

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

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

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

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

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[24]
- Doxorubicin[a,25]
- Ifosfamide/doxorubicin[26]

Small Cell Lung Cancer
- Topotecan[27]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[28]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[29,30]
- TIP (paclitaxel, ifosfamide, cisplatin)[31]

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

See References, MGF-A (3 of 4)

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for treatment by cancer site.
[b]In general, dose-dense regimens require growth factor support for chemotherapy administration.
[c]Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

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

- ***This list is not comprehensive***; **there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for treatment by cancer site are considered when updating this list of examples.**
- **The type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-2).**
- **The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)**

Occult Primary- Adenocarcinoma
- Gemcitabine/docetaxel[32]

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

Cervical Cancer
- Cisplatin/topotecan[38-40]
- Paclitaxel/cisplatin[a,40]
- Topotecan[41]
- Irinotecan[42]

Colorectal Cancer
- FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[43]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,44]
- Epirubicin/cisplatin/5-fluorouracil[45]
- Epirubicin/cisplatin/capecitabine[45]

Non-Hodgkin's Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,46]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[47,48] including regimens with pegylated liposomal doxorubicin[49,50]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[51]
- Cisplatin/vinorelbine[52]
- Cisplatin/docetaxel[51,53]
- Cisplatin/etoposide[54]
- Carboplatin/paclitaxel [a,d,55]
- Docetaxel[53]

Ovarian Cancer
- Carboplatin/docetaxel[56]

Pancreatic Cancer
- FOLFIRINOX[e]

Prostate Cancer
- Cabazitaxel[f,57]

Small Cell Lung Cancer
- Etoposide/carboplatin[58]

Testicular Cancer
- Etoposide/cisplatin[59]

Uterine Sarcoma
- Docetaxel[60]

See References, MGF-A (4 of 4)

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

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

[e]A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[62] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSF was administered to 42.5% of patients who received FOLFIRINOX).[63] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

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

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CHEMOTHERAPY REGIMEN REFERENCES

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

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

[2]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.

[3]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.

[4]Kosaka Y, Rai Y, Masuda N, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. Support Care Cancer 2015;23(4):1137-1143.

[5]Gilbar P, McPherson I, Sorour N, Sanmugarajah J. High incidence of febrile neutropenia following adjuvant breast chemotherapy with docetaxel, carboplatin and trastuzumab. Breast Cancer Manag 2014;3:327-333.

[6]Chihara D, Kantarjian H, O'Brien S, et al. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukemia: update of a phase II trial. Br J Haematol 2016 Sep;174(5):760-6.

[7]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.

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

[9]Gutierrez M, Chabner B, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-Year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.

[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:iv25-30.

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

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

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

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

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

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

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

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

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

[20]Lee CK, Barlogie B, Munshi N, Zangari M, Fassas A, Jacobson J, van Rhee F, Cottler-Fox M, Muwalla F, Tricot G. DTPACE: An effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol 2003;21:2732-2739.

[21]Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176-185.

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

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

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

- **Pegfilgrastim (category 1)**
  - **One dose of 6 mg per cycle of treatment.**
    - ◊ **Based on clinical trial data, pegfilgrastim should be administered the day after chemotherapy (category 1).[e]**
    - ◊ **For patients who cannot return to the clinic for next-day administration, there is an FDA-approved delivery device available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application).[f,g]**
    - ◊ **Administration of pegfilgrastim up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.**
  - **There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).**
  - **There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 weeks.**
  - **There are insufficient data to support use for cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.**

- **Prophylactic use of G-CSF in patients given concurrent chemotherapy and radiation is not recommended.**
- **Subcutaneous route is preferred for all G-CSF listed above.**
- **For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

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

[a]Tbo-filgrastim is a human G-CSF approved by the FDA through an original biologic license application. All of these G-CSF are indicated for reducing the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.

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

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

[d]Neutrophil counts should be monitored, as indicated, appropriate to the setting.

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[f]Rarely, there is a failure to inject that requires further medical attention.

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MYELOID GROWTH FACTORS FOR THERAPEUTIC USE

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

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

MGF Doses for Therapeutic Use:[c]

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

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

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

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and incorporation of plerixafor with either approach.

Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

- **Single-agent growth factor:**[1-3]
  - **Filgrastim or filgrastim-sndz[a] or tbo-filgrastim**
    - ◊ **Dose: 10–32 mcg/kg/d by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5 and continue until leukapheresis.**
- **Combination chemotherapy followed by filgrastim/filgrastim-sndz[a]/tbo-filgrastim with the goal of mobilization during count recovery**[4-6] **that may result in higher collection yields with fewer days of apheresis but increased rate of hospitalizations for neutropenic fever.**[7] **This approach may also reduce burden of residual tumor.**
  - **Filgrastim/filgrastim-sndz[a]/tbo-filgrastim is started about 24 hours after completion of chemotherapy.**
- **Concurrent filgrastim/filgrastim-sndz[a] + sargramostim (category 2B)**
  - **Filgrastim/filgrastim-sndz[a] 7.5 mcg/kg each morning, sargramostim 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.**[8]
- **Filgrastim/filgrastim-sndz[a]/tbo-filgrastim + plerixafor**[9-14]
  - **Plerixafor is FDA approved in combination with G-CSF for the purpose of mobilizing autologous hematopoietic stem cells to the peripheral blood in patients with non-Hodgkin lymphoma and multiple myeloma.**
  - **Existing literature suggests that a preemptive "just in time" strategy of adding it for patients who do not mount a sufficient CD34+ cell count is highly successful.**[15-17]
  - **There is limited data on parameters for predicting poor mobilization and which patients may benefit from upfront use of plerixafor. Risk factors that have been associated with poor mobilization include older age, extensive prior therapy, prior radiation to marrow containing regions, or multiple cycles of certain agents such as fludarabine or lenalidomide. See Discussion.**
  - **Dosing for MGF and plerixafor:**
    - ◊ **Filgrastim/filgrastim-sndz[a]/tbo-filgrastim dose: 10 mcg/kg/d x 4 days.**
    - ◊ **On the evening of day 4 of growth factors, start plerixafor by subcutaneous injection 11 hours prior to initiation of apheresis (day 5 collection the next morning).**
    - ◊ **Plerixafor dose based on patient weight:**
      - **– ≤ 83 kg: 20 mg dose or select dose based on 0.24 mg/kg actual body weight.**
      - **– > 83 kg: select dose based on 0.24 mg/kg actual body weight.**
    - ◊ **Repeat plerixafor dose up to 4 consecutive days.**
    - ◊ **Renal impairment: If creatinine clearance is ≤ 50 mL/min, decrease dose by one-third to 0.16 mg/kg.**

Continued
See References, MGF-D (3 of 4)
See Toxicity Risks with Myeloid Growth Factors (MGF-E)

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

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

Mobilization of Allogeneic Donors

- **Allogeneic hematopoietic cell donors:**[18-21]
  - **Filgrastim (preferred) or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)**
    - ◊ **Dose: 10 mcg/kg/d by subcutaneous injection, start collection on day 4 or 5.**[22-24]
  - **Plerixafor (category 2B): Use in normal donors is under study.**[25-27]
- **For granulocyte transfusion:**
  - **Filgrastim or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)**
    - ◊ **Single dose: 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8–24 hours prior to collection.**[28]

Supportive Care Options

- **Filgrastim[b,29] or filgrastim-sndz[a] or tbo-filgrastim**
  - **Post-autologous hematopoietic cell, haploidentical transplant, or cord blood transplant**
  - **5 mcg/kg/d. Begin day +5 post transplant until recovery of ANC (eg, >1.5 x 10^9/L x 2 d).[c]**
- **Pegfilgrastim**[30-36]
  - **Post-autologous hematopoietic cell transplant**

See References, MGF-D (3 of 4)

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

[a]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.
[b]Filgrastim accelerates neutrophil recovery but has not impacted survival. See Discussion for details.
[c]For additional dosing information refer to the package insert: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=97cc73cc-b5b7-458a-a933-77b00523e193. (Accessed February 27, 2018.)

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT
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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT
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[35]Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim appears equivalent to daily dosing of filgrastim to treat neutropenia after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010;10:186-191.

[36]Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 2010;16:678-685.

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

TOXICITY RISKS WITH MYELOID GROWTH FACTORS

Filgrastim and Derivative Products Including Pegfilgrastim[a,b,c]

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

Sargramostim[a,c]

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

[a]See full prescribing information for specific product information.
[b]Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim and pegfilgrastim.
[c]The toxicities listed are from the prescribing information and are based on studies from different patient populations. For filgrastim and derivative products, the toxicities are based on non-myeloid malignancies. For sargramostim, the toxicities are based primarily on studies from leukemia and transplant patients, and the listed toxicities may reflect intravenous route of administration and may differ from those of subcutaneous administration.
[d]See Discussion for details.
[e]Lyman et al reported an increase in absolute and relative risk of AML/MDS of 0.41% and 1.92, respectively, related to G-CSF. Overall mortality was decreased. See Discussion for details and reference.

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise indicated.

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Overview

Myeloid growth factors (MGFs) are a class of biologic agents that regulate the proliferation, differentiation, survival, and activation of cells in the myeloid lineage. In patients with cancer receiving myelosuppressive chemotherapy, MGFs are primarily used to reduce the incidence of neutropenia. Neutropenia is defined as an absolute neutrophil count (ANC) of <500 neutrophils/mcL or anticipated decline to ≤500 in the next 48 hours.[1] Neutropenia can progress to febrile neutropenia (FN, ≥38.3°C orally or ≥38.0°C for a duration over 1 hour), which is a major dose-limiting toxicity of chemotherapy that often requires prolonged hospitalization and broad-spectrum antibiotic use.[2] Occurrences of severe neutropenia or FN can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome. A review by Dale et al [3] reported that about 25% to 40% of treatment-naive patients develop FN with common chemotherapy regimens. Development of FN increases diagnostic and treatment costs and often leads to longer hospital stays. In addition, correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.[4]

The risk of FN is related to the treatment regimen and delivered dose intensity. However, a survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin's lymphoma (NHL) has shown that the rates of myelosuppression and delivered dose intensity are underreported.[5] A recent systematic review of randomized controlled trials published over the past decade involving adults with NHL receiving myelosuppressive chemotherapy found that reporting of neutropenic events occurred in only a quarter of the study arms. Additionally, use of MGF support was variable and inconsistent, and little or no information was provided on delivered chemotherapy dose intensity.[6] Due to individual patient risk factors, the rates of myelosuppression with the same or similar regimens varies greatly, making it difficult to determine the actual risk for neutropenic complications associated with common chemotherapy regimens.[5] Thus, differences in the reported rates of myelotoxicity may be attributed to intrinsic variation in the patient population as well as differences in the delivered dose intensities.

Although early studies investigated a role for macrophage colony-stimulating factor[7,8] and interleukin-3[9-11] in alleviating FN, these guidelines will focus on the two MGFs that have shown the most promise in terms of clinical use: granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). For simplicity, the term "MGF" will be utilized when the data are supported by studies for both G-CSF and GM-CSF.

Filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim are G-CSFs currently approved by the U.S. Food and Drug Administration (FDA) for the prevention of chemotherapy-induced neutropenia. Although data are variable and rapidly evolving, filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim can all be used for the prevention of chemotherapy-induced FN.[12] Both tbo-filgrastim and pegfilgrastim are restricted in their FDA approvals for use in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy. Filgrastim-sndz was approved as a biosimilar allowing its use for the broader indications of the originator product, filgrastim (see *Biosimilars*). Tbo-filgrastim was approved by the FDA in an original biologic license application in August 2012[13,14] and therefore has a more restricted indication.[15] Additional indications for filgrastim and filgrastim-sndz include treatment for patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy, patients with cancer receiving bone marrow transplant, patients undergoing peripheral blood

progenitor cell (PBPC) collection and therapy, and patients with severe chronic neutropenia. Filgrastim is also approved by the FDA for the treatment of patients acutely exposed to myelosuppressive doses of radiation.[16] While European guidelines also include lenograstim as a recommended G-CSF in solid tumors and non-myeloid malignancies,[17] it is not approved for use in the United States and is therefore not addressed in these guidelines.

The only GM-CSF that is FDA-approved is sargramostim, although some clinical trials have used the GM-CSF molgramostim. Molgramostim is not recommended by the panel due to increased adverse events compared to sargramostim[18] as well as the lack of FDA approval. Sargramostim is limited to use following induction therapy for AML and in various hematopoietic cell transplantation (HCT) settings. It should be noted that there is a lack of head-to-head comparative studies on the clinical benefits of G-CSFs versus GM-CSFs.

The NCCN Guidelines for Myeloid Growth Factors are focused on the use of MGFs in the cancer setting. The guidelines primarily address the use of MGFs in adult patients with solid tumors and non-myeloid malignancies. Use of growth factors in the treatment of hematologic malignancies are discussed in the NCCN Guidelines for Myelodysplastic Syndromes, the NCCN Guidelines for Chronic Myeloid Leukemia, the NCCN Guidelines for Acute Myeloid Leukemia and the NCCN Guidelines for Hairy Cell Leukemia.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Myeloid Growth Factors, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: myeloid growth factors and cancer; colony stimulating factors and cancer; filgrastim and cancer; tbo-filgrastim and cancer; filgrastim-sndz and cancer; pegfilgrastim and cancer; and sargramostim and cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[19]

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

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

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Benefits and Risks of MGFs

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

Studies have shown that the prophylactic use of MGFs reduced the incidence, length, and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, non-small cell lung

cancer, and NHL patients.[20-38] Additionally, the benefit of GM-CSF therapy was seen in the treatment of myeloid malignancies.[39] MGFs improved the delivery of full dose-intensity chemotherapy on schedule, although this has not been shown to lead to better response or higher overall survival (OS) in most studies.[20,22,24,27-30,34,40,41] However, in node-positive breast cancer[34,42] and aggressive lymphoma,[36,43,44] dose-dense regimens supported by MGFs improved disease-free survival and/or OS compared to conventional chemotherapy. Furthermore, primary G-CSF prophylaxis (defined as G-CSF administration within 5 days of beginning chemotherapy) was associated with a reduced risk of neutropenia-related hospitalization in breast cancer patients (n = 8745).[37]

Meta-analyses confirmed the efficacy of prophylactic MGFs in decreasing the rates of infection and risk of neutropenia.[45-48] The meta-analysis from Clark et al[47] included 13 studies, in which 6 studies involved treatment of patients with G-CSF; 6 studies involved treatment of patients with GM-CSF; and one 3-arm study included G-CSF, GM-CSF, and placebo. In total, 1518 patients were evaluated for overall mortality, infection-related mortality, length of hospitalization, and time to neutrophil recovery. While overall mortality did not appear to reach statistical significance (odds ratio [OR], 0.68; 95% CI, 0.43–1.08; *P* = .10), infection-related mortality was significantly reduced with the use of MGFs (OR, 0.51; 95% CI, 0.26–1.00; *P* = .05). A clear reduction in the length of hospitalization (hazard ratio [HR], 0.63; 95% CI, 0.49–0.82; *P* = .0006) and time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; *P* < .0001) was also observed with the addition of MGFs.

In a systematic review of 17 randomized trials including 3493 adult patients with solid tumors and lymphoma, primary prophylaxis with G-CSF reduced the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; *P* < .001) and improved the relative dose intensity of the chemotherapy delivered with an average difference between study arms of 8.4% (*P* = .001).[49] For the first time, this analysis also reported a substantial reduction in the risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; *P* = .018) and early death during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; *P* = .002). The survival advantage was confirmed in a systematic review by Lyman et al[50] of 25 randomized controlled trials that involved >12,000 patients undergoing chemotherapy with or without G-CSF support. With an average follow-up of 5 years, G-CSF support was associated with a 3.4% reduction in absolute risk and an RR of 0.9 for all-cause mortality, although an increased risk for AML and myelodysplastic syndromes (MDS) was observed. Notably, the degree of benefit correlated with the chemotherapy dose intensity.

Several randomized trials have demonstrated improved outcomes with the use of tbo-filgrastim for the prevention of FN. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.[51] 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.[52,53] Toxicities were similar between the two agents. A meta-analysis of the 3 trials concluded tbo-filgrastim to be non-inferior to filgrastim for the reduced incidence of FN, irrespective of the myelotoxicity of the chemotherapy regimen.[54] Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.[55,56]

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

associated with G-CSF prophylaxis is mild to moderate bone pain in 10% to 30% of patients.[38,57-63] This is usually effectively controlled by non-narcotic analgesics.[57,58] The meta-analysis by Kuderer et al[64] also confirmed a heightened risk of musculoskeletal pain associated with MGF use (RR, 4.03; 95% CI, 2.15–7.52; $P < .001$).[49]

There have been reports of rare cases of splenic rupture with G-CSF use, some of which were fatal.[65-70] These cases occurred in patients with underlying hematopoietic disorders, patients with solid tumors, and healthy donors of PBPCs. The exact mechanism of G-CSF–induced splenic rupture is unknown, but is thought to involve intrasplenic accumulation of circulating granulocytes and myeloid precursors.[62] Although G-CSF–induced splenic rupture is rare, it is potentially life-threatening. Therefore, physicians should monitor patients closely for signs of splenic rupture, including abdominal pain (especially in the upper left quadrant), nausea, vomiting, and progressively worsening anemia. Prospective studies on health status, baseline spleen size, and complete blood count (CBC) may be required to identify risk factors for rupture in individual patients.[64]

Additionally, some patients develop allergic reactions involving the skin, respiratory system, or cardiovascular system. Other potential toxicities include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.[57,58,71] Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease, but not for patients with sickle cell trait.[72-74] Worsening of amyloidosis following G-CSF administration has also been reported; however, this is based on two case reports in patients who were already prone to life-threatening complications.[75,76]

Pulmonary toxicity has been reported following 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-induced pulmonary toxicity has been reported with G-CSF use in a retrospective study of 141 patients.[77] Additionally, in a systematic review of case reports by Azoulay et al,[78] 70 cases of G-CSF–related pulmonary toxicity were identified in neutropenic patients with cancer. Thirty-six patients had received bleomycin, but the majority of patients had also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). The toxicity potential for patients following the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen is less clear, although bleomycin is given every 3 weeks in this regimen as opposed to every 2 weeks as in ABVD. Due to the risk of pulmonary complications, the routine use of G-CSF is not recommended in conjunction with the most common chemotherapy regimens for classical Hodgkin lymphoma (ABVD and Stanford V). Furthermore, two studies have shown that ABVD can be safely administered at full dose without G-CSF support.[79,80] However, due to the high incidence of toxicity and treatment delays, G-CSF support is recommended for patients with Hodgkin's lymphoma treated with the escalated BEACOPP regimen.

Adverse events have also been reported with GM-CSF use. An early study of patients with advanced malignancy evaluated side effects following administration of GM-CSFs. Adverse reactions were seen in 65% of these patients, though they were not severe and were reversible. These reactions included mild myalgias, facial flushing, low-grade fever, headache, bone discomfort, nausea, and dyspnea.[81] A side-effect profile of GM-CSF, completed several years later, reported a lower rate of 20% to 30% mild-to-moderate adverse events, and attributed this decline to improved dosing and delivery.[82] Though uncommon, severe side effects have also been reported with GM-CSF use. Less than 1% of patients develop blood clots, which may lead to pulmonary embolism or stroke in rare cases.[83-85] There have also been reports of capillary leak syndrome,[86-88] a condition in which fluids move

from the vascular system into the interstitial space resulting in hypotension and reduced blood flow to internal organs.[83] While this is more common with GM-CSF use, it has also been reported to occur with G-CSFs.[89,90]

Although there have been suggestions of a potentially increased risk for AML/MDS with MGF administration from epidemiologic studies, this was not observed in individual randomized trials.[65,91-93] The meta-analysis by Lyman et al[50] reported a 0.41% increase in absolute risk and an RR of 1.92 for the development of AML/MDS related to G-CSF use. It is not possible from this meta-analysis to determine whether the risk for AML/MDS is secondary to G-CSF or related to the higher total doses of chemotherapy. As discussed above, overall mortality was nevertheless decreased. These data mirror an earlier report based on the SEER database that showed an elevated risk of developing AML/MDS in patients on either G-CSF or GM-CSF support.[93] One caveat of the study was that it could not exclude the possibility that the increase was due to the use of MGFs in cases that were more likely to progress into AML/MDS, regardless of the presence or absence of adjuvant therapy.

The recommendations in the NCCN Guidelines for Myeloid Growth Factors are based on therapeutic efficacy and clinical benefit of treatment. However, in addition to evaluating the clinical benefits and risks of MGF therapy, an increasing number of studies have assessed the financial implications of its use. Over the last decade, the costs of inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.[94] Economic analyses of MGFs have yielded mixed results, depending on the context of usage.[95-99] While the addition of MGFs to treatment regimens inevitably raises drug costs, it may actually equate to substantial savings in comparison to the costs of hospitalization and subsequent treatment of neutropenia. Recently developed pharmacoeconomic models of MGF use have reflected these clinical observations by modeling sequential chemotherapy regimens to account for FN risk on a per-cycle basis, and by accounting for chemotherapy dose reductions and consequent survival losses.[100]

Additionally, a recent study by Fust et al evaluated the cost effectiveness of no prophylaxis, primary G-CSF prophylaxis (administration in the first cycle and every subsequent cycle of chemotherapy), or secondary G-CSF prophylaxis (administration in the cycle immediately following the first cycle with a neutropenic event and continuation until the end of the chemotherapy) to reduce the incidence of FN in breast cancer and NHL patients. Results showed that primary prophylaxis with pegfilgrastim was more cost-effective compared to other prophylaxis strategies; however, it is important to note that these data were interpreted from a Belgian payer perspective.[101]

Selective use of MGFs in patients at an increased risk for neutropenic complications may also enhance cost-effectiveness. Pawloski et al recently developed an evidence-based, individualized neutropenia risk estimation algorithm based on electronic health record (EHR) data.[102] The resulting risk model demonstrated good performance (Hosmer-Lemeshow goodness-of-fit test = 0.24) in a retrospective external cohort and may facilitate future research directed at the individualization of neutropenic risk evaluation.

Biosimilars

A biosimilar is a biologic that is highly similar to the FDA-approved originator product with the exception of minor differences in clinically inactive components and no differences regarding efficacy, safety, and purity. Biosimilars have the same amino acid sequence; however, they may differ at the protein level due to the nature and complexity of biologic products. Differences may be seen in the three-dimensional

structure, the glycosylation sites, the isoform profiles, and the level of protein aggregation.[103,104] Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biological activity, efficacy, and safety.[105] If overall safety and efficacy remain unaffected, biosimilars may be approved for the same indications and can be substituted for the originator product. If the biosimilar is also designated as interchangeable, alternating between the biosimilar and the originator product is acceptable and is not expected to result in higher toxicity or diminished efficacy. However, if the biosimilar is not deemed interchangeable, alternating between the biosimilar and originator product is not recommended.

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim. Data have shown filgrastim-sndz to have identical protein structure, mass, size, charge, and hydrophobicity to the originator product.[106] Pharmacokinetic and pharmacodynamic modeling further confirmed that the mechanism of action is the same and occurs through the binding of the G-CSF receptor.[107] Clinical data leading to the approval of filgrastim-sndz were predominately based on data from healthy volunteers and data in patients with cancer in the context of the prevention of chemotherapy-induced neutropenia.

The FDA approved filgrastim-sndz for the following indications: 1) to decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; 2) to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy of patients with AML; 3) to reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation; 4) to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and 5) to reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.[108]

Although a potential concern regarding immunogenicity exists with biosimilars, immunogenicity is anticipated to be low to nonexistent with filgrastim biosimilars based on the lack of immunogenicity seen with filgrastim and the nature of filgrastim as an unglycosylated protein. Filgrastim-sndz was evaluated in limited clinical studies of healthy volunteers or cancer patients with the incidence of antibodies binding to filgrastim reaching 3% (11 out of 333 patients).[108] Further analysis of these patients showed no evidence of neutralizing antibodies, suggesting that there is no increased risk of immunogenic adverse events or reduction of efficacy.[109]

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

Prophylactic Use of MGFs

Risk Assessment

The risk for chemotherapy-induced FN should be evaluated prior to the first cycle of chemotherapy. The risk assessment includes disease type, chemotherapy regimen (high-dose, dose-dense, or standard-dose), patient risk factors, and treatment intent (curative/adjuvant vs. palliative). Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to either an overall high-risk group (>20% risk of FN), intermediate-risk group (10%–20% risk), or low-risk group (<10% risk) (see *Evaluation, Risk Assessment, and Prophylactic Use* in the algorithm). Of note, there is currently no consensus nomogram for risk assessment. While the NCCN Panel outlines criteria to aid in the assessment of FN risk, independent clinical judgment should be exercised based on the patient's situation (see *Additional Evaluation of Patient Risk Factors for Prophylactic Use* in the algorithm). The NCCN Panel also recommends that patients receiving cytotoxic chemotherapy as part of a clinical trial be evaluated for prophylactic use of MGFs based on both regimen-specific and patient-specific risk factors, unless precluded by trial specifications.

Chemotherapy Regimens and Risk for FN

The development of FN is a common dose-limiting toxicity of many single-agent and combination chemotherapy regimens that is directly related to the dose intensity of the regimen. Chemotherapy regimens for which clinical trial data show an FN incidence of >20% in chemotherapy-naive patients are considered by the panel to be high risk. It should be noted that the addition of monoclonal antibodies to chemotherapy regimens has the potential to increase the risk of FN. Of particular concern is rituximab, an anti-CD20 monoclonal antibody used in treatment of CD20+ hematologic malignancies, which is known to have an independent potential to cause severe neutropenia. Rituximab has been associated with prolonged, delayed-onset neutropenia both with or without chemotherapy.[110]

The algorithm lists common chemotherapy regimens associated with a high risk or intermediate risk of developing FN based on published data (see *Examples of Disease Settings and Chemotherapy Regimens with a High/Intermediate Risk for Febrile Neutropenia* in the algorithm). These lists are not comprehensive and are meant to only serve as examples, as the exact risk will depend on the agent, dose, and treatment setting. 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.

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. [111] Patient factors may elevate the overall risk to a high-risk category, where prophylactic MGFs are more routinely recommended. Many regimens for breast and lung cancers are associated with an intermediate risk of neutropenic complications, deeming it important to identify which patients would be considered high risk for FN development. Even a low-risk regimen does not necessarily preclude the use of MGFs in a patient with high-risk factors.

The most important risk factor for developing severe neutropenia is older age, notably >65 years, in patients who receive full chemotherapy dose intensity (see NCCN Guidelines for Older Adult Oncology).[112-117] Other risk factors include prior chemotherapy or radiotherapy, pre-existing neutropenia or tumor involvement in the bone marrow, poor performance status, comorbidities including renal or liver dysfunction,

HIV infection, and pre-existing conditions such as neutropenia or infection (see *Additional Evaluation of Patient Risk Factors for Prophylactic Use* in the algorithm). Most of these have been confirmed as independent risk factors for neutropenic complications in a risk model developed by Lyman et al that was validated in a study population of 3760 patients with cancer beginning chemotherapy treatment.[118] This model and its associated risk factors have been retrospectively validated both internally and externally in an independent patient population.[119]

Patients at High Risk for FN

The NCCN Guidelines recommend prophylactic use of MGFs if the risk of developing FN is >20%. The most recent updates of the ASCO and EORTC guidelines both adopted the 20% threshold for considering routine prophylactic MGF support.[12,120]

These consistent recommendations are based on the results of several large randomized trials that have documented a significant reduction of FN following primary prophylaxis when the risk of FN without prophylaxis is 20%. For example, Vogel et al[23] reported the results of a double-blind, randomized, placebo-controlled, multicenter study to demonstrate whether prophylactic MGF support with pegfilgrastim would significantly reduce FN with a regimen that had previously been associated with an expected FN incidence of 20%.[23] Women with breast cancer receiving docetaxel at 100 mg/m^2 every 3 weeks were randomized to receive a placebo injection (n = 465) or pegfilgrastim (n = 463), each administered 24 hours after chemotherapy. The placebo group had a 17% overall incidence of FN; by contrast, the pegfilgrastim group had a 1% incidence. In the pegfilgrastim group, the incidence of hospitalization was reduced from 14% to 1%, and the use of IV anti-infectives was reduced from 10% to 2% (P < .001). In cycle 1, there was an 11% rate of FN in the placebo group versus a <1% rate in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN while the pegfilgrastim group had a rate of <1%.

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.[21] In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with 9 patients (10%) in the antibiotics plus G-CSF group (P = .01). In cycles 2 through 5, the incidences of FN were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis combined with primary antibiotic prophylaxis was effective in reducing FN and infections in patients with small cell lung cancer when given with the first cycle of chemotherapy. Furthermore, this strategy could be considered for other patients with cancer who have a high risk of FN. However, evidence on antimicrobial prophylaxis use, and associated chemotherapy-related infection risk, in U.S. clinical practice is limited. A retrospective study found that 22% of all non-metastatic breast cancer, 15% of non-metastatic colorectal cancer, 15% of non-metastatic lung cancer, and 21% of NHL patients received antimicrobial prophylaxis in ≥1 chemotherapy cycle.[121] Chemotherapy-related infection risk ranged from 3% to 6% across cancer types among subjects who received antimicrobial prophylaxis; 38% to 67% of these patients required hospitalization. Therefore, the use of antimicrobial prophylaxis during myelosuppressive chemotherapy is not uncommon in clinical practice, although a minority of patients still develop serious infections.

The NCCN, ASCO, and EORTC guidelines all recognize a variety of special circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens are at a high risk for FN due to bone marrow compromise or comorbidities. Prophylactic MGF is recommended for any patient considered to be at high risk, regardless of the treatment intent.

Patients at Intermediate Risk for FN

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

Patients at Low Risk for FN

For low-risk patients, as defined by risk <10%, routine use of MGF is not recommended as alternative treatment options are appropriate and more cost-effective.[94,122,123] However, MGF may be considered if the patient is receiving curative or adjuvant treatment and is at a significant risk for serious medical consequences of FN, including death.

Evaluation of Subsequent Chemotherapy Cycles

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

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

Dosing and Administration

Filgrastim, filgrastim-sndz, tbo-filgrastim, pegfilgrastim, and sargramostim are FDA-approved options for the prevention of FN. While data from randomized studies support the use of filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on its use following induction therapy for AML and in various HCT settings. The subcutaneous administration of filgrastim, filgrastim-sndz, tbo-filgrastim, or pegfilgrastim is a category 1 recommendation for the prevention of FN. Sargramostim is no longer recommended in this setting. The NCCN Panel does not routinely recommend prophylactic antibiotics for standard-dose chemotherapy. In addition, prophylactic use of MGFs in patients given concurrent chemotherapy and radiation has not been evaluated and is therefore not recommended.

Filgrastim, Tbo-filgrastim, Filgrastim-sndz

Initial doses of filgrastim are administered the next day or up to 3 to 4 days after completion of chemotherapy in a daily dose of 5 mcg/kg until post-nadir ANC recovery is to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. Neutrophil counts should be monitored as indicated appropriate to the setting. The NCCN Panel

recommends treatment of patients through post-nadir recovery since studies have shown shorter durations of G-CSF treatment to be less efficacious.[124]

Pegfilgrastim

A systematic literature review evaluating the relative merits of same-day versus next-day dosing of pegfilgrastim found that administration of pegfilgrastim at least 24 hours after myelosuppressive chemotherapy resulted in improved patient outcomes across a variety of tumor types.[125] Furthermore, a retrospective evaluation by Weycker et al found that 50% of all FN hospitalization episodes, outcomes, and costs among cancer chemotherapy patients who were candidates for G-CSF prophylaxis occurred in those who either did not receive it or received it inconsistent with guideline recommendations, including receipt of pegfilgrastim on the same day as chemotherapy.[124]

Clinical trials both in support of and against same-day pegfilgrastim have been published. The original rationale for not giving same-day pegfilgrastim was the potential for increased neutropenia resulting from MGF stimulation of myeloid progenitors at the time of cytotoxic chemotherapy.[126-128] In a direct comparison, Kaufman et al[129] administered either same-day or next-day pegfilgrastim in women with breast cancer receiving docetaxel, doxorubicin, and cyclophosphamide. FN was observed in 33% of patients treated in the same-day group compared with only 11% of patients treated in the next-day group.[129] A similar trend was seen in a prospective, randomized, double-blind trial of patients receiving CHOP or CHOP-like therapy for NHL, where same-day pegfilgrastim was associated with enhanced myelosuppression and no reduction in leukopenia was seen.[130] However, despite longer duration of grade 4 neutropenia in the same-day group, there was no increase in the overall incidence of neutropenia, and the increased duration did not meet the non-inferiority margin. However, the study still recommends administration of pegfilgrastim 24 hours after chemotherapy.

Vance et al[131] published a retrospective review of same-day pegfilgrastim in patients with breast cancer receiving dose-dense doxorubicin and no increased neutropenia was observed. Another retrospective study from a community-based oncology practice showed similar incidence of myelosuppressive adverse events when comparing the two groups.[132] This study of 159 patients spanned 15 different tumor types and 50 different chemotherapy regimens.[132] A double-blind phase II study in patients with non-small cell lung cancer treated with carboplatin and docetaxel showed no increase of neutropenia nor any adverse events in patients receiving same-day pegfilgrastim compared with patients receiving next-day pegfilgrastim treatment.[133] Another study in patients with lung cancer showed an unexpectedly low rate of severe neutropenia (only 2 patients per group), suggesting that same-day filgrastim is a reasonable option.[133] Other retrospective studies in patients with gynecologic malignancies have also demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours of chemotherapy.[134,135]

Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient per chemotherapy cycle (category 1). Since most clinical studies administer the agent the day after chemotherapy completion, next-day administration is preferred.[58] Based on trials of filgrastim, panelists agreed that giving pegfilgrastim up to 3 to 4 days after chemotherapy is also reasonable. In addition, panelists recognized that some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize burdens on long-distance patients.[136] However, the recent FDA approval of a delivery device that can be applied the same day as chemotherapy and set to deliver the full dose of pegfilgrastim the following day

(approximately 27 hours after application) is an alternative to same-day administration for patients who cannot return to the clinic for next-day administration of pegfilgrastim.[137]

The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle lengths. Based on phase III clinical trials,[23,138] use of pegfilgrastim after chemotherapy regimens given every 3 weeks is a category 1 recommendation. Pegfilgrastim use is a category 2A recommendation for chemotherapy regimens given every 2 weeks, based on phase II studies.[139-144] There are insufficient data to support the dose and schedule for weekly regimens; therefore, pegfilgrastim should not be used.

Therapeutic Use of MGFs

Compared to prophylactic use, there is less evidence supporting the therapeutic use of MGFs for FN as an adjunct to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials,[47] Clark et al reported a shorter length of hospitalization (HR, 0.63; 95% CI, 0.49–0.82; *P* = .0006) and a shorter time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; *P* < .00001), but no improvement in OS, with the use of therapeutic MGFs. In an update to this review, Estcourt et al concluded that there is insufficient evidence to determine whether therapeutic MGFs affect all-cause mortality.[145] An earlier meta-analysis by Berghmans et al[146] also found no difference in mortality, but they were unable to assess other clinical benefits of MGF therapy. Conversely, in a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one patient risk factor to therapeutic G-CSF or placebo, the G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days, *P* = .0004), antibiotic therapy (median 5 vs. 6 days, *P* = .013), and hospital stay (median 5 vs. 7 days, *P* = .015).[147]

The NCCN Panel recommends that patients with FN who previously received prophylactic G-CSFs should continue with the same G-CSF. However, since pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional MGFs.[148] For patients who have not received prophylactic MGFs, the NCCN Panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome. These include: old age (>65 years); sepsis syndrome; severe (ANC <100 neutrophils/mcL) or anticipated prolonged (>10 days) neutropenia; pneumonia; invasive fungal infections or other clinically documented infections; hospitalization; and prior episode(s) of FN. If risk factors are present, MGFs should be considered. Filgrastim, filgrastim-sndz, or sargramostim may be administered in the therapeutic setting. Tbo-filgrastim and pegfilgrastim have only been studied for prophylactic use.

Dosing and Administration

If MGFs were not given prophylactically, filgrastim, filgrastim-sndz, and sargramostim are the recommended MGFs for the therapeutic treatment of FN in selected high-risk patients as outlined above (also see *Therapeutic Use of Myeloid Growth Factors for Febrile Neutropenia* in the algorithm). Filgrastim or filgrastim-sndz should be given at a daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) and sargramostim should be given at a dose of 250 mcg/m^2/d (rounding to the nearest vial size by institution-defined weight limits). Treatment should continue through post-nadir recovery. If G-CSFs were given prophylactically, the same G-CSF should be continued in the therapeutic setting.

Mobilization and Post Hematopoietic Cell Transplant

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

Mobilization with MGFs in the Autologous Setting

Mobilization of PBPCs by G-CSFs has largely replaced bone marrow collection for autologous transplantation due to the ease of collection, avoidance of general anesthesia, and more rapid recovery of blood counts.[149] Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and the incorporation of plerixafor with either approach. Most data are focused on filgrastim,[150-154] although studies suggest that single-dose pegfilgrastim may have similar efficacy.[155]

While apheresis usually commences on the fourth or fifth day of G-CSF initiation when it is used as a single agent, studies have shown that the addition of the CXCR4 inhibitor plerixafor to chemomobilization regimens accelerates the increase in PBPC count.[156-164] Plerixafor, in combination with G-CSF, is FDA-approved for mobilizing autologous hematopoietic stem cells to the peripheral blood in patients with NHL or multiple myeloma. The addition of plerixafor as a preemptive ("just in time") strategy in patients with insufficient CD34+ cell count after mobilization with growth factor with or without chemotherapy has been highly successful.[158,159,165,166] Patients who may benefit from such a strategy include those who are older, have been extensively pretreated, have had radiation to marrow-containing regions, or have had multiple cycles of certain agents such as fludarabine or lenalidomide.[157-160,165] However, it has been difficult to choose which patients will benefit from upfront addition of plerixafor; clinical trials that demonstrate clinical and cost-effectiveness of upfront plerixafor as compared to preemptive use are needed as parameters defining poor mobilization are not fully understood. Traditionally, parameters such as older age (>60 years) and platelet count (<100,000) have been used to predict poor mobilization. However, recent data suggest that prior exposure to lenalidomide and white blood cell count (<4000) were more strongly associated with poor mobilization than platelet count.[167] Additional studies have suggested there may also be genetic parameters that contribute to mobilization outcome.[168] Thus, there is increasing interest in developing predictive models for poor mobilization to identify patients most likely to benefit from upfront plerixafor. Olivieri et al recently proposed a predicted poor mobilizer (pPM) score, using criteria such as increasing age, diagnosis of NHL, positive bone marrow biopsy, cytopenias before mobilization, and previous mobilization failure, to help identify patients at high risk for poor mobilization.[169] Once validated in prospective trials designed to demonstrate clinical effectiveness, this model may become highly useful in avoiding likely mobilization failures. Another predictive model proposed by Musto et al used 4 parameters (age, baseline low peripheral blood cell count, use of lenalidomide, and hematologic toxicity developed during induction) to predict poor mobilization among multiple myeloma patients.[170] However, age and hematologic toxicity developed during induction were the only parameters that maintained statistical significance after multivariate analysis. Therefore, randomized trials are needed to validate the parameters proposed in predictive models for poor mobilization.

The effects of pegfilgrastim on mobilization are not well known.[155] One retrospective analysis demonstrated that pegfilgrastim resulted in a better PBPC yield than filgrastim, requiring less use of rescue plerixafor.[171] Another phase I clinical trial involving 12 patients with lymphoma or myeloma indicated that plerixafor plus pegfilgrastim is a simple, safe, and effective mobilization regimen in both poor and good mobilizers, and is superior to pegfilgrastim alone.[172] However, larger

randomized trials that address the effect of plerixafor when used in combination with pegfilgrastim are needed.

While filgrastim-sndz has been accepted as an equivalent treatment option to filgrastim for patients with FN, there is discussion among medical professionals regarding its equivalency in hematopoietic cell mobilization or in patients with chronic neutropenia.[173] There are data to support the use of filgrastim-sndz in the autologous HCT setting.[174-179] However, the panel acknowledges the limitations of these studies regarding long-term outcomes and the potential impact of the different manufacturing processes for biosimilars. Therefore, while it is reasonable to substitute with filgrastim-sndz, clinicians should be aware of any complications presented in the literature or in their patients. Accurate and timely disclosure of any variation in expected outcome with the biosimilar compared to the originator filgrastim will be of paramount importance.

Studies using GM-CSFs as single mobilization agents or in sequential combination with G-CSFs also reported good yields of PBPC in normal donors.[180-182] Although both MGFs have been used for mobilization, G-CSFs have been favored for this purpose.[183] The use of concurrent filgrastim or filgrastim-sndz and sargramostim is a category 2B recommendation. For select patients with NHL or multiple myeloma, filgrastim, filgrastim-sndz, or tbo-filgrastim can be given followed by plerixafor.

The NCCN Panel recommends administration of filgrastim, filgrastim-sndz, or tbo-filgrastim as a single agent[150,184,185] or as part of a chemo-mobilization regimen,[186-188] starting about 24 hours after completion of chemotherapy. Combination chemomobilization regimens may result in higher collection yields with fewer days of apheresis and may reduce residual tumor burden, but may also increase the rate of hospitalizations for neutropenic fever.[189] Several regimens are effective in chemomobilization of hematopoietic progenitors, including cyclophosphamide,[187] ICE,[188] DHAP,[188] VTD-PACE,[186] and others.

Mobilization with MGFs in the Allogeneic Setting

Initially, there were concerns about mobilization in the allogeneic setting due to normal donor toxicity and the risk for graft-versus-host disease (GVHD) in the recipient, but studies have demonstrated G-CSFs to be well-tolerated by donors without an effect on long-term survival.[151-153] Tbo-filgrastim has also been shown to mobilize PBPCs for allogeneic transplantation in both healthy donors and in patients with multiple myeloma and lymphoma; however, the data are limited and mobilization is not listed as an approved indication.[190-192] Studies of filgrastim-sndz have been predominately in the settings of autologous PBPC mobilization and in support of count recovery after transplantation, whereas data are sparse in the allogeneic setting. Smaller studies in allogeneic progenitor cell donors have suggested that there are no short-term safety issues;[193-195] however, long-term data are needed. A single retrospective study of filgrastim-sndz in comparison to filgrastim for mobilization in normal donors reported that 3 out of 18 donors in the filgrastim-sndz group failed mobilization, while there were no mobilization failures in the filgrastim group.[196] Neutrophil and platelet count recoveries after allogeneic transplant were similar in both arms. The World Marrow Donor Association recommends against the use of filgrastim biosimilars in unrelated donors based on extrapolation from autologous transplant data.[197]

The NCCN Panel recommends single-agent filgrastim (category 2A, preferred), filgrastim-sndz (category 2B), or tbo-filgrastim (category 2B) for allogeneic hematopoietic cell mobilization and for granulocyte transfusion. The use of plerixafor in normal donors (category 2B) is currently under study.[198-200]

MGFs as Part of Supportive Care After Transplant

Consensus is lacking on the use of MGFs in the post-transplant setting. G-CSF administration after high-dose chemotherapy and autologous PBPC transplantation has been shown to expedite neutrophil recovery in prospective randomized trials.[201-205] However, results were inconclusive on the impact of G-CSFs on duration of hospital stay, infections, and survival. A systematic review comparing filgrastim and pegfilgrastim in the autologous setting, which included a randomized trial of 80 patients,[206] concluded that the two are at least equally effective.[207]

Similarly, data are conflicting on G-CSF use as a supportive care measure for allogeneic transplant recipients, with some studies associating G-CSFs with worse clinical outcomes.[208] However, it has been used routinely to alleviate the delayed recovery of blood counts after umbilical cord blood transplant, because there is a significant delay in the rate and kinetics of neutrophil and platelet engraftment after cord blood transplant as compared to marrow or mobilized PBPC grafts.[209]

The NCCN Panel recommends the use of filgrastim, filgrastim-sndz, tbo-filgrastim, or pegfilgrastim in the supportive care setting for post-autologous HCT.[206,210-216] Filgrastim, filgrastim-sndz, and tbo-filgrastim are also recommended for haploidentical stem cell transplant and cord blood transplant.[209]

Dosing and Administration

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

Severe Chronic Neutropenia

The NCCN Guidelines for Myeloid Growth Factors focus on chemotherapy-induced neutropenia in the cancer setting; therefore, severe chronic neutropenia that requires G-CSF therapy is only briefly discussed below. G-CSF is established as an effective treatment for cyclic, congenital, and idiopathic neutropenia based on a randomized controlled trial involving 123 patients.[217] In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers, and infections. Subsequent observational studies showed that patients with idiopathic and cyclic neutropenia generally responded to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF administration (1–3 mcg/kg/d). Congenital neutropenia patients generally require higher doses (3–10 mcg/kg/d). All patients should have doses adjusted to maintain a blood neutrophil level in the normal or low-normal range. Acute adverse effects include bone pain, arthralgias, and myalgias, which usually diminish in the first few weeks of treatment. The greatest concern is that patients with the diagnosis of severe congenital neutropenia are at risk for myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, as reflected by the requirement of higher doses of G-CSFs, 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 HCT. For further reading on chronic neutropenia, refer to the website developed by The Severe Chronic Neutropenia International Registry: http://depts.washington.edu/registry/index.html.

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