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Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Growth Factors

Version 2.2019 — March 27, 2019

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[Summary of the Guidelines Updates](#)

Management of Neutropenia

- [Evaluation, Risk Assessment, and Prophylactic Use of Myeloid Growth Factors \(MGF-1\)](#)
- [Additional Evaluation of Patient Risk Factors for Prophylactic Use of MGFs \(MGF-2\)](#)
- [Secondary Prophylaxis with MGFs \(MGF-3\)](#)
- [Therapeutic Use of MGFs \(MGF-4\)](#)
- [Examples of Disease Settings and Chemotherapy Regimens with a High/Intermediate Risk for Febrile Neutropenia \(MGF-A\)](#)
- [G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery \(MGF-B\)](#)
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Management of Cancer- and Chemotherapy-Induced Anemia

- [Evaluation of Anemia \(ANEM-1\)](#)
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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/clinicians.aspx](#).

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

See [NCCN Categories of Evidence and Consensus](#).

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Updates in Version 2.2019 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 1.2019 include:

MS-1

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

Updates in Version 1.2019 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 2.2018 of the NCCN Guidelines for Myeloid Growth Factors include:

General

- NCCN Guidelines for Hematopoietic Growth Factors is a new guideline that combines the prior NCCN Guidelines for Myeloid Growth Factors, and the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia.

MGF-1

- Footnote f added: In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.
- Footnote h modified: G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, *filgrastim-aafi*, tbo-filgrastim, and pegfilgrastim, *pegfilgrastim-jmdb* and *pegfilgrastim-cbqv*.

MGF-4

- Page heading modified: Therapeutic Use of Myeloid Growth Factors (MGF) for Febrile Neutropenia
- Pathway added for patients who present with acute exposure to myelosuppressive doses of RT. Therapeutic MGF is recommended.
- Patients receiving or those who received prophylactic G-CSF
 - ▶ First pathway modified: Patients receiving daily prophylactic filgrastim, filgrastim-sndz, *filgrastim-aafi*, or tbo-filgrastim
 - ▶ Second pathway modified: Patients who have received long-lasting prophylactic pegfilgrastim, *pegfilgrastim-jmdb* or *pegfilgrastim-cbqv*
- Footnote o modified: ~~See Possible Indications for the Initiation of Therapeutic MGF for Management of Febrile Neutropenia (MGF-C).~~ *Risk factors/possible indications for therapeutic MGF include 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, and prior episode of febrile neutropenia.*
- Footnote q modified: ~~Tbo-filgrastim and Pegfilgrastim/pegfilgrastim-jmdb/pegfilgrastim-cbqv~~ have only been studied for prophylactic use. Filgrastim, filgrastim-sndz, *filgrastim-aafi*, tbo-filgrastim or sargramostim may be used therapeutically...
- Footnote r added: Filgrastim/filgrastim-sndz/filgrastim-aafi/tbo-filgrastim: Daily dose of 5 mcg/kg; Sargramostim: used in clinical trials at a dose of 250 mcg/m²/d. Continue therapeutic MGF until post-nadir ANC recovery to normal or near normal levels by laboratory standards.
- Footnote s added: Therapeutic options include filgrastim/filgrastim-sndz/filgrastim-aafi, tbo-filgrastim, pegfilgrastim/pegfilgrastim-jmdb/pegfilgrastim-cbqv, and sargramostim.

[Continued](#)

UPDATES



Updates in Version 1.2019 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 2.2018 of the NCCN Guidelines for Myeloid Growth Factors include:

MGF-A (1 of 5)

- Fourth bullet added: In general, dose-dense regimens require myeloid growth factor support to maintain dose intensity and schedule.
- Examples of regimens with a high risk for febrile neutropenia:
 - Bone cancer regimens added:
 - ◊ VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)
 - ◊ VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)
 - ◊ VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)
- Head and Neck Squamous Cell Carcinoma regimen added: TPF (docetaxel, cisplatin, 5-fluorouracil)
- Hodgkin lymphoma regimen added: Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)
- The following testicular cancer regimen has been moved from the list of examples of high-risk regimens to the list of examples of intermediate-risk regimens on MGF-A (2 of 5): BEP (bleomycin, etoposide, cisplatin)
- Footnote c added: Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSF. See Toxicity Risks with Myeloid Growth Factors (MGF-D).

MGF-A (2 of 5)

- Examples of regimens with an intermediate risk for febrile neutropenia:
 - Bone cancer regimens added:
 - ◊ Cisplatin/doxorubicin
 - ◊ VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)
 - Breast cancer regimen removed: FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel

MGF-A (3 of 5), (4 of 5), and (5 of 5)

- References have been updated.

MGF-B

- First bullet, added the following prophylactic G-CSF option: filgrastim-aafi (category 1)
- Second bullet
 - Prophylactic G-CSF options added: pegfilgrastim-jmdb/pegfilgrastim-cbqv
 - First sub-bullet modified: One dose of 6 mg per cycle of treatment
 - Sub-bullets added:
 - ◊ There should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy.
 - ◊ If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment.
- Footnote b modified: Filgrastim-sndz and filgrastim-aafi are FDA-approved biosimilars. ~~is the first biosimilar to be approved by the FDA. The panel lacks sufficient data for consideration of filgrastim-aafi, which was recently approved by the FDA as a growth factor.~~ See Discussion for more details. (Also on MGF-C)
- Footnote removed: The panel lacks sufficient data for consideration of pegfilgrastim-jmdb which was recently approved by the FDA as a growth factor.

MGF-C

- Filgrastim-aafi has been added as an option where filgrastim/filgrastim-sndz is listed with the same category of evidence.

MGF-C (2 of 4)

- Table has been added with recommended plerixafor dose, along with the reference in footnote d: U.S. Food and Drug Administration. Plerixafor label information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022311s018lbl.pdf. Accessed January 30, 2019.

MGF-D

- Toxicity risk warnings for sargramostim have been simplified.

[Continued](#)

UPDATES



Updates in Version 1.2019 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 3.2018 of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia include:

[ANEM-2](#)

- Footnote e added: The AABB has made recommendations regarding appropriate levels for RBC transfusion. See Discussion for details.

[ANEM-3](#)

- Below the table, added: When considering RBC transfusion, see AABB Clinical Practice Guidelines: Tobian AA, Heddle NM, Wiegmann TL, Carson JL. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. *Transfusion* 2016;56:2627-2630.

[ANEM-A \(1 of 5\)](#)

- Added footnote **: No response is defined as hemoglobin increase less than 1 g/dL and remains below 10 g/dL after the initial 4 weeks of epoetin or 6 weeks of darbepoetin. Discontinue therapy after 8 weeks if no response.

[ANEM-A \(2 of 5\)](#)

- Footnote e added: See prescribing information for perioperative DVT prophylaxis.

[ANEM-B](#)

- Table updated to include ferric carboxymaltose (in select cases) and ferumoxytol (in select cases).
 - ▶ Footnote c modified: Ferric carboxymaltose has not been prospectively evaluated *in patients with cancer- or chemotherapy-induced anemia* and therefore should only be considered when other parenteral iron preparations fail.
 - ▶ Footnote d modified: Ferumoxytol is indicated for the treatment of iron deficiency anemia *in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or those with chronic kidney disease*. There are no data to show the efficacy of ferumoxytol in patients with cancer. Ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.
- Footnote a added: Five of six studies suggest that parenteral iron products improve Hb response rates in treating absolute or functional iron deficiency in patients with cancer who are receiving ESAs.
- Footnote b, last line added: Ferric carboxymaltose has been associated with severe phosphate deficiency.

[ANEM-C \(1 of 2\)](#)

- Second bullet modified: "...pure oxygen (400 mm Hg, SaO₂ = 1.0) *by mechanical ventilation* has been..."
- Third bullet modified: "...use pediatric tubes, *return discard in closed system*..."
- Fifth bullet modified: Consider use of ESAs for select patients by FDA dosing/dosing adjustments, *given there is no option for transfusion*.
- Last bullet and sub-bullet text added:
 - ▶ Blood substitutes: A clinician may obtain access to investigational blood substitute products for a single patient by submitting an Expanded Access - Investigational New Drug Application (IND) through the FDA.

[ANEM-C \(2 of 2\)](#)

- References added.

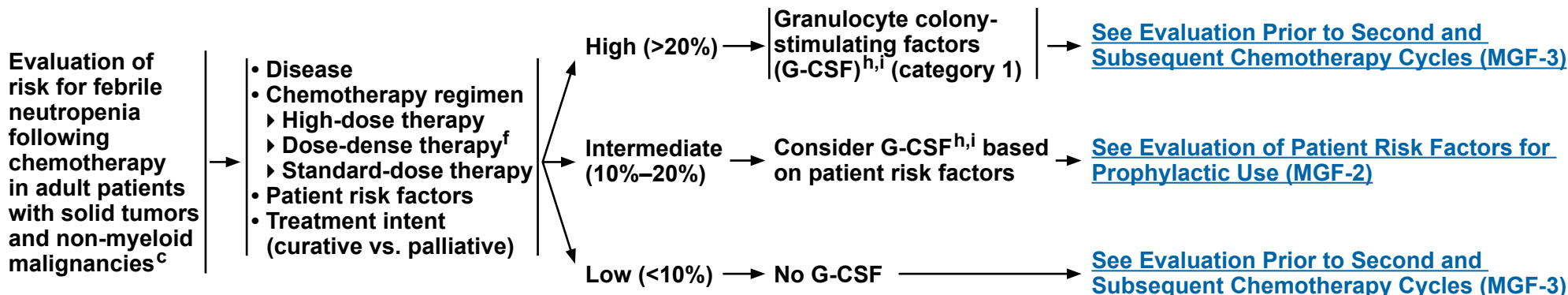


EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE^{a,b}

RISK ASSESSMENT^d FOR FEBRILE NEUTROPENIA^e

OVERALL FEBRILE NEUTROPENIA RISK

PROPHYLACTIC USE OF G-CSF FOR FEBRILE NEUTROPENIA CURATIVE/ADJUVANT OR PALLIATIVE SETTING^g



^aThe NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.

^bPatients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with myeloid growth factor (MGF) as clinically indicated, unless precluded by trial specifications.

^cFor 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](#).

^dThere 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](#)).

^eFebrile neutropenia is defined as single temperature: $\geq 38.3^{\circ}\text{C}$ orally or $\geq 38.0^{\circ}\text{C}$ 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](#).

^fIn general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

^g[See Toxicity Risks with Myeloid Growth Factors \(MGF-D\)](#).

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

ⁱThere 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.

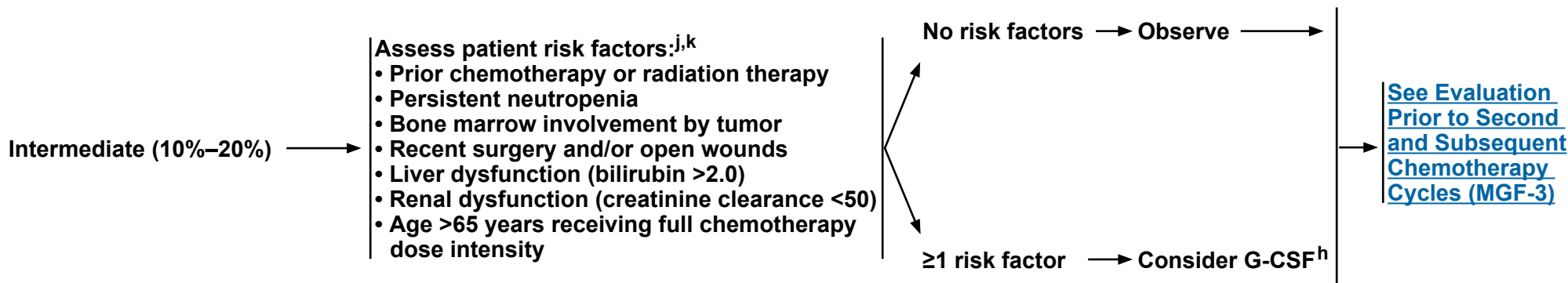
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



OVERALL FEBRILE NEUTROPENIA^e RISK

PATIENT RISK FACTORS ASSESSMENT

PROPHYLACTIC USE OF G-CSF FOR FEBRILE NEUTROPENIA



^eFebrile 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.](#)

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

^jOther 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 hematopoietic 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)

^kOther factors may warrant the use of G-CSF (eg, chronic immunosuppression in the post-transplant setting, including organ transplant).

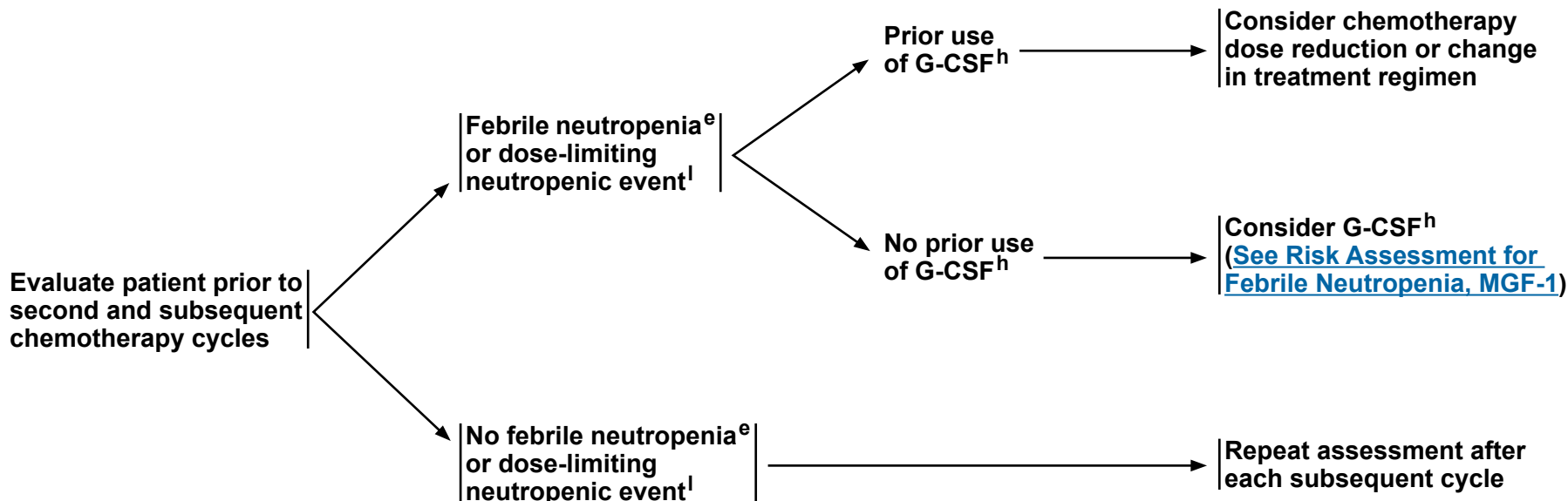
Note: All recommendations are category 2A unless otherwise indicated.

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EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



^eFebrile 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.](#)

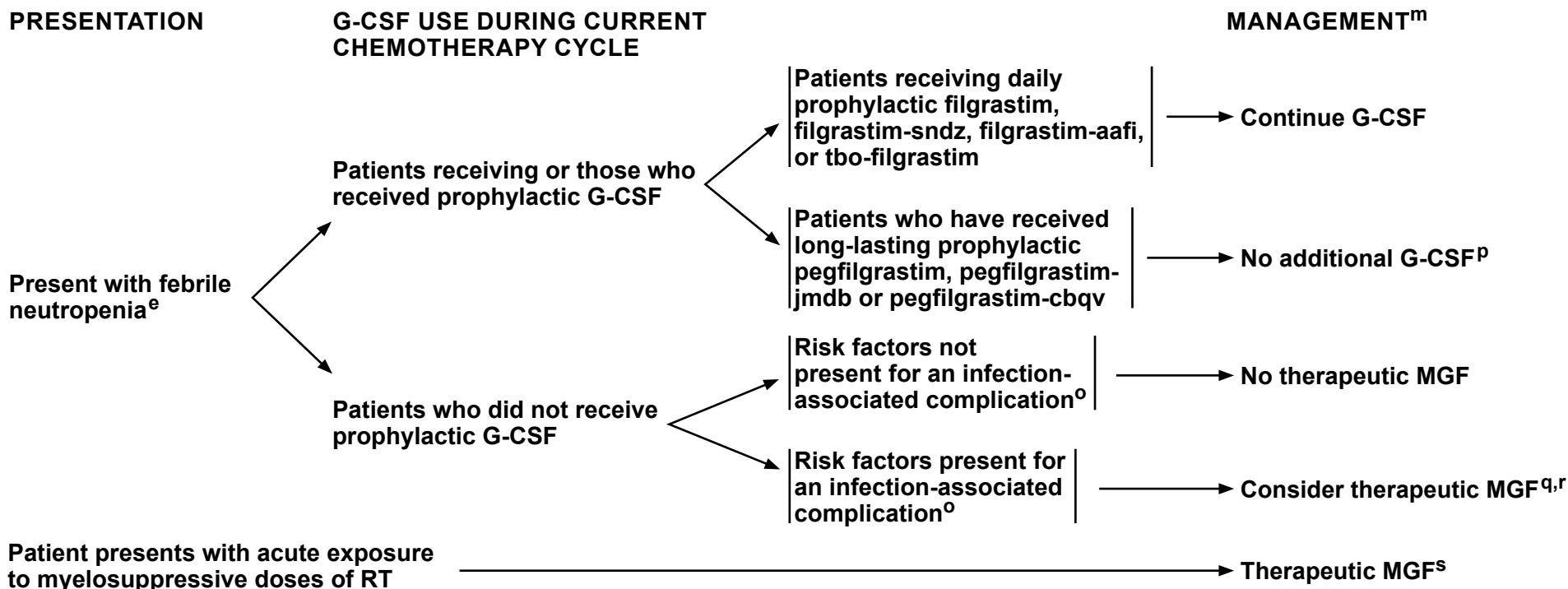
^hG-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, filgrastim-aafi, tbo-filgrastim, pegfilgrastim, pegfilgrastim-jmdb and pegfilgrastim-cbqv. [See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery \(MGF-B\).](#)

^lDose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy.

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

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THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGF)^{e,m,n}



^eFebrile 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.](#)

^mFor antibiotic therapy recommendations for fever and neutropenia, see the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.](#)

ⁿThe decision to use MGF in the therapeutic setting is controversial. [See Discussion](#) for further details.

^oRisk factors/possible indications for therapeutic MGF include 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, and prior episode of febrile neutropenia.

^pThere 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.

^q[See Discussion](#) for further details. Pegfilgrastim/pegfilgrastim-jmdb/pegfilgrastim-cbqv have only been studied for prophylactic use. Filgrastim, filgrastim-sndz, filgrastim-aafi, tbo-filgrastim or sargramostim may be used therapeutically with initial dosing and discontinued at time of neutrophil recovery.

^rFilgrastim/filgrastim-sndz/filgrastim-aafi/tbo-filgrastim: Daily dose of 5 mcg/kg; Sargramostim: used in clinical trials at a dose of 250 mcg/m² per day. Continue therapeutic MGF until post-nadir ANC recovery to normal or near normal levels by laboratory standards.

^sTherapeutic options include filgrastim/filgrastim-sndz/filgrastim-aafi, tbo-filgrastim, pegfilgrastim/pegfilgrastim-jmdb/pegfilgrastim-cbqv, and sargramostim.

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](#))
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Acute Lymphoblastic Leukemia (ALL)

- Select ALL regimens as directed by treatment protocol ([See NCCN Guidelines for ALL](#))

Bladder Cancer

- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)¹

Bone Cancer

- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)²
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)³
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)⁴

Breast Cancer

- Dose-dense AC followed by T (doxorubicin, cyclophosphamide, paclitaxel)⁵
- TAC (docetaxel, doxorubicin, cyclophosphamide)⁶
- TC^{a,b} (docetaxel, cyclophosphamide)⁷
- TCH^a (docetaxel, carboplatin, trastuzumab)⁸

Head and Neck Squamous Cell Carcinoma

- TPF (docetaxel, cisplatin, 5-fluorouracil)⁹⁻¹¹

Hodgkin Lymphoma

- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)¹²
- Escalated BEACOPP^c (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)¹³

Kidney Cancer

- Doxorubicin/gemcitabine¹⁴

Non-Hodgkin's Lymphomas

- Dose-adjusted EPOCH^a (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)¹⁵
- ICE (ifosfamide, carboplatin, etoposide)^{a,16,17}
- Dose-dense CHOP-14^a (cyclophosphamide, doxorubicin, vincristine, prednisone)^{18,19}
- MINE^a (mesna, ifosfamide, mitoxantrone, etoposide)²⁰
- DHAP^a (dexamethasone, cisplatin, cytarabine)²¹
- ESHAP^a (etoposide, methylprednisolone, cisplatin, cytarabine)²²
- HyperCVAD^a (cyclophosphamide, vincristine, doxorubicin, dexamethasone)^{23,24}

Melanoma

- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)²⁵

Multiple Myeloma

- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)²⁶ ± bortezomib (VTD-PACE)²⁷

Ovarian Cancer

- Topotecan^{a,28}
- Docetaxel²⁹

Soft Tissue Sarcoma

- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)³⁰
- Doxorubicin^{a,31}
- Ifosfamide/doxorubicin³²

Small Cell Lung Cancer

- Topotecan³³

Testicular Cancer

- VEP (vinblastine, ifosfamide, cisplatin)³⁴
- VIP (etoposide, ifosfamide, cisplatin)³⁵
- TIP (paclitaxel, ifosfamide, cisplatin)³⁵

[See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A \(2 of 5\)](#)

^aGuidelines 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](#).

^bRisk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

^cRisk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSF. [See Toxicity Risks with Myeloid Growth Factors \(MGF-D\)](#).

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.

[References](#)



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](#))
- In general, dose-dense regimens require myeloid growth factor support to maintain dose intensity and schedule.

Occult Primary- Adenocarcinoma

- Gemcitabine/docetaxel³⁶

Bone Cancer

- Cisplatin/doxorubicin³⁷
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)³⁸

Breast Cancer

- Docetaxel^{a,39,40}
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)^{a,41}
- Paclitaxel every 21 days^{a,42}

Cervical Cancer

- Cisplatin/topotecan⁴³⁻⁴⁵
- Paclitaxel/cisplatin^{a,45}
- Topotecan⁴⁶
- Irinotecan⁴⁷

Colorectal Cancer

- FOLFOX^a (fluorouracil, leucovorin, oxaliplatin)⁴⁸

Esophageal and Gastric Cancers

- Irinotecan/cisplatin^{a,49}
- Epirubicin/cisplatin/5-fluorouracil⁵⁰
- Epirubicin/cisplatin/capecitabine⁵⁰

Non-Hodgkin's Lymphomas

- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)^{a,51}
- CHOP^a (cyclophosphamide, doxorubicin, vincristine, prednisone)^{52,53} including regimens with pegylated liposomal doxorubicin^{54,55}

Non-Small Cell Lung Cancer

- Cisplatin/paclitaxel⁵⁶
- Cisplatin/vinorelbine⁵⁷
- Cisplatin/docetaxel^{56,58}
- Cisplatin/etoposide⁵⁹
- Carboplatin/paclitaxel^{a,d,60}
- Docetaxel⁵⁸

Ovarian Cancer

- Carboplatin/docetaxel⁶¹

Pancreatic Cancer

- FOLFIRINOX^e

Prostate Cancer

- Cabazitaxel^{f,62}

Small Cell Lung Cancer

- Etoposide/carboplatin⁶³

Testicular Cancer

- BEP^c (bleomycin, etoposide, cisplatin)⁶⁴⁻⁶⁶
- Etoposide/cisplatin⁶⁷

Uterine Sarcoma

- Docetaxel⁶⁸

^aGuidelines 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](#).

^cRisk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSF. [See Toxicity Risks with Myeloid Growth Factors \(MGF-D\)](#).

^dIf carboplatin dose is AUC >6 and/or patient is of Japanese ancestry.

^eA small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting⁶⁹ 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).⁷⁰ While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

^fThe 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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G-CSF FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim (category 1), tbo-filgrastim^a (category 1), filgrastim-sndz^b (category 1), or filgrastim-aafi^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 myelosuppressive chemotherapy and treat through post-nadir recovery.^{c,d}
- Pegfilgrastim (category 1), pegfilgrastim-jmdb, or pegfilgrastim-cbqv
 - ▶ One dose of 6 mg
 - ◊ Based on clinical trial data, pegfilgrastim/pegfilgrastim-jmdb/pegfilgrastim-cbqv should be administered the day after myelosuppressive chemotherapy (category 1).^f
 - ◊ There should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy.
 - ◊ If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment.
 - ◊ 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).^{g,h}
 - ◊ 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 \(MGF-D\)](#)

^aTbo-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.

^bFilgrastim-sndz and filgrastim-aafi are FDA-approved biosimilars. [See Discussion](#) for more details.

^cStudies suggest that shorter durations of G-CSF 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.)

^dNeutrophil counts should be monitored, as indicated, appropriate to the setting.

^fLyman 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.

^gRarely, there is a failure to inject that requires further medical attention.

^hYang BB, Morrow PK, Wu X, et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 2015;75:1199-1206.

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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, filgrastim-sndz,^a filgrastim-aafi,^a or tbo-filgrastim

◊ Dose: 10–32 mcg/kg per day 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/filgrastim-aafi^a/tbo-filgrastim with the goal of mobilization during count recovery⁴⁻⁶ 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/filgrastim-aafi^a/tbo-filgrastim is started about 24 hours after completion of chemotherapy.

• Concurrent filgrastim/filgrastim-sndz^a/filgrastim-aafi^a + sargramostim (category 2B)

▶ Filgrastim/filgrastim-sndz^a/filgrastim-aafi^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/filgrastim-aafi^a/tbo-filgrastim + plerixafor⁹⁻¹⁴

▶ 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's lymphoma and multiple myeloma.

▶ Existing literature suggests that a preemptive "just in time" strategy of adding plerixafor for patients who do not mount a sufficient CD34+ cell count is highly successful.¹⁵⁻¹⁷

▶ There are 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: [See MGF-C \(2 of 4\)](#)

[See Toxicity Risks with Myeloid Growth Factors \(MGF-D\)](#)

^aFilgrastim-sndz and filgrastim-aafi are FDA-approved biosimilars. [See Discussion](#) for more details.

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[Continued](#)

[References](#)

MGF-C
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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

► Dosing for MGF and plerixafor:

- ◊ Filgrastim/filgrastim-sndz^a/filgrastim-aafi^a/tbo-filgrastim dose: 10 mcg/kg per day 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).
- ◊ Repeat plerixafor dose up to 4 consecutive days.
- ◊ Recommended plerixafor dose:^d

Estimated Creatinine Clearance	Dose	
	Body weight ≤83 kg	Body weight >83 kg and <160 kg
>50 (mL/min)	20 mg or 0.24 mg/kg once daily	0.24 mg/kg once daily (not to exceed 40 mg/d)
≤50 (mL/min)	13 mg or 0.16 mg/kg once daily	0.16 mg/kg once daily (not to exceed 27 mg/d)

Mobilization of Allogeneic Donors

• Allogeneic hematopoietic cell donors:¹⁸⁻²¹

- Filgrastim (preferred), filgrastim-sndz^a (category 2B), filgrastim-aafi^a (category 2B), or tbo-filgrastim (category 2B)
 - ◊ Dose: 10–16 mcg/kg per day 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, filgrastim-sndz^a (category 2B), filgrastim-aafi^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} filgrastim-sndz,^a filgrastim-aafi,^a or tbo-filgrastim
 - Post-autologous hematopoietic cell transplant, haploidentical transplant, or cord blood transplant
 - 5 mcg/kg per day. Begin day 5–7 post transplant until recovery of ANC (eg, >1.5 x 10⁹/L x 2 d).^c
- Pegfilgrastim³⁰⁻³⁶. Post-autologous hematopoietic cell transplant

[See Toxicity Risks with Myeloid Growth Factors \(MGF-D\)](#)

^aFilgrastim-sndz and filgrastim-aafi are FDA-approved biosimilars. [See Discussion](#) for more details.

^bFilgrastim accelerates neutrophil recovery but has not impacted survival. [See Discussion](#) for details.

^cFor additional dosing information refer to the package insert.

^dU.S. Food and Drug Administration. Plerixafor label information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022311s018lbl.pdf. Accessed March 7, 2019.

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.

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

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

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[Continued](#)

MGF-C
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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT REFERENCES

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TOXICITY RISKS WITH MYELOID GROWTH FACTORS

Filgrastim and Pegfilgrastim Including Derivative Products^{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**
 - ▶ **Respiratory symptoms**
 - ▶ **Cardiovascular symptoms:** Use with caution in patients with preexisting cardiac disease.
 - ▶ **Renal and hepatic dysfunction:** Monitor patients who display renal or hepatic dysfunction prior to initiation of treatment.
- **Adverse events occurring in >10% of patients receiving sargramostim**
 - ▶ **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**

^aSee full prescribing information for specific product information.

^bNot all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim, pegfilgrastim, and biosimilars.

^cThe 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.

^eLyman 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.

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Management of Cancer- and Chemotherapy-Induced Anemia

HEMOGLOBIN CONCENTRATION TO PROMPT AN EVALUATION OF ANEMIA

EVALUATION OF ANEMIA^{a,b}

Hemoglobin
(Hb) ≤11 g/dL
or ≥2 g/dL
below baseline

- CBC with indices
- Blood smear morphology

Evaluate anemia for possible cause as indicated^b ([see Discussion](#)):

- First check
 - Reticulocyte count^c and mean corpuscular volume (MCV)
- Then consider
 - Hemorrhage (stool guaiac, endoscopy)
 - Hemolysis (ie, direct antiglobulin test [DAT], disseminated intravascular coagulation [DIC] panel, haptoglobin, indirect bilirubin, lactate dehydrogenase)
 - Nutritional (ie, iron, total iron-binding capacity, ferritin, B₁₂, folate)^d
 - Inherited (ie, prior history, family history)
 - Renal dysfunction (Glomerular filtration rate [GFR] <60 mL/min/1.73 m²)
 - Radiation-induced myelosuppression
 - Hormone dysfunction (ie, hypogonadism, adrenal dysfunction, hyper/hypothyroidism)
- [See Evaluation of Iron Deficiency \(ANEM-5\)](#)

Treat as indicated

No cause identified

[See Risk Assessment and Indications for Transfusion \(ANEM-2\)](#)

Myelodysplastic syndromes

[See NCCN Guidelines for Myelodysplastic Syndromes](#)

Myeloid malignancies or
Acute lymphoblastic leukemia

[Treat underlying disease per NCCN Guideline](#)
[See NCCN Guidelines Table of Contents](#)

^aThe NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.

^bThis is a basic evaluation for possible causes of anemia.

^cCorrect reticulocyte count for degree of anemia. [See Discussion](#).

^dThe ferritin value indicating iron deficiency is laboratory-specific. In general, the lower the level of ferritin, the higher the probability that the patient has true iron deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin. Additionally, if serum iron studies are not performed while the patient is fasting or if the patient has taken a recent oral iron tablet, serum iron levels may be falsely elevated, and thus also falsely elevate the percent transferrin saturation. Fasting is preferred when testing for serum iron and total iron-binding capacity.

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

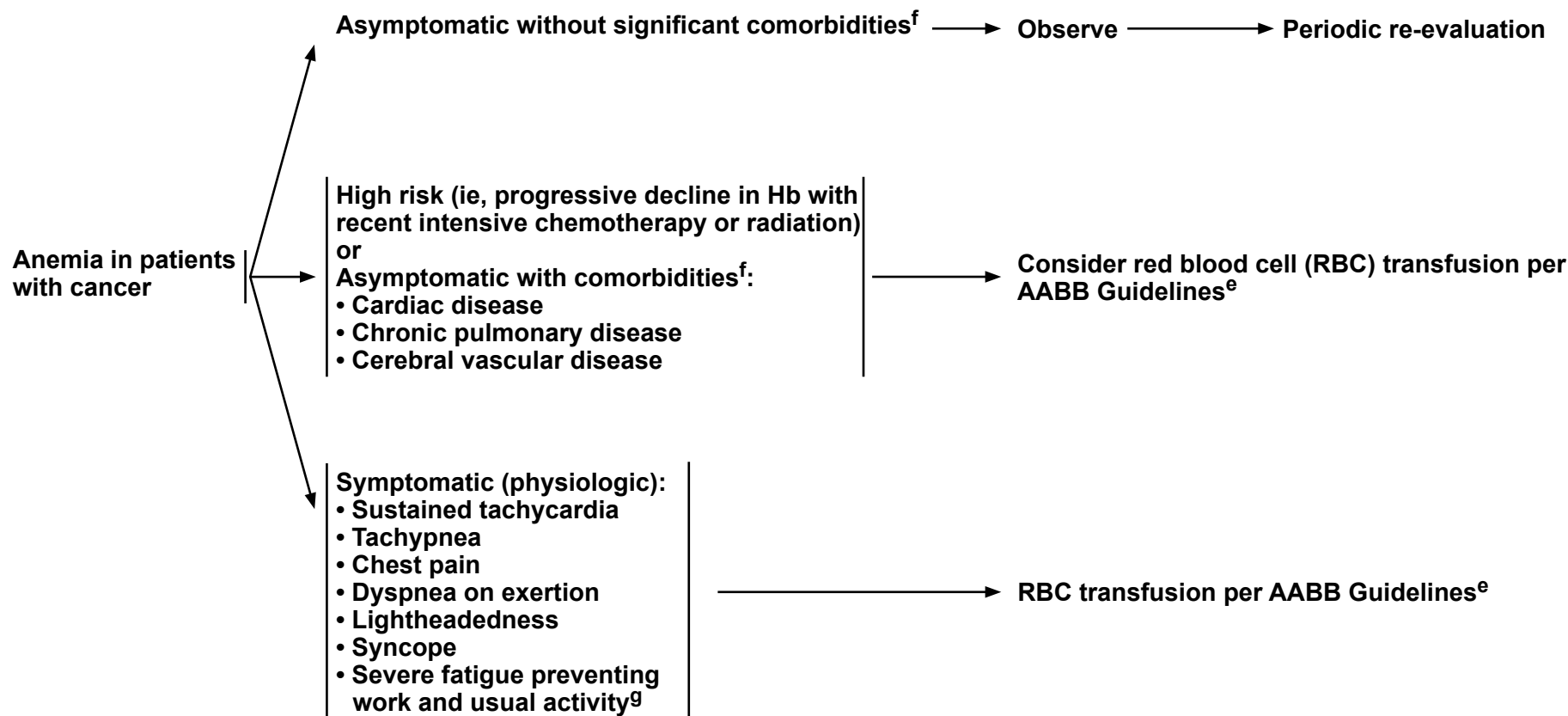
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Management of Cancer- and Chemotherapy-Induced Anemia

RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING^e



[See Comparison of Risks and Goals of ESA Use Versus RBC Transfusion \(ANEM-3\)](#)

[See Special Categories in Considering ESA Use \(ANEM-4\)](#)

^eThe AABB has made recommendations regarding appropriate indications for RBC transfusion. [See Discussion](#) for details.

^fDegree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating RBC transfusion.

^gFatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI) are examples of standardized measures for assessing patient-reported fatigue.

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Management of Cancer- and Chemotherapy-Induced Anemia

COMPARISON OF RISKS AND GOALS OF ESA USE VERSUS RBC TRANSFUSION^h

Discuss the following risks and goals with patients when considering anemia treatment options:

	ESA in the Cancer Setting	RBC Transfusion
Risks	<ul style="list-style-type: none">• Increased thrombotic events• Possible decreased survival• Time to tumor progression shortened	<ul style="list-style-type: none">• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury)• Transfusion-associated circulatory overload (TACO)• Virus transmission (eg, hepatitis, HIV)• Bacterial contamination• Iron overload• Increased thrombotic events• Possible decreased survival• Alloimmunization• Increased risk of poor response to future platelet transfusions due to HLA immunization
Goals	<ul style="list-style-type: none">• Transfusion avoidance• Gradual improvement in anemia-related symptoms	<ul style="list-style-type: none">• Rapid increase of Hb and hematocrit levels• Rapid improvement in anemia-related symptoms

[See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects \(ANEM-A\)](#)

When considering ESAs:

- Discuss the risks of ESAs with patients including the potential for tumor growth, death, blood clots, and serious heart problems.
- Refer patients to the following medication guides for more information on the benefits and risk of ESAs: [Epoetin Alfa Medication Guide](#), [Epoetin Alfa-epbx Medication Guide](#) and [Darbepoetin Alfa Medication Guide](#)

When considering RBC transfusion, see AABB Clinical Practice Guidelines: Tobian AA, Heddle NM, Wiegmann TL, Carson JL. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. Transfusion 2016;56:2627-2630.

^h[See Discussion](#) for detailed information regarding the risks and benefits of ESA use and RBC transfusion.

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

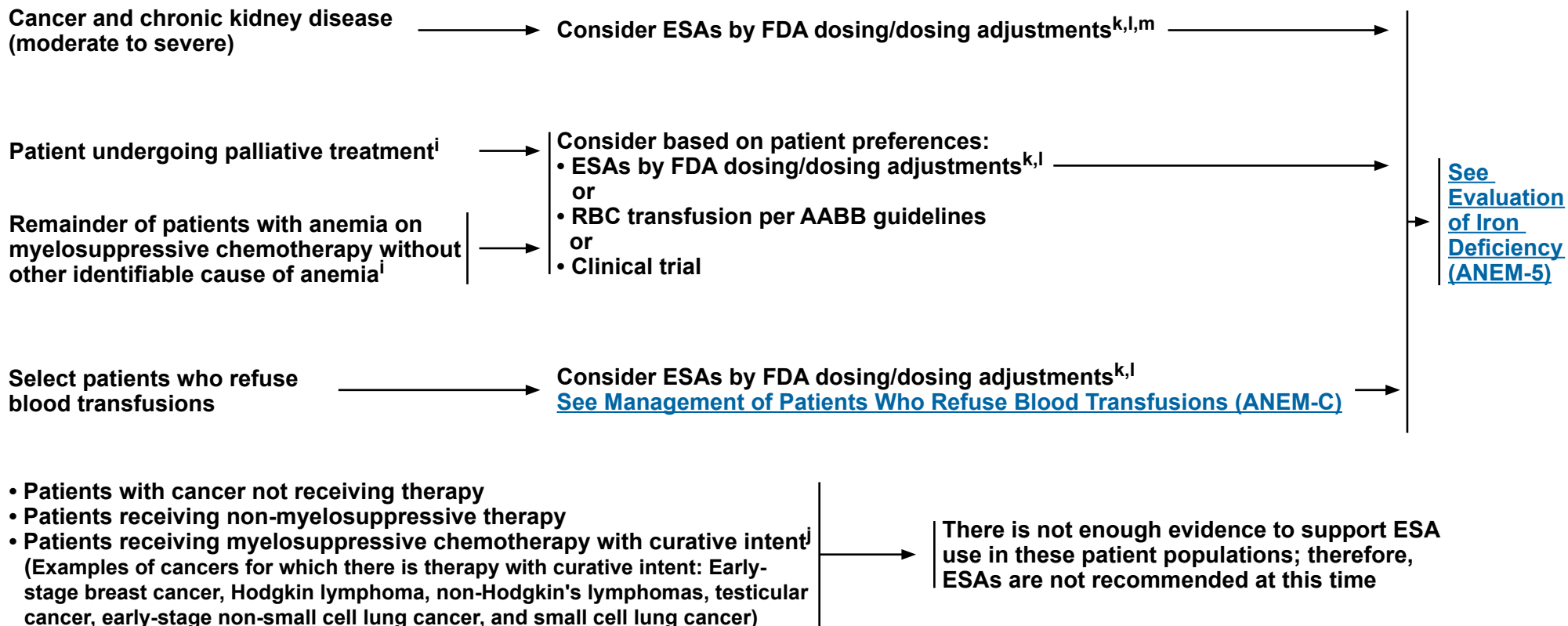
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Management of Cancer- and Chemotherapy-Induced Anemia

SPECIAL CATEGORIES IN CONSIDERING ESA USE



ⁱ[See Comparison of Risks and Goals of ESA Use Versus RBC Transfusion \(ANEM-3\).](#)

^jA few studies suggest that patients with small cell lung cancer on myelosuppressive chemotherapy may not have an increase in mortality when receiving ESAs. Oncologic Drugs Advisory Committee March 2008; Pirker et al. J Clin Oncol 2008;26:2342-3249; Grote et al. J Clin Oncol 2005;23:9377-9386.

^k[See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects \(ANEM-A\).](#)

^lPatients with previous risk factors for thrombosis are at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, known heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. ([See NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease](#)).

^mThe hemoglobin threshold for treatment and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease. For more details on the use of ESAs in patients with cancer and chronic kidney disease, [see Discussion](#).

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Management of Cancer- and Chemotherapy-Induced Anemia

EVALUATION OF IRON DEFICIENCY

IRON STATUS

MANAGEMENT

Iron studies:
Iron panel (serum
iron, total iron-binding
capacity, serum ferritin)^d

Absolute iron deficiencyⁿ
(ferritin <30 ng/mL AND
TSAT <20%)

Consider IV or oral
iron supplementation

Hb increases
after 4 wk

Periodic evaluation (repeat
ferritin and TSAT)

No Hb increase
after 4 wk

See pathway below for
functional iron deficiency

Functional iron deficiency in
patients receiving ESAs^{o,p}
(ferritin 30–500 ng/mL AND
TSAT <50%)

Consider IV iron supplementation^{r,s,t}
with erythropoietic therapy

[See Discussion](#) for clinical
examples of iron status

Possible functional iron
deficiency^{o,p,q} (ferritin >500–
800 ng/mL AND TSAT <50%)

No iron supplementation needed
or
Consider IV iron supplementation for select patients

No iron deficiency
(ferritin >800 ng/
mL OR TSAT ≥50%)

IV or oral iron supplementation is not needed

[See Parenteral Iron Preparations \(ANEM-B\)](#)

^dThe ferritin value indicating iron deficiency is laboratory-specific. In general, the lower the level of ferritin, the higher the probability that the patient has true iron deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin. Additionally, if serum iron studies are not performed while the patient is fasting or if the patient has taken a recent oral iron tablet, serum iron levels may be falsely elevated, and thus also falsely elevate the percent transferrin saturation. Fasting is preferred when testing for serum iron and total iron-binding capacity.

ⁿIf the ferritin and TSAT are discordant, the low ferritin value should take precedence in determining whether IV iron will be of benefit.

^oIn clinical trials using IV iron plus an ESA, a higher response rate is seen when iron is used for patients with a TSAT <20%. For patients who received IV iron that had baseline TSATs >20%, the response rate to IV iron is both diminished and prolonged as the TSAT increased from 20% to 50%. Therefore, the decision to offer IV iron to this subset of patients should be reserved for those in whom benefits are likely to outweigh risks.

^pOnly 1 of 6 studies (Henry DH, et al. Oncologist 2007;12:231-242) of IV iron therapy in patients with cancer provided a TSAT guideline for monitoring.

^qAlthough patients with ferritin levels of >500–800 ng/mL may have functional iron deficiency, as evidenced by clinical trials in patients with cancer, there are insufficient data to support the routine use of IV iron in this setting. Administration of IV iron to such patients should be individualized with the goal of avoiding allogeneic transfusion.

^rIV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective.

[See Parenteral Iron Preparations \(ANEM-B\)](#).

^sAlthough all combinations of serum ferritin and TSAT could be found in at least one of six randomized controlled trials evaluating the use of IV iron with an ESA, eligibility criteria testing for serum ferritin and TSAT generally ranged from >10 to <900 ng/mL and >15% to <60%, respectively.

^tThere are insufficient data to routinely recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency anemia.

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Management of Cancer- and Chemotherapy-Induced Anemia

ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (1 of 5)^{a,b,c,d,e}

INITIAL DOSING

TITRATION FOR NO RESPONSE**

TITRATION FOR RESPONSE

PACKAGE INSERT DOSING SCHEDULE

Epoetin alfa or epoetin alfa-epbx ^{c,1} 150 units/kg 3 times per wk by subcutaneous injection	→	Increase dose of epoetin alfa or epoetin alfa-epbx ^{c,1} to 300 units/kg 3 times per wk by subcutaneous injection
or		
Epoetin alfa or epoetin alfa-epbx ^{c,1} 40,000 units every wk by subcutaneous injection	→	Increase dose of epoetin alfa or epoetin alfa-epbx ^{c,1} to 60,000 units every wk by subcutaneous injection
or		
Darbepoetin alfa 2.25 mcg/kg every wk by subcutaneous injection	→	Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection
or		
Darbepoetin alfa 500 mcg* every 3 wks by subcutaneous injection		

- The dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid RBC transfusion.
- If Hb reaches a level needed to avoid transfusion or increases >1 g/dL in any 2-week period, reduce dose by 25% for epoetin alfa or epoetin alfa-epbx^{c,1} and by 40% for darbepoetin alfa.

ALTERNATIVE REGIMENS^f

Darbepoetin alfa 100 mcg fixed dose every wk by subcutaneous injection	→	Increase darbepoetin alfa to up to 150–200 mcg fixed dose every wk by subcutaneous injection ²
or		
Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection ⁷	→	Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection ³
or		
Darbepoetin alfa 300 mcg* fixed dose every 3 wks by subcutaneous injection	→	Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection ⁴
or		
Epoetin alfa ^e 80,000 units every 2 wks by subcutaneous injection ⁵		
or		
Epoetin alfa ^e 120,000 units every 3 wks by subcutaneous injection ⁶		

[See Footnotes and References \(ANEM-A 2 of 5\)](#)

[See Erythropoietic Therapy - Adverse Effects \(ANEM-A 3 of 5\)](#)

*Data indicate that darbepoetin alfa 300 mcg is equivalent in terms of efficacy to darbepoetin alfa 500 mcg for initial dosing.⁷

**No response is defined as hemoglobin increase less than 1 g/dL and remains below 10 g/dL after the initial 4 weeks of epoetin, or 6 weeks of darbepoetin. Discontinue therapy after 8 weeks if no response.

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Management of Cancer- and Chemotherapy-Induced Anemia

ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 of 5)

FOOTNOTES AND REFERENCES FOR ANEM-A (1 of 5)

Footnotes

- ^aThe head-to-head comparisons of epoetin alfa versus darbepoetin alfa are inconclusive with regard to superiority of one drug over another. Schwartzberg LS, Yee LK, Senecal FM, et al. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;9:696-707. Waltzman R, Croot C, Justice G, et al. Randomized comparison of epoetin alfa (40 000 U weekly) and darbepoetin alfa (200 mcg every 2 weeks) in anemic patients with cancer receiving chemotherapy. *Oncologist* 2005;10:642-650. Grant MD, Piper M, Bohlius J, et al. AHRQ Comparative Effectiveness Reviews. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
- ^bLess-frequent dosing regimens of darbepoetin or epoetin alfa could be considered as an alternative to dose reduction.
- ^cThe epoetin alfa and darbepoetin alfa dosages and regimens included in this table have been evaluated in patients with cancer receiving chemotherapy. Epoetin alfa-epbx has been studied in patients with chronic kidney disease; there are limited data in patients with cancer.
- ^dIV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See [Discussion](#) for details.)
[See Parenteral Iron Preparations \(ANEM-B\).](#)
- ^eSee prescribing information for perioperative DVT prophylaxis.
- ^fThere are no data on alternative dosing schedules for epoetin alfa-epbx.

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[See Erythropoietic Therapy -
Dosing and Titration \(ANEM-A 1 of 5\)](#)

[See Erythropoietic Therapy-
Adverse Effects \(ANEM-A 3 of 5\)](#)

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

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Management of Cancer- and Chemotherapy-Induced Anemia

ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 of 5)

Survival of Patients with Cancer

- Studies have reported possible decreased survival in patients with cancer receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in patients receiving erythropoietic drugs for correction of anemia and target Hb levels of >12 g/dL.¹⁻⁸ One analysis in patients with cancer not receiving active therapy found decreased survival in patients treated with ESAs.⁶ Please refer to the FDA website for additional information: <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM109375>. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa, or epoetin alfa-epbx) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.
- While three meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,^{9,10-12} two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.^{13,14}
- Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.¹⁵⁻¹⁷
- The risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL.
- Additional prospective clinical trials designed and powered to measure survival of patients with cancer are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus RBC transfusion. ([See Comparison of Risks and Goals of ESA Use Versus RBC Transfusion - ANEM-3](#)).
- Recent studies suggest that use of ESAs may be deleterious when used in patients with metastatic breast cancer. [See Discussion](#).

[Erythropoietic Therapy - Adverse
Effects continued \(ANEM-A 4 of 5\)](#)

[See References
\(ANEM-A 5 of 5\)](#)

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 of 5)

Thrombosis

- Early trials of recombinant human erythropoietin reported that a high-target hematocrit ($42 \pm 3\%$) was found to have an increased number of vascular events (arterial and venous).
- Erythropoietin has a thrombogenic potential independent of Hb levels.¹⁸ Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc.
(See [NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease](#))
- Five meta-analyses reported an increase in relative risk of thrombotic events ranging from 48% to 69% with ESA use.^{9,12-14,19} The absolute risk of venous thromboembolism was 7.5% in patients treated with ESAs compared to 4.9% in control patients.⁹
- A clinical trial in chronic kidney disease demonstrated a 92% increase in the relative risk of stroke (absolute risk 5.0% vs. 2.6%) with darbepoetin alfa.²⁰

Hypertension/Seizures

- Blood pressure should be controlled in all patients prior to initiating therapy with erythropoietic drugs and must be monitored regularly in treated patients.
- Seizures have been reported in patients with chronic renal failure receiving erythropoietic drugs.
- Hb level should be monitored to decrease the risk of hypertension and seizures. (See [Titration for Response ANEM-A 1 of 5](#))

ESA-Neutralizing Antibodies (Pure red cell aplasia, PRCA)

- Between 1998–2004, 197 cases of PRCA were reported in patients treated with erythropoietin.²¹ Over 90% of these cases occurred with Eprex, an epoetin alfa product used outside of the United States. Patients who develop a loss of response to erythropoietic drugs should be evaluated for possible PRCA, and if present, all erythropoietic drugs should be discontinued.²²
- In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia. Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa.²³ This interpretation resulted in a class label change for all ESAs. The toxicity has been reported predominantly in patients with chronic renal failure receiving ESAs by subcutaneous administration. Any patient who develops a sudden loss of response to an ESA, accompanied by a severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, ESAs should be withheld and plasma should be sent for evaluation of assays for binding and neutralizing antibodies. ESAs should be discontinued in patients with antibody-mediated anemia. Patients should not be immediately switched to other ESA products as antibodies may cross-react.

[See References \(ANEM-A 5 of 5\)](#)

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Management of Cancer- and Chemotherapy-Induced Anemia

ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 of 5)

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Management of Cancer- and Chemotherapy-Induced Anemia

PARENTERAL IRON PREPARATIONS^{1-6,a}

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran ^{15,b}	Ferric Gluconate ^{16,b}	Iron Sucrose ^{17,b}	Ferric Carboxymaltose ^{21,b,c,f} (in select cases)	Ferumoxytol ^{22,23,b,d,f} (in select cases)
Test dose ^e	Test dose required: 25 mg slow IV push	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction
Dosage ^{14,f}	100 mg IV over 5 min ³ • Repeated dosing once weekly for 10 doses to total of 1 g or • Total dose infusion given over several hours ^{18,g} ‣ Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h ¹⁹	125 mg IV over 60 min ^{2,4,5,8} • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommended based on published trial results ⁸ • Total treatment course = 1000 mg	200 mg IV over 60 min ⁶ (repeated every 2–3 wks) or 200 mg IV over 2–5 min (repeated every 1–4 wks) • Individual doses over 300 mg are not recommended ²⁰ • Total treatment course = 1000 mg	750 mg IV for patients weighing ≥50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course = 1500 mg or 15 mg/kg body weight IV for patients <50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course not to exceed 1500 mg	510 mg IV dose over 15 min • Repeat 510 mg dose 3–8 days later • Total treatment course = 1020 mg
Routes	IV; IM (not recommended)	IV	IV	IV	IV

^aFive²⁻⁶ of six⁸ studies suggest that parenteral iron products improve Hb response rates in treating absolute or functional iron deficiency in patients with cancer who are receiving ESAs.

^bExamples of adverse events associated with FDA-approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness. Adverse effects associated with low-molecular-weight iron dextran may be delayed 24–48 hours. Ferric carboxymaltose has been associated with severe phosphate deficiency.

^cFerric carboxymaltose has not been prospectively evaluated in patients with cancer- or chemotherapy-induced anemia and therefore should only be considered when other parenteral iron preparations fail.⁷

^dFerumoxytol is indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or those with chronic kidney disease. There are no data to show the efficacy of ferumoxytol in patients with cancer. Ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.¹³

^ePremedications should be given prior to the IV iron test dose as reactions to the test dose may be severe.

^fFor additional details about iron dosing, see prescribing information.

^gDose (mL) = 0.0442 (Desired Hgb - Observed Hgb) x LBW + (0.26 X LBW); Dose (mg) = Dose (mL) x 50 mg/mL. LBW = Lean Body Weight (kg); Hgb = Hemoglobin (g/dL). If dose exceeds 1000 mg, remaining dose may be given after 4 weeks if inadequate hemoglobin response.

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[References](#)



PARENTERAL IRON PREPARATIONS¹⁻⁶

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NCCN Guidelines Version 2.2019

Management of Cancer- and Chemotherapy-Induced Anemia

MANAGEMENT OF CANCER- AND CHEMOTHERAPY-INDUCED ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSIONS¹⁻⁸

- There are limited available data on the best management of cancer- and chemotherapy-induced anemia for patients who refuse blood transfusions.
- In extreme cases of severe, life-threatening anemia, pure oxygen (400 mm Hg, SaO₂ = 1.0) by mechanical ventilation has been used to increase blood oxygenation.
- To reduce blood loss, minimize phlebotomy, use pediatric tubes, return discard in closed system, and batch test.
- Prior to initiation of myelosuppressive chemotherapy:
 - Consider anemia risk when making treatment decisions
 - Consider daily folic acid and B₁₂ supplementation
 - Evaluate and correct baseline coagulation abnormalities
 - In patients with high clinical suspicion of folate and vitamin B₁₂ deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using intravenous (IV) iron.
- Consider use of ESAs for select patients by FDA dosing/dosing adjustments, given there is no option for transfusion.
 - ESAs are NOT recommended for:
 - ◇ Patients with cancer not receiving chemotherapy
 - ◇ Patients receiving non-myelosuppressive therapy
 - ◇ Patients receiving myelosuppressive chemotherapy with curative intent
 - Therefore, If ESAs are prescribed off-label for the indications listed immediately above, patients should be made aware of the potential increased risks of thrombosis and tumor progression, and should know that under these circumstances the ESAs are being used off-label.
- Blood substitutes
 - A clinician may obtain access to investigational blood substitute products for a single patient by submitting an Expanded Access - Investigational New Drug Application (IND) through the FDA.⁴

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[References](#)



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Management of Cancer- and Chemotherapy-Induced Anemia

MANAGEMENT OF CANCER- AND CHEMOTHERAPY-INDUCED ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSIONS

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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

Hematopoietic growth factors are defined by their ability to promote proliferation and differentiation of hematopoietic progenitors into mature blood cells.¹ Colony-stimulating factors are hematopoietic growth factors responsible for the regulation of growth and differentiation of cells in the myeloid and erythroid lineages. Myeloid growth factors (MGFs), including granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), are primarily used to reduce the incidence of neutropenia in patients with solid tumors receiving myelosuppressive chemotherapy. Erythropoiesis-stimulating agents (ESAs), including epoetin alfa and darbepoetin alfa, are primarily used to manage cancer- and chemotherapy-induced anemia (CIA). Management of neutropenia and CIA are integral parts of supportive care for patients undergoing treatment for cancer.

Clinically significant neutropenia is defined as an absolute neutrophil count (ANC) of <500 neutrophils/mcL or an anticipated decline to ≤500 in the next 48 hours.² Febrile neutropenia (FN, ≥38.3°C orally or ≥38.0°C for a duration over 1 hour) is a major dose-limiting toxicity of chemotherapy that often requires prolonged hospitalization and broad-spectrum antibiotic use.³ Occurrences of severe neutropenia or FN can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome.⁴ Development of FN also increases treatment costs and leads to longer hospital stays. Correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.⁵

These guidelines will focus on the two MGFs that have shown the most promise in terms of clinical use: G-CSF and 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, filgrastim-aafi, pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv

are G-CSFs currently approved by the U.S. Food and Drug Administration (FDA) to decrease the incidence of FN in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy.⁶⁻¹² Filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, and pegfilgrastim-cbqv were approved as biosimilars allowing their use for the broader indications of the originator products (see *Biosimilars* below for more information). Tbo-filgrastim was approved by the FDA in an original biologic license application¹³ and therefore has a more restricted indication.⁸ 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 sargramostim¹⁴ as well as the lack of FDA approval. Sargramostim is used following induction therapy for acute myeloid leukemia (AML) and in various hematopoietic cell transplantation (HCT) settings. It should be noted that there are few head-to-head comparative studies on the clinical benefits of G-CSF versus GM-CSF. Both G-CSF and GM-CSF are also indicated for children and adults exposed to acute myelosuppressive doses of radiation (acute radiation syndrome).

CIA is prevalent, occurring in 30% to 90% of patients with cancer.¹⁵ Correction of CIA can be achieved by providing supportive care, including transfusion with packed red blood cells (PRBCs) or administration of ESAs, with or without iron supplementation. The first ESA approved by the FDA for the treatment of anemia in patients receiving myelosuppressive chemotherapy was epoetin alfa, a recombinant human erythropoietin (rhEpo).¹⁶ A second-generation rhEpo, darbepoetin alfa, with a longer half-life than epoetin alfa, has also been FDA-approved for this indication.¹⁷ In 2018, the FDA approved epoetin alfa-epbx as the first epoetin alfa biosimilar, allowing its use for the same indications as the originator product.^{18,19}

The pathophysiologic origins of anemia can be grouped into three categories: 1) decreased production of functional red blood cells (RBCs);

2) increased destruction of RBCs; and 3) blood loss. Anemia is characterized by a decrease in hemoglobin (Hb) concentration, RBC count, and/or hematocrit (Hct) to subnormal levels. The degree of anemia can be graded according to the anemia scale provided by the National Cancer Institute (Table 1).

Table 1. National Cancer Institute Anemia Scale

Grade	Scale (hemoglobin level in g/dL)
1 (mild)	10 – <lower limit of normal
2 (moderate)	8 – <10
3 (severe)	6.5 – <8
4 (life-threatening)	<6.5
5 (death)	Death

Source: Adapted from the [Common Terminology Criteria for Adverse Events](#).

The NCCN Guidelines for Hematopoietic Growth Factors is divided into two sections outlining the evaluation, prevention, and management of neutropenia and anemia, respectively. The purpose of these guidelines is two-fold: 1) to operationalize the evaluation and treatment of neutropenia and anemia in adult patients with cancer, especially those who are receiving chemotherapy; and 2) to enable the patient and clinician to assess management options for neutropenia and anemia in the context of an individual patient's condition.

These guidelines are mainly focused on patients with solid tumors and lymphoid blood cancers. Use of hematopoietic growth factors in the treatment of myeloid disorders or leukemias 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 this update of the NCCN Guidelines for Hematopoietic 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; filgrastim biosimilar and cancer; pegfilgrastim and cancer; pegfilgrastim biosimilar and cancer; anemia and cancer; anemia and chemotherapy; erythropoiesis stimulating agents and cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.²⁰

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following types: 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 selected by the panel for review during the Guidelines update meeting 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.

Biosimilars

The Biologics Price Competition and Innovation Act passed in 2009 established the pathway for approval of biosimilars with the goal of reducing expenditure for costly biologic drugs.²¹ The first U.S. approval of

a biologic on the biosimilar pathway occurred in 2015,²² and since that time there has been rapid approval of additional agents. A biosimilar is a biological product that is highly similar to the FDA-approved originator product with the exception of minor differences in clinically inactive components and no differences in efficacy, safety, and purity.²³ 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.²³ Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biological activity, efficacy, and safety.^{24,25} If overall safety and efficacy are equivalent, biosimilars may be approved for the same indications and can be substituted for the originator product. If a biosimilar is 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, there are currently no biosimilars designated as interchangeable by the FDA.

Biosimilars are supported by limited clinical data at the time of approval. Therefore, data must be extrapolated 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 natural 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.

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim.^{7,22} Data have shown filgrastim-sndz to have identical protein structure, mass, size, charge, and hydrophobicity to the originator product.²⁶ Pharmacokinetic and pharmacodynamic modeling further confirmed that the mechanism of action is the same and occurs through binding to the G-CSF receptor.²⁷

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. 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).⁷ 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.²⁸ A phase III trial of 218 patients with breast cancer receiving myelosuppressive chemotherapy with TAC (docetaxel, doxorubicin, and cyclophosphamide) showed no clinically meaningful differences regarding efficacy, safety, or immunogenicity between filgrastim and filgrastim-sndz, even in patients who alternated between the two in subsequent chemotherapy cycles.²⁹ A recently published combined analysis of this and another phase III trial on the safety of filgrastim-sndz in breast cancer patients also concluded that filgrastim-sndz has a safety profile consistent with previous studies of reference filgrastim.³⁰ Furthermore, several retrospective studies have also reported similar efficacy between filgrastim-sndz and filgrastim for prophylaxis of chemotherapy-induced neutropenia.³¹⁻³⁴

Tbo-filgrastim was approved as a biologic and not as a biosimilar in the United States, but had been approved as a biosimilar in Europe. Several studies have demonstrated similar outcomes with the use of tbo-filgrastim compared to filgrastim for the prevention of FN. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.³⁵ Tbo-filgrastim was equivalent to filgrastim and superior to placebo in reducing the duration of severe

neutropenia and incidence of FN. Two other randomized studies of patients with lung cancer and non-Hodgkin's lymphoma (NHL) receiving chemotherapy also reported similar efficacy of tbo-filgrastim and filgrastim.^{36,37} Toxicities were similar between the two agents. A meta-analysis of the 3 trials concluded tbo-filgrastim to be non-inferior to filgrastim in reducing the incidence of FN.³⁸ Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.^{39,40} Tbo-filgrastim has also demonstrated low immunogenicity in cancer patients receiving chemotherapy with no evidence of neutralizing antibodies or immunogenic adverse events.⁴¹

In 2018, the FDA approved a second filgrastim biosimilar, filgrastim-aafi, and the first pegfilgrastim biosimilars, pegfilgrastim-jmdb and pegfilgrastim-cbqv, for the same indications as their reference products.^{9,11,12,42-44} The FDA's approval of these biosimilars was based on review of evidence including structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data. A phase III randomized equivalence study in 279 patients receiving docetaxel/doxorubicin chemotherapy for breast cancer found filgrastim-aafi to be bioequivalent to filgrastim in terms of efficacy and safety, with similar incidence of FN, treatment-related bone pain, and mean time to neutrophil recovery.⁴⁵ The prospective, non-interventional, longitudinal VENICE study, which observed the tolerability, safety, and efficacy of filgrastim-aafi in 386 patients receiving chemotherapy, concluded that filgrastim-aafi was effective and well-tolerated in both the primary and secondary prophylactic settings.⁴⁶ The majority of patients (95.6%) experienced no change in chemotherapy dose or schedule due to FN and less than one-third (29.8%) of patients experienced one or more treatment-related adverse events. Two other non-interventional studies reached similar conclusions regarding the bioequivalence of filgrastim-aafi to reference filgrastim in both the prophylactic and therapeutic settings.^{47,48}

Pegfilgrastim-jmdb has been shown to have high analytical and functional similarity to pegfilgrastim, with similar structure, molecular mass, physicochemical characteristics, impurities, and G-CSF receptor binding affinity.^{49,50} A phase I randomized equivalence trial concluded that pegfilgrastim-jmdb demonstrated similar pharmacokinetics, pharmacodynamics, and safety to pegfilgrastim in healthy volunteers.⁵¹ In a multicenter randomized phase III efficacy and safety trial, breast cancer patients receiving myelosuppressive chemotherapy with pegfilgrastim-jmdb support showed no difference in the duration of severe neutropenia, time to ANC nadir, duration of post-nadir recovery, or treatment-related adverse events compared to patients receiving reference pegfilgrastim.⁵² Pegfilgrastim-jmdb has also demonstrated low immunogenic potential in healthy volunteers and in cancer patients receiving myelosuppressive chemotherapy.⁵³ Although data are limited, pegfilgrastim-cbqv was shown to have a similar safety profile and bioequivalent pharmacokinetics and pharmacodynamics to pegfilgrastim in 122 healthy volunteers in a multicenter randomized crossover study.^{54,55} No serious treatment-related adverse events were observed with the use of pegfilgrastim-cbqv.

In 2018, the FDA approved the first epoetin alfa biosimilar, epoetin alfa-epbx, for the treatment of anemia caused by chronic kidney disease (CKD) or chemotherapy.^{18,19} The FDA's approval of epoetin alfa-epbx was based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data. Epoetin alfa-epbx is also known as epoetin zeta, which was approved as a biosimilar in Europe in December 2007.⁵⁶ Several studies have demonstrated that epoetin zeta is effective and well tolerated for treating CIA, regardless of solid tumor type.⁵⁷⁻

⁶¹ Although there are limited data on the efficacy of epoetin alfa-epbx in treating CIA, two studies concluded that there is no clinically meaningful difference in efficacy or safety between epoetin alfa-epbx and epoetin alfa

in the treatment of anemia in patients with CKD.^{62,63} The panel therefore extrapolates that there would be no clinical difference between these two agents in the treatment of CIA.

Management of Neutropenia

Benefits of MGFs

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 or for patients presenting with acute exposure to myelosuppressive doses of radiation.

Many studies have shown that the prophylactic use of MGFs reduced the incidence, duration, and severity of chemotherapy-related neutropenia and FN in patients with various cancers.⁶⁴⁻⁸³ Additionally, the benefit of GM-CSF therapy was seen in the treatment of myeloid malignancies.⁸⁴ MGFs improved the delivery of full dose-intensity chemotherapy on schedule, although this has not been shown to lead to higher overall survival (OS) in most studies.^{64-66,71-74,78,85,86} The exceptions to this are node-positive breast cancer^{78,87} and aggressive lymphoma,^{80,88,89} where dose-dense regimens supported by MGFs have improved disease-free survival and/or OS compared to conventional chemotherapy. Primary G-CSF prophylaxis (defined as G-CSF administration within 5 days of beginning chemotherapy) has been shown to reduce the risk of neutropenia-related hospitalization in breast cancer patients.⁸¹

Meta-analyses and systematic reviews have confirmed the efficacy of prophylactic MGFs in decreasing the risk of neutropenia and the subsequent rates of infection and hospitalization.⁹⁰⁻⁹⁵ The meta-analysis by Clark et al⁹² 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 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; $P < 0.001$) and significantly improved the relative dose intensity (RDI) of the chemotherapy delivered with an average RDI difference of 8.4% between G-CSF-treated and non-G-CSF-treated patients ($P = .001$).⁹⁴ 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; $P = .002$) with use of G-CSF. This survival advantage was confirmed in a systematic review by Lyman et al⁹⁵ 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 of mortality and an RR of 0.9 for all-cause mortality. Notably, the degree of survival benefit correlated with the chemotherapy dose intensity received by the patient.

The recommendations in the NCCN Guidelines regarding the use of MGFs are based on therapeutic efficacy and clinical benefit. However, in addition to evaluating the clinical benefits of MGF therapy, an increasing number of studies have assessed the financial implications of their use. Over the last decade, the costs of inpatient hospitalization have escalated, changing the FN risk threshold on a pure cost basis from 40% to approximately 20% for the cost-saving use of G-CSF prophylaxis.⁹⁶ Therefore, if the risk of FN is

>20% in a given patient, the overall costs of treatment are substantially reduced with G-CSF prophylaxis. 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 FN. 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.⁹⁷ Economic analyses of MGFs have yielded mixed results, depending on the context of usage.⁹⁸⁻¹⁰² Selective use of MGFs in patients at an increased risk for neutropenic complications may enhance cost-effectiveness.^{96,103} Pawloski et al recently developed an evidence-based, individualized neutropenia risk estimation algorithm based on electronic health record (EHR) data.¹⁰³ 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. Additionally, the use of biosimilars represents a new opportunity for cost containment in oncology care, as biosimilars are typically more affordable than their originator products.^{25,104-107}

Risks of MGFs

While MGFs may result in improved outcomes, they are also associated with toxicities (see *Toxicity Risks with Myeloid Growth Factors* in the algorithm). Toxicities associated with filgrastim are expected to be similar for pegfilgrastim and filgrastim/pegfilgrastim biosimilars, although not all toxicities have been reported with each preparation. To date, the main consistently observed adverse reaction associated with G-CSF prophylaxis is mild to moderate bone pain in 10% to 30% of patients.^{6,10,82,108-111} This is usually effectively controlled by non-narcotic analgesics.^{109,112} A systematic review by Kuderer et al also reported a

heightened risk of musculoskeletal pain associated with MGF use (RR, 4.03; 95% CI, 2.15–7.52; $P < .001$).⁹⁴

Rare cases of splenic rupture have been reported with G-CSF use, some of which were fatal.¹¹³⁻¹¹⁹ These cases occurred in patients with underlying hematopoietic disorders, patients with solid tumors, and healthy donors of peripheral blood progenitor cells (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 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

Some patients may develop allergic reactions to MGFs involving the skin, respiratory system, or cardiovascular system. Other potential toxicities include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.^{6,10,120} Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease receiving G-CSF, but not for patients with sickle cell trait.¹²¹⁻¹²³ Significant toxicity in amyloidosis patients following G-CSF administration has also been described in two case reports.^{124,125} There has also been a low fraction of fatalities in amyloidosis patients undergoing stem cell mobilization.¹²⁶

The risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSF. In a retrospective study of 141 patients with Hodgkin's lymphoma receiving ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy, the rate of bleomycin-induced pulmonary toxicity was 26% in patients receiving G-CSF compared with 9% in patients who did not receive it ($P = .014$).¹²⁷ 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 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). Two studies have shown that ABVD can be safely administered at full dose without G-CSF support.^{128,129} 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.¹³⁰ 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.¹³¹ 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.¹³²⁻¹³⁴ There have also been reports of capillary leak syndrome,¹³⁵⁻¹³⁷ a condition in which fluids move from the vascular system into the interstitial space resulting in hypotension and reduced blood flow to internal organs.¹³² While this is more common with GM-CSF use, it has also been reported to occur with G-CSF.^{138,139}

Although there have been suggestions of a potentially increased risk for development of AML and myelodysplastic syndrome (MDS) following MGF administration from epidemiologic studies, this has not been observed in individual randomized trials.^{113,140-142} The meta-analysis by Lyman et al⁹⁵ reported a 0.41% increase in absolute risk (95% CI, 0.10%–0.72%; $P = .009$) and an estimated RR of 1.92 (95% CI, 1.19–3.07; $P = .007$) for the

development of AML/MDS related to G-CSF use. While it was not possible from this meta-analysis to determine whether the risk for AML/MDS is secondary to G-CSF or related to higher total doses of chemotherapy, overall mortality was nevertheless decreased by the addition of G-CSF support. An updated meta-analysis and systematic literature review by Lyman et al largely came to the same conclusions, reporting an increased risk for the development of secondary malignancies including AML/MDS (RR, 1.85; 95% CI, 1.19–2.88; $P < .01$) and improved survival (mortality RR, 0.86; 95% CI, 0.80–0.92; $P < .0001$) in patients receiving primary G-CSF support.¹⁴³ These data mirror an earlier report based on the SEER database that also showed a slightly elevated risk of developing AML/MDS in patients receiving MGF support.¹⁴² One caveat of this study was that it could not exclude the possibility that the increased risk 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.

Prophylactic Use of MGFs

Risk Assessment

The risk of FN is related to the treatment regimen, delivered dose intensity, and patient risk factors. The risk for 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-specific risk factors, and treatment intent (curative/adjuvant vs. palliative). Based on the chemotherapy regimen, 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). Patients in the high-risk group should receive prophylactic G-CSF (category 1). Prophylactic G-CSF should also be considered for patients in the intermediate-risk group based on patient risk factors (see *Patient Risk Factors for Developing FN* below). Patients in the low-risk group should not receive prophylactic G-CSF. There is currently no consensus nomogram for FN 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 individual patient's situation. 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 chemotherapy regimens that is directly related to the dose intensity of the regimen. Chemotherapy regimens for which clinical trial data show an incidence of FN >20% in chemotherapy-naïve 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 mainly 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 and without chemotherapy.¹⁴⁴

The algorithm lists common chemotherapy regimens associated with a high 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 serve as examples. Other agents/regimens may also have a high or intermediate risk for FN. In general, dose-dense regimens require MGF support to maintain dose intensity and schedule. It is emphasized that the chemotherapy regimen is only one component of risk assessment and needs to be combined with patient risk factors and treatment setting to estimate 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.¹⁴⁵ Patient risk 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, making it important to identify which patients would be considered high risk for FN development based on individual factors. Even a low-risk regimen may warrant the use of MGFs in a patient with clinical high-risk factors for the development of FN.

The most important risk factor for the development of severe neutropenia is older age (>65 years; see [NCCN Guidelines for Older Adult Oncology](#)).¹⁴⁶⁻¹⁵¹ Other risk factors include prior exposure to chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by the tumor, poor performance status, recent surgery and/or open wounds, renal or liver dysfunction, and HIV infection (see *Patient Risk Factors Assessment* in the algorithm).¹⁵² Most of these have been confirmed as independent risk factors for the development of 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.¹⁵³ This model and its associated risk factors have been retrospectively validated both internally and externally in an independent patient population.¹⁵⁴ Other patient-specific factors, such as chronic immunosuppression in the post-transplant setting (including organ transplant) may also warrant the use of G-CSF.

Patients at High Risk for FN

The NCCN Guidelines recommend prophylactic use of G-CSF if a patient's risk of developing FN is >20% (category 1). The most recent updates of the ASCO and EORTC guidelines have also adopted the 20%

threshold for considering routine prophylactic MGF support.^{155,156} These consistent recommendations are based on the results of several large randomized trials that have documented a significant reduction in FN following primary G-CSF prophylaxis when the risk of FN without prophylaxis is >20%. For example, a randomized, placebo-controlled, phase III trial of breast cancer patients receiving TC (docetaxel and cyclophosphamide) chemotherapy found that the incidence of FN was significantly lower in patients receiving prophylactic G-CSF than in patients receiving placebo (1.2% vs. 68.8%, respectively; $P < .001$).¹⁵⁷ In addition, patients in the G-CSF group had lower rates of hospitalization and antibiotic use. Similarly, the phase III GEICAM 9805 trial involving breast cancer patients treated with TAC (docetaxel, doxorubicin, and cyclophosphamide) chemotherapy showed that the rate of FN was reduced from 23.8% to 3.5% with the use of prophylactic G-CSF.¹⁵⁸

The NCCN Guidelines recognize a variety of circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens are at a high risk for FN due to bone marrow compromise, comorbidities, or other patient-specific risk factors. Prophylactic G-CSF is recommended for any patient considered to be at high patient-specific risk, regardless of the treatment regimen or 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. For patients receiving intermediate-risk chemotherapy regimens, the panel recommends individualized consideration of prophylactic G-CSF use based on the presence of patient-specific risk factors. Patients with ≥ 1 risk factor should be considered for prophylactic G-CSF, while patients with no risk factors should be observed. The panel also recommends physician-patient discussion of the risk-benefit ratio of G-CSF use 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 palliative, the use of G-CSF is a difficult decision and requires careful discussion between the physician and patient. If the increased risk for FN is due to patient risk factors, G-CSF use is reasonable. However, if the risk is due to the chemotherapy regimen, 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 patients receiving low-risk chemotherapy regimens, as defined by an FN risk of <10%, routine use of G-CSF prophylaxis is not recommended.^{96,159,160} G-CSF may be appropriate if the patient is receiving therapy with curative intent or adjuvant treatment and is at significant patient-specific risk for FN.

Evaluation Prior to Subsequent Chemotherapy Cycles

After the first cycle of chemotherapy, patient evaluation should be performed prior to each subsequent cycle to determine the FN risk categorization. If the patient experienced an episode of FN or a dose-limiting neutropenic event (a nadir count 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. Prophylactic G-CSF support should be considered for such patients who had not received prior G-CSF. In patients who did receive prior G-CSF, the panel recommends a chemotherapy dose reduction or a change in treatment regimen unless there is an impact on patient survival. If the patient did not develop FN or a dose-limiting neutropenic event in the first cycle and is thought to be benefiting from chemotherapy, the assessment of patient-specific risk

factors should be repeated prior to each subsequent chemotherapy cycle and a decision rendered regarding the indication for prophylactic G-CSF.

Dosing and Administration

Filgrastim, tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and sargramostim are FDA-approved options for the prevention of FN. While data from randomized studies support the use of G-CSF in patients with solid malignancies, randomized studies of the GM-CSF sargramostim have focused on its use following induction therapy for AML and in various HCT settings. Sargramostim is no longer recommended for the prevention of FN in patients with solid tumors receiving myelosuppressive chemotherapy. For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see the [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#). In addition, prophylactic use of G-CSF in patients given concurrent chemotherapy and radiation has not been evaluated in prospective randomized studies and is therefore not recommended.

Filgrastim and Filgrastim Biosimilars

The subcutaneous administration of filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi is a category 1 recommendation for the prevention of FN. Initial doses of filgrastim or filgrastim biosimilars are administered the next day or up to 3 to 4 days after completion of myelosuppressive 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.¹⁶¹

Pegfilgrastim and Pegfilgrastim Biosimilars

Pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv are pegylated versions of filgrastim designed to have a longer half-life, which allows for less frequent dosing. Based on clinical trial data, pegfilgrastim should be administered the day after myelosuppressive chemotherapy (category 1).¹⁶² The rationale for not giving same-day pegfilgrastim is the potential for exacerbation of neutropenia resulting from stimulation of hematopoietic progenitor cells at the time of cytotoxic chemotherapy, resulting in loss of the progenitors.^{163,164} A systematic literature review evaluating the relative merits of next-day versus same-day pegfilgrastim found that delivery of pegfilgrastim at least 24 hours after myelosuppressive chemotherapy resulted in improved patient outcomes across a variety of tumor types.¹⁶² Additionally, a recent retrospective analysis found that administration of pegfilgrastim 24 to 72 hours after chemotherapy was significantly associated with maintenance of chemotherapy dose intensity in patients with various cancers.¹⁶⁵ Furthermore, a retrospective evaluation found that 50% of all FN hospitalization episodes among cancer chemotherapy patients occurred in those who either did not receive pegfilgrastim or received pegfilgrastim on the same day as chemotherapy.¹⁶¹ A large-scale retrospective evaluation of 53,814 patients receiving intermediate- or high-risk chemotherapy regimens also found the incidence of FN to be significantly higher in patients administered pegfilgrastim prophylaxis either the same day or 4 to 5 days after chemotherapy compared to those receiving pegfilgrastim on days 1 to 3 following chemotherapy.¹⁶⁶ In a direct comparison, Kaufman et al¹⁶⁷ administered either same-day or next-day pegfilgrastim in women with breast cancer receiving chemotherapy with TAC. 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.¹⁶⁷ A similar trend was seen in a prospective, randomized trial of patients receiving CHOP or CHOP-like therapy for NHL, where same-day pegfilgrastim was associated with enhanced myelosuppression.¹⁶⁸

Based on these data, the NCCN Guidelines recommend administration of pegfilgrastim (category 1), pegfilgrastim-jmdb (category 2A), or pegfilgrastim-cbqv (category 2A) the day after myelosuppressive chemotherapy. Administration up to 3 to 4 days after myelosuppressive chemotherapy is also reasonable based on trials of filgrastim. Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient. In addition, panelists recognized that some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize travel burdens on long-distance patients.¹⁶⁹ 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.¹⁷⁰

The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle lengths. In general, there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy. If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment. Based on phase III clinical trials,^{68,171} use of pegfilgrastim for 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.¹⁷²⁻¹⁷⁷ There are insufficient data to support the use of pegfilgrastim 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. A multicenter trial 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. Patients in the G-CSF arm had 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, $P = .015$) than patients in the control arm.¹⁷⁸ In a Cochrane meta-analysis including 1518 patients from 13 trials, 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.⁹² In an update to this review, Estcourt et al concluded that there is insufficient evidence to determine whether therapeutic MGFs affect all-cause mortality.¹⁷⁹ Therefore, while there are clinical benefits to MGF therapy for FN, it remains unknown as to whether these benefits translate into a survival advantage.

The NCCN Panel recommends that patients presenting with FN who are receiving or had previously received prophylactic filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi should continue with the same G-CSF. However, since pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv are long-acting, those who have received these agents prophylactically should not be treated with additional G-CSF.¹⁸⁰ There are no studies that have addressed the therapeutic use of filgrastim for FN in patients who have already received prophylactic pegfilgrastim, pegfilgrastim-jmdb, or pegfilgrastim-cbqv. However, pharmacokinetic data of pegfilgrastim demonstrates high levels during neutropenia suggesting that additional G-CSF use may not be beneficial; additional G-CSF may however be considered in patients with prolonged neutropenia. For patients with FN who have not received prophylactic G-CSF, the NCCN Panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome. These include: age >65 years; sepsis syndrome; ANC <100 neutrophils/mcL; anticipated prolonged (>10 days) neutropenia; pneumonia or other clinically documented infection; invasive fungal

infections; hospitalization at the time of fever; and prior episode(s) of FN. If risk factors for infection-related complications are present, therapeutic MGFs should be considered. Filgrastim, filgrastim-sndz, filgrastim-aafi, tbo-filgrastim, or sargramostim may be administered in the therapeutic setting. Pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv have only been studied for prophylactic use and are not recommended for therapeutic use at this time.

Filgrastim, pegfilgrastim, and sargramostim are FDA-approved for the treatment of patients presenting with acute exposure to myelosuppressive doses of radiation.^{6,10,132} The panel endorses use of filgrastim-sndz, filgrastim-aafi, tbo-filgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv in this setting. The goals of using MGFs to treat radiation-induced myelosuppression are to shorten the duration of severe neutropenia, minimize the severity of neutropenia-associated complications, and improve survival.¹⁸¹ According to the U.S. Department of Health and Human Services Radiation Emergency Medical Management guidance, initiation of MGFs should be strongly considered for patients who received ≥ 2 Gy whole body exposure or ≥ 2 Gy significant partial body exposure, have an ANC of ≤ 500 cells/mm³, will likely have prolonged periods of significant neutropenia, or have significant radiation exposure plus trauma and/or burns, which worsens the clinical outcome compared to radiation exposure alone.¹⁸¹ Most of the data in support of MGF use in this setting are derived from animal studies and case reports concerning patients involved in radiation accidents.¹⁸²⁻¹⁹¹

Dosing and Administration

Filgrastim, filgrastim-sndz, filgrastim-aafi, tbo-filgrastim, and sargramostim are the recommended MGFs for the therapeutic treatment of FN in selected high-risk patients as outlined above who had not received prophylactic G-CSF. Filgrastim, filgrastim-aafi, tbo-filgrastim, or filgrastim-sndz should be given at a daily dose of 5 mcg/kg and sargramostim

should be given at a daily dose of 250 mcg/m². Treatment should continue through post-nadir recovery. For patients presenting with acute exposure to myelosuppressive doses of radiation, filgrastim, filgrastim-aafi, tbo-filgrastim, or filgrastim-sndz should be given at a daily dose of 10 mcg/kg; pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv should be given as a single dose of 6 mg; and sargramostim should be given at a daily dose of 250 mcg/m².¹⁸¹ MGFs should be administered as soon as possible after acute radiation exposure.

Mobilization and Post Hematopoietic Cell Transplant

MGFs are commonly administered in the HCT setting, either for mobilization of hematopoietic progenitor cells or as supportive care after transplantation. Mobilization of PBPCs by G-CSF-containing regimens has largely replaced bone marrow collection for HCT due to the ease of collection, avoidance of general anesthesia, and more rapid recovery of blood counts.¹⁹² Additionally, PBPC transplants are associated with a more rapid recovery of granulocytes and platelets after transplantation and lower transplant-related mortality compared to bone marrow transplants.¹⁹² Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and the incorporation of plerixafor with either approach.

Mobilization of Hematopoietic Progenitor Cells in the Autologous Setting

Studies have shown that single-agent filgrastim or filgrastim biosimilars are effective in mobilizing hematopoietic progenitor cells in the autologous HCT setting.¹⁹³⁻¹⁹⁵ Combination chemotherapy followed by filgrastim or filgrastim biosimilars may result in higher collection yields with fewer days of apheresis, but at an increased rate of hospitalizations for neutropenic fever.¹⁹⁶⁻¹⁹⁹ This approach may also reduce the burden of residual tumor. Several regimens are effective in chemomobilization of hematopoietic

progenitor cells, including cyclophosphamide,¹⁹⁶ ICE,¹⁹⁷ DHAP,¹⁹⁷ VTD-PACE,¹⁹⁸ and others. Studies using GM-CSF as a single agent for mobilization or in sequential combination with G-CSF have also reported good yields of PBPCs in normal donors.²⁰⁰⁻²⁰² However, a randomized phase III trial comparing filgrastim, sargramostim, and sequential sargramostim and filgrastim following administration of myelosuppressive chemotherapy in the autologous HCT setting found that patients who received filgrastim alone yielded more CD34+ cells (median 7.1 vs 2.0 x 10⁶ kg per apheresis, *P* = .0001) and had faster recovery of ANC (median 11 vs. 14 days, *P* = .0001) compared to patients receiving sargramostim alone. Importantly, there were no significant differences in outcomes between groups receiving filgrastim alone and the sequential regimen.²⁰³ Therefore, the use of concurrent filgrastim or a filgrastim biosimilar with sargramostim is a category 2B recommendation.

The CXCR4 inhibitor plerixafor, in combination with G-CSF, is FDA-approved for mobilizing autologous hematopoietic progenitor cells to the peripheral blood in patients with NHL or multiple myeloma.²⁰⁴ Numerous studies have shown that the addition of plerixafor to mobilization regimens accelerates the rise in PBPC count.²⁰⁵⁻²¹³ The addition of plerixafor as a preemptive (“just in time”) strategy in patients with insufficient CD34+ cell counts after mobilization with growth factor with or without chemotherapy has been highly successful.^{207,208,214-216} Poor mobilization is generally defined as failure to achieve the target level of at least 2 × 10⁶ CD34+ cells/kg body weight.²¹⁷ However, there are limited data on parameters for predicting poor mobilization and identifying 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.^{209,218-226} Traditionally, parameters such as older age (>60 years) and low platelet count (<100,000) have been used to predict poor mobilization. However, recent data suggest that prior

exposure to lenalidomide and low white blood cell count (<4000) are more strongly associated with poor mobilization than platelet count.²²⁷ Additional studies have suggested there may also be genetic parameters that contribute to mobilization outcome.²²⁸ 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.

Historically, predicting mobilization failure based on baseline patient characteristics or risk factors has been highly inaccurate.²⁰⁹ Thus, there is increasing interest in developing new 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.²²⁹ If validated in prospective trials, 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.²³⁰ However, age and hematologic toxicity developed during induction were the only parameters that maintained statistical significance after multivariate analysis. Well-designed randomized trials are needed to validate the parameters proposed in predictive models for poor mobilization.

Most data on mobilization of hematopoietic progenitor cells in the autologous setting are focused on filgrastim.^{193,231-234} While some studies suggest that single-dose pegfilgrastim may have similar efficacy,²³⁵⁻²⁴⁰ there are limited high-quality data supporting the use of pegfilgrastim in this setting. Larger randomized trials that address the efficacy of pegfilgrastim for mobilization, with or without plerixafor, are needed.

Therefore, pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv are not recommended for mobilization at this time.

While filgrastim biosimilars have been accepted as equivalent options to filgrastim for FN prophylaxis, there is discussion among medical professionals regarding their equivalency in hematopoietic cell mobilization.^{241,242} There are data to support the use of filgrastim-sndz and tbo-filgrastim in the autologous HCT setting.²⁴³⁻²⁵⁰ 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 biosimilars, 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 biosimilars compared to the originator filgrastim will be of paramount importance.

Dosing and Administration

The NCCN Panel recommends administration of filgrastim, filgrastim-sndz, filgrastim-aafi, or tbo-filgrastim as a single agent¹⁹³⁻¹⁹⁵ or as part of a chemomobilization regimen,¹⁹⁶⁻¹⁹⁸ starting about 24 hours after completion of chemotherapy, at a dose of 10 to 32 mcg/kg per day in daily or twice-daily dosing. Apheresis usually commences on the 4th or 5th day of G-CSF initiation when it is used as a single agent. If used concurrently with sargramostim, filgrastim, filgrastim-sndz, filgrastim-aafi, or tbo-filgrastim should be administered at a dose of 7.5 mcg/kg each morning with sargramostim administered at a dose of 7.5 mcg/kg each evening. Leukapheresis should begin on day 5. If used in conjunction with plerixafor, filgrastim, filgrastim-sndz, filgrastim-aafi, or tbo-filgrastim should be administered at 10 mcg/kg per day for 5 days. On the evening of day 4, plerixafor should be administered by subcutaneous injection 11 hours prior to initiation of apheresis on day 5. Plerixafor dosing is based on patient

weight (See *Myeloid Growth Factors in Mobilization and Post Hematopoietic Cell Transplant* in the algorithm for more information).

Mobilization of Hematopoietic Progenitor Cells in the Allogeneic Setting

Initially, there were concerns about using G-CSF for mobilization in the allogeneic setting due to normal donor toxicity and the risk for graft-versus-host disease (GVHD) in the recipient. However, studies have demonstrated filgrastim to be well-tolerated by donors without an effect on long-term survival in the recipient.²³¹⁻²³³ Tbo-filgrastim has also been shown to effectively mobilize PBPCs for allogeneic transplantation in healthy donors; however, the data are limited and mobilization is not listed as an FDA-approved indication.^{251,252} 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. Small studies have suggested that filgrastim-sndz is effective for mobilization in healthy allogeneic donors with no short-term safety issues;²⁵³⁻²⁵⁶ however, long-term data are needed. The World Marrow Donor Association recently published a review on the use of biosimilar filgrastim for healthy donor mobilization in 1287 volunteers.²⁴² Mobilization of CD34+ cells as well as treatment-related adverse events were found to be similar between filgrastim-sndz, tbo-filgrastim, and reference filgrastim, although the authors cite a lack of long-term follow-up for both reference filgrastim and biosimilars. There was no evidence of a higher risk of filgrastim antibody formation using biosimilars. Based on this increased experience, the WMDA now recommends the use of filgrastim biosimilars for the mobilization of peripheral blood progenitor cells in healthy donors in the allogeneic HCT setting.

Dosing and Administration

The NCCN Panel recommends single-agent filgrastim (category 2A; preferred), filgrastim-sndz (category 2B), filgrastim-aafi (category 2B), or tbo-filgrastim (category 2B) for allogeneic donor cell mobilization at a dose of 10 to 16 mcg/kg per day by subcutaneous injection, with collection beginning on day 4 or 5. The use of plerixafor in normal donors (category 2B) is currently under study.²⁵⁷⁻²⁵⁹ As previously mentioned, pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv are not recommended for mobilization at this time. For granulocyte transfusion, the panel recommends filgrastim (category 2A), filgrastim-sndz (category 2B), filgrastim-aafi (category 2B), or tbo-filgrastim (category 2B) at a single subcutaneous dose of 5 mcg/kg with dexamethasone 10 mg PO administered 8 to 24 hours prior to collection.²³⁴

MGFs as Part of Supportive Care After HCT

Consensus is lacking on the use of MGFs in the post-transplant setting. Filgrastim administration after high-dose chemotherapy and autologous HCT has been shown to expedite neutrophil recovery in prospective randomized trials.²⁶⁰⁻²⁶⁵ However, results were inconclusive on the impact of filgrastim on duration of post-HCT hospital stay, infections, and survival. Several studies comparing filgrastim and pegfilgrastim in the post-autologous transplant setting concluded that the two are at least equally effective.²⁶⁶⁻²⁷³ Data are conflicting on G-CSF use as a supportive care measure for allogeneic transplant recipients, with some studies associating G-CSF with worse clinical outcomes.²⁷⁴ However, G-CSF 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.²⁷⁵

Dosing and Administration

The NCCN Panel recommends the use of filgrastim,²⁶⁵ filgrastim-sndz,³¹ filgrastim-aafi, or tbo-filgrastim following autologous HCT, haploidentical transplant or cord blood transplant at a dose of 5 mcg/kg per day beginning day +5 to 7 post-transplant until recovery of ANC. Pegfilgrastim is also recommended in the supportive care setting for post-autologous HCT^{257,259-264}

Severe Chronic Neutropenia

These guidelines focus on the management of 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.²⁷⁶ 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 per day). Congenital neutropenia patients generally require higher doses (3–10 mcg/kg per 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 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-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 for severe chronic neutropenia is HCT. For further reading on

severe chronic neutropenia, refer to the website developed by The Severe Chronic Neutropenia International Registry:

<http://depts.washington.edu/registry/index.html>.

Management of Cancer- and Chemotherapy-Induced Anemia

Etiology of Anemia Associated with Cancer and Myelosuppressive Chemotherapy

Causes of anemia in patients with cancer are often multifactorial.²⁷⁷ Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, nutritional deficiencies, hereditary disease, renal insufficiency, hormone dysfunction, or a combination of these factors.^{278,279} The malignancy itself can lead to or exacerbate anemia in a number of ways.²⁸⁰ Cancer cells may directly suppress hematopoiesis through bone marrow infiltration. They may also produce cytokines that lead to iron sequestration, which decreases RBC production and may shorten RBC survival. Chronic blood loss at tumor sites from blood vessels or organ damage can also exacerbate anemia in patients with cancer. Additional indirect effects may include nutritional deficiencies caused by loss of appetite, hemolysis by immune-mediated antibodies, or changes in coagulation parameters. For this myriad of reasons, anemia is prevalent among patients with cancer at initial presentation. For example, 32% of NHL patients and 49% of patients with gynecologic cancers are anemic at diagnosis.^{281,282} Patients with lung cancer have a particularly high incidence of CIA.²⁸³

In addition, many chemotherapy agents produce myelosuppression, which contributes to anemia.²⁸³ Chemotherapeutic agents induce anemia by directly impairing hematopoiesis in the bone marrow, including disruption of RBC precursor production.²⁸⁰ Additionally, the nephrotoxic effects of some cytotoxic agents (eg, platinum-containing agents) can result in

decreased production of erythropoietin by the kidneys.²⁸⁰ RT to the skeleton has also been associated with hematologic toxicity. In a retrospective analysis of 210 patients undergoing craniospinal RT for treatment of primary tumors of the central nervous system, approximately one-third of patients developed grade 3/4 hematologic toxicities.²⁸⁴

Newer modalities, such as immunotherapies, may also produce anemia, though data are limited.^{285,286} A recent study recognized hemolytic anemia as a potential complication of treatment with nivolumab, an anti-PD-1 antibody.²⁸⁷ Although a definitive link has not been clearly established, several reported cases of autoimmune hemolytic anemia after use of nivolumab have been recently documented in the literature, including a case of fatal autoimmune hemolytic anemia refractory to steroids in a patient treated for metastatic lung cancer.²⁸⁸⁻²⁹⁰ In another case report, a 52-year-old woman with malignant melanoma undergoing sequential treatment with ipilimumab (an anti-CTLA-4 antibody) and pembrolizumab (another anti-PD-1 antibody) presented with acute autoimmune hemolytic anemia with PRCA, a potentially life-threatening complication.²⁹¹ Clinicians should become familiar with the adverse effects of immunotherapy drugs, including hemolytic anemia, and be observant for other less-documented clinical conditions as these therapies become more prevalent in cancer care.

The myelosuppressive effects of particular cytotoxic agents are likely to accumulate over the course of repeated cycles of therapy, resulting in a steady increase in the rate and severity of anemia with additional chemotherapy cycles. For example, in the European Cancer Anaemia Survey (ECAS),²⁸² the rate of anemia (Hb level <12 g/dL) was found to increase from 19.5% in cycle 1 to 46.7% by cycle 5.²⁸² An increase in the fraction of grade 2 to 3 anemia was also associated with a greater number of chemotherapy cycles. Other factors to consider when evaluating the risk for CIA include the nadir Hb level, the time to the nadir Hb level (roughly

estimated at 2 weeks, but time can vary), and whether an Hb measurement is considered to be pre- or post-nadir.²⁸⁰

Initial Evaluation of Anemia

Given the wide variation in Hb levels among healthy subjects, a universal “normal” value is difficult to define. According to the NCCN Panel, an Hb level ≤ 11 g/dL should prompt an evaluation of anemia in a patient with cancer. For patients with a high baseline level, a drop ≥ 2 g/dL is also cause for concern and assessment. As discussed above, a patient with cancer may suffer from anemia as the result of a combination of causes, some of which may not be directly related to the cancer (reviewed by Gilreath et al²⁷⁷). The overall goals of evaluation are to characterize the anemia and identify any potentially correctable underlying comorbidities prior to initiating treatment.

Initial characterization of anemia involves a CBC with indices to determine if other cytopenias are present. A visual review of the peripheral blood smear morphology is critical to confirm the size, shape, and Hb content of RBCs. A detailed history and physical exam must also be taken. The history should include the onset and duration of symptoms, comorbidities, family history, and whether there has been any exposure to antineoplastic drugs or radiation. Common complaints are syncope, exercise dyspnea, headache, vertigo, chest pain, fatigue that is disruptive to work and daily activities, and abnormal menstruation in female patients. Pallor may be apparent. A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that cancer-related fatigue is less likely to be ameliorated by rest (see [NCCN Guidelines for Cancer-Related Fatigue](#)).²⁹² The above clinical manifestations are neither sensitive nor specific to the type of anemia. Clinicians should watch for signs of underlying etiologies such as jaundice, splenic enlargement, neurologic symptoms, blood in the stool, petechiae, and heart murmur, among others.

Approaches to Evaluation

There are two common approaches to evaluating anemia: morphologic and kinetic. A complete evaluation should utilize both. The morphologic approach is a characterization of anemia by the mean corpuscular volume (MCV), or average RBC size, reported in the initial CBC and classified as follows:

- Microcytic (<80 fL)—most commonly caused by iron deficiency; other etiologies include thalassemia, anemia of chronic disease, and sideroblastic anemia.
- Macrocytic (>100 fL)—most commonly caused by medications²⁹³ and alcoholism, both of which are forms of non-megaloblastic anemia. MDS also causes mild macrocytosis. Macrocytosis seen in megaloblastic anemia is most frequently caused by vitamin deficiency resulting from inadequate intake (folic acid or B₁₂) or inadequate absorption of B₁₂ from lack of intrinsic factor or antibodies to parietal cells. Macrocytosis accompanies increased reticulocyte counts following brisk hemorrhage or hemolysis.
- Normocytic (80–100 fL)—may be due to hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation, or renal insufficiency. The key follow-up test is the reticulocyte (immature RBC) count (see below).

The kinetic approach focuses on the underlying mechanism of anemia, distinguishing among the production, destruction, and loss of RBCs. The most basic RBC index is the reticulocyte index (RI) that corrects the reticulocyte count against the degree of anemia as measured by Hct. The reticulocyte count, often represented as a percentage, reflects the number of reticulocytes per number of total RBCs. The RI is calculated based on the reticulocyte count and is an indicator of the RBC production capacity by the bone marrow. The normal RI ranges from 1.0 to 2.0.

- $RI = \text{Reticulocyte count (\%)} \times [(\text{observed Hct})/(\text{expected Hct})]$, where the expected Hct is equal to 45%.

Reticulocytes normally persist in the circulation for 24 hours before becoming erythrocytes. However, as anemia increases, younger reticulocytes are released from the marrow requiring them to remain in circulation for 2 to 3 days before converting to erythrocytes, thereby giving a falsely high RI value. The reticulocyte production index (RPI) is an adjusted index that takes this into account and is calculated using the following formula:

- $RPI = RI \times (1/RMT)$, where RMT is the reticulocyte maturation time constant determined by the observed Hct (see Table 2).
- Low RI/RPI ratio (<1) indicates decreased RBC production, suggesting iron deficiency, B₁₂/folate deficiency, aplastic anemia, or bone marrow dysfunction due to cancer or cancer-related therapy (eg, radiation, myelosuppressive chemotherapy).
- High RI/RPI ratio (>1) indicates normal RBC production, suggesting blood loss or hemolysis in the anemic patient.

Table 2. Correction Factor for RPI Calculation

Hematocrit %	Reticulocyte maturation time (RMT) in days
40–45	1.0
35–39	1.5
25–34	2.0
15–24	2.5
<15	3.0

Additional signs and symptoms of common underlying ailments and/or informative diagnostic tests as follows:

- Nutritional deficiency—low iron and elevated total iron-binding capacity (TIBC) and/or low vitamin B₁₂ or red cell folate levels

(commonly tested together with iron studies). Ferritin values are also useful in evaluating iron stores. Fasting values are preferred for serum iron and TIBC studies.

- Hemorrhage—stool guaiac positive, endoscopy findings.
- Hemolysis—direct antiglobulin test positive, disseminated intravascular coagulation panel positive, low haptoglobin levels, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH).
- Renal dysfunction—glomerular filtration rate <60 mL/min/1.73 m² for ≥3 consecutive months.
- Inherited anemia—personal and family history.
- Sideroblastic anemia—sideroblasts present in bone marrow biopsy.
- Hormone dysfunction—hypogonadism, adrenal dysfunction, hyper/hypothyroidism.

Any other cause of anemia that may be rectified independent of cancer therapy should be treated as indicated. When no such etiology is identified, the effects of cancer-related inflammation and/or myelosuppressive chemotherapy (if applicable) should be considered the cause of anemia. If this is the case, a risk assessment of the anemic patient is necessary to determine the initial intervention plan. The decision regarding the best treatment option is dependent on many factors. While PRBC transfusion is best for symptomatic patients requiring an immediate boost in Hb levels, consideration of ESA therapy and/or iron supplementation may be warranted for the long-term management of anemia in high-risk patients or in asymptomatic patients with comorbidities.

Red Blood Cell Transfusion

The decision to offer PRBC transfusion should not be made on the basis of whether the Hb level of the patient has reached a certain threshold or

“trigger”. Instead, the NCCN Panel outlines three general categories: 1) asymptomatic without significant comorbidities, for which observation and periodic re-evaluation are appropriate; 2) high risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation) or asymptomatic with comorbidities (eg, cardiac disease, chronic pulmonary disease, cerebral vascular disease), for which transfusion can be considered; and 3) symptomatic, for which patients should receive transfusion. Physiologic symptoms warranting the use of PRBC transfusion include sustained tachycardia, tachypnea, chest pain, dyspnea on exertion, lightheadedness, syncope, or severe fatigue preventing work and usual activities.

The clinical manifestations of anemia are associated with the onset, severity, and duration of the anemia, as well as other factors influencing tissue demands for oxygen. When anemia onset is acute, symptoms are likely to be more pronounced, whereas physiologic adjustments that compensate for the lower oxygen-carrying capacity of the blood can occur with the gradual onset of anemia. These adaptive measures include heightened cardiac output, increased coronary flow, altered blood viscosity, and changes in oxygen consumption and extraction. The presence of preexisting cardiovascular, pulmonary, or cerebral vascular disease may compromise the ability of a patient to tolerate anemia. Hence, decisions related to whether immediate correction of anemia is needed must be based on an assessment of individual patient characteristics, severity of anemia, presence and severity of comorbidities, and the clinical judgment of the physician. For example, even when an anemic patient has no physiologic symptoms or significant comorbidities, transfusion may be appropriate if there is an anticipated progressive decline in Hb level following anti-cancer treatment.

PRBCs are the blood product of choice for transfusion to correct anemia. These are concentrated from centrifuged whole blood donations or collected by apheresis. They are anticoagulated and may contain added

preservatives. Further enhancements include leukoreduction, γ-irradiation, freezing, and washing. Patients who are immunocompromised may need PRBCs that are cytomegalovirus (CMV) negative. Leukoreduction is often sufficient to reduce the risk of CMV transmission. For example, patients who are candidates for or undergoing autologous or allogeneic HCT require blood products that have undergone leukocyte reduction and γ-irradiation to reduce the risks of transfusion-associated GVHD, viral transmission, and alloimmunization. One unit of PRBCs (300 cc) can have an Hct ranging from 50% to 80%, and typically contains 42.5 to 80 g of Hb (with 147–278 mg of iron) or 128 to 240 mL of pure RBCs.²⁹⁴

Benefits and Risks of Red Blood Cell Transfusion

The major benefit of transfusion with PRBCs, offered by no other anemia treatment, is a rapid increase in Hb and Hct levels and thus, a rapid improvement in anemia-related symptoms. Hence, PRBC transfusion is the only option for patients who require immediate correction of anemia. Transfusion of 1 unit (300 cc) of PRBCs has been estimated to result in an average increase in Hb level by 1 g/dL or in Hct level by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.^{294,295} It should be noted that patients receiving concomitant fluid resuscitation may not experience an Hb increase of 1 g/dL per unit of blood transfused.

Results from a number of studies evaluating the impact of transfusion on mortality in patients with cancer have been conflicting, with some studies showing a survival benefit for patients receiving transfusion. For example, in a study of 56 consecutive patients with unresectable esophageal cancer receiving chemoradiation therapy, blood transfusion was associated with an increase in OS (HR, 0.26; 95% CI, 0.09–0.75, $P = .01$).²⁹⁶ A retrospective study of data collected from 605 patients with carcinoma of the cervix evaluated Hb levels prior to therapy and through completion of therapy. Patients with high Hb levels prior to therapy had a significant increase in disease-free survival and OS. Patients who were transfused to

increase Hb levels had a survival rate that was similar to patients who had the same initial Hb value but did not receive transfusion. Therefore, blood transfusion may reduce the negative prognostic implications of low Hb.²⁹⁷

Risks associated with PRBC transfusion include transfusion-related reactions (eg, hemolytic, non-hemolytic, febrile, lung injury), transfusion-associated circulatory overload, virus transmission (ie, hepatitis, HIV), bacterial contamination, iron overload (reviewed by Spivak, Gascon, and Ludwig²⁹⁸), increased thrombotic events, and alloimmunization of RBCs or platelets. Since 1984, the introduction of numerous safety interventions to screen the U.S. blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections.^{299,300} Bacterial infection is the most common form, and occurred as frequently as 1 in 3000 random-donor samples before the mandate of bacterial screening in 2004.³⁰⁰ Since the implementation of screening, fewer than 10 deaths from bacterial sepsis per year have been reported in PRBC transfusion patients. Pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse event.^{301,302}

Khorana et al³⁰³ analyzed data from discharge summaries of patients with cancer admitted to 60 U.S. medical centers between 1995 and 2003 and found increased risks ($P < .001$) of venous thromboembolism (VTE) (OR, 1.60; 95% CI, 1.53–1.67), arterial thromboembolism (OR, 1.53; 95% CI, 1.46–1.61), and in-hospital mortality (OR, 1.34; 95% CI, 1.29–1.38) associated with PRBC transfusions.³⁰³ However, the increased thrombotic events and decreased survival may reflect a bias of more severe anemia and/or more advanced cancer in patients who required transfusions. A cause-effect relationship could not be established due to the retrospective nature of the study. Therefore, greater investigation into the relationship between blood transfusions and the incidence of VTE and mortality is warranted.

RBC alloimmunization can be a significant complication for patients who are chronically transfused. It has been reported that 15% of transfusion-dependent patients with MDS or chronic myelomonocytic leukemia have alloimmunization.^{304,305} Platelet alloimmunization may also occur. Antibodies against HLA antigens can cause platelet transfusion refractoriness, which can translate into increased patient bleeding, prolonged hospitalization, and decreased survival.^{306,307}

The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anemia (eg, patients with MDS).³⁰⁸ However, iron overload is unlikely to occur in patients receiving transfusions that are limited to the time period corresponding to chemotherapy treatment (usually <1 year). As previously mentioned, each transfusion of PRBCs contains 147 to 278 mg of excess iron that cannot be excreted.²⁹⁴ When iron stores become saturated, iron remains as non-transferrin-bound iron.³⁰⁹ After as few as 10 to 20 transfusions of PRBCs, excess iron will have deposited in the liver, heart, skin, and endocrine organs. Patients experiencing iron overload may present with fatigue, dark skin, arthralgia, hepatomegaly, cardiomyopathy, or endocrine disorders. Therefore, the benefits of PRBC transfusion need to be weighed against the risks of cumulative cardiac and hepatic toxicities.^{310,311} Serum ferritin levels and any associated end-organ dysfunction need to be monitored in patients requiring chronic PRBC transfusions. While a survival benefit to chelation therapy has not been shown in patients requiring transfusion support for CIA or MDS, a ferritin level ≥ 1000 mcg/L with elevated TSAT triggers concern for iron overload.³¹² Imaging modalities such as FerriScan and T2 star-weighted cardiac MRI provide useful organ-specific iron overload assessments.^{313,314} Patients treated with curative intent who are in remission and have received >15 units of PRBCs should be considered for phlebotomy to remove excess iron.

Red Blood Cell Transfusion Goals and Basic Principles

The overall goal of PRBC transfusion is to treat or prevent deficiencies in the oxygen-carrying capacity of the blood in order to improve oxygen delivery to bodily tissues. In 2016, the AABB (formerly the American Association of Blood Banks) published clinical practice guidelines based on a systematic review of randomized controlled trials evaluating transfusion Hb thresholds for RBC transfusion.³¹⁵ AABB recommendations include: 1) using an Hb level of 7 g/dL as a threshold for hospitalized adult patients who are hemodynamically stable; 2) using an Hb level of 8 g/dL as a threshold for patients undergoing orthopedic surgery, cardiac surgery, or those with pre-existing cardiovascular disease; and 3) using RBC units selected at any point within their licensed dating period rather than limiting patients to transfusion of only fresh RBC units. However, there was a lack of evidence to provide specific recommendations for the cancer population. NCCN Panelists agree that no single target Hb level is appropriate for all cases and that the balance between transfusion risks and benefits should be evaluated on an individual basis. Clinicians are urged to exercise their clinical judgment based on patient symptoms, cancer course and treatment, comorbidities, and patient preference.

Prior to transfusion, PRBCs must be crossmatched to confirm compatibility with ABO and other antibodies in the recipient. There is no evidence to support routine premedication with acetaminophen or an antihistamine to prevent allergic and febrile non-hemolytic transfusion reactions.^{316,317} However, if repeated transfusions are required, leukocyte-reduced blood and the use of premedication may minimize adverse transfusion reactions. In most instances, PRBCs should be transfused by the unit, and reassessment should be conducted after each transfusion. When considering PRBC transfusion, refer to the 2016 AABB clinical practice guidelines.³¹⁸

Patients with CIA Who Refuse Blood Transfusions

Patients with CIA who refuse blood transfusions are occasionally seen in clinical practice. Religious beliefs or personal preferences may prohibit such patients from using blood products. For such patients, clinicians should consider the risk of anemia when making treatment decisions. Although there are limited available data on the best management of CIA in patients who refuse blood transfusions, several strategies can be employed to reduce anemia in this patient population, including minimizing blood loss,³¹⁹⁻³²³ use of ESAs,^{322,324,325} or use of blood substitute products.^{319,322,324-327} Strategies to reduce blood loss include batching routine laboratory testing, using pediatric blood collection tubes, minimizing phlebotomy, and returning discard in a closed system.³¹⁹⁻³²³ Additionally, consider daily folic acid and vitamin B₁₂ supplementation prior to initiation of myelosuppressive chemotherapy. Nutritional sufficiency for iron, folate, and vitamin B₁₂ should be evaluated and deficiencies corrected. Iron deficiency should be corrected using intravenous (IV) iron. Baseline coagulation abnormalities should also be fully evaluated and corrected prior to myelosuppressive treatment.

The majority of data regarding the use of ESAs in patients who refuse blood transfusions comes from published case reports and small cohort series involving patients who are Jehovah's Witnesses. These types of reports carry inherent bias and vary significantly in reporting of outcomes, regimens, and dosing.³²⁴ A 2008 analysis of 14 case reports of Jehovah's Witness patients receiving ESA therapy in a variety of clinical situations concluded that while administration of ESAs enhanced Hb levels in each situation, time to the start of treatment, dosage, route of administration, and treatment duration varied widely among included studies.³²⁸ Additionally, there was a lack of data regarding Jehovah's Witness patients with CIA. More recent case reports on Jehovah's Witness patients, including two involving patients with cancer, have reported similar results on the effectiveness of ESAs in increasing Hb levels.³²⁹⁻³³⁴ In one

case report, a 57-year-old male Jehovah's Witness diagnosed with CIA secondary to aggressive NHL was administered darbepoetin alfa once per week. This therapy increased his Hb level from 7.5 g/dL to 11.5 g/dL within 1 month and enabled completion of intensive chemotherapy.³²⁹

Although there is a lack of prospective data, ESAs should be considered given that there is no option for transfusion in such patients.^{322,324} ESAs are not recommended for the following: 1) patients with cancer who are not receiving chemotherapy; 2) patients receiving non-myelosuppressive chemotherapy; or 3) patients receiving myelosuppressive chemotherapy with curative intent. If ESAs are prescribed off-label for these indications, patients should be made aware of the potential increased risks of thrombosis and tumor progression and should know that under these circumstances the ESAs are being used off-label. It should be noted that the effects of ESA therapy on Hb level may not be evident for several days after administration. Therefore, in extreme cases of severe, life-threatening anemia, pure oxygen (400 mm Hg, $S_AO_2 = 1.0$) by mechanical ventilation can be used to increase blood oxygenation.³³⁵

Although not FDA-approved, clinicians may obtain access to investigational blood substitute products, also known as hemoglobin-based oxygen carriers (HBOCs), for single-patient compassionate use under the FDA's Expanded Access program.^{319,322,324-327,336} HBOCs are cell-free Hb molecules typically derived from animals that offer advantages over transfusions, including transportability, the lack of need for refrigeration or crossmatching, and reduced risks of infectious and allergic complications.³²⁴ Despite these benefits, few products have advanced to phase III trials and no products have produced a significant decrease in the need for transfusions (in patients who accept transfusion support). The use of HBOCs has been associated with serious adverse reactions.³²⁷ A 2008 meta-analysis by Natanson et al concluded that patients treated with an HBOC had a 1.3- and 2.7-fold increased risk of mortality and myocardial infarction, respectively, when compared with patients who had

undergone conventional treatment with or without blood products.³³⁷ However, with compassionate use, HBOCs have successfully treated Jehovah's Witnesses with severe anemia in emergent settings.^{326,338-342} Therefore, while HBOCs may represent a lifesaving modality in the setting of severe anemia in patients who refuse blood transfusions, further evaluation of these products in clinical trials is needed. Since a case series evaluation has suggested that delay in receipt of HBOCs is independently associated with mortality in patients who refuse blood transfusions, clinicians should consider starting the regulatory process for procurement of HBOCs early on in the course of treatment.³⁴³

Erythropoietic Therapy

RBC production is normally controlled by erythropoietin, a cytokine produced in the kidneys. ESAs have been shown to stimulate erythropoiesis in patients with low RBC levels, though not all patients have disease that responds to ESA therapy. In a study of 2192 patients with cancer receiving ESA therapy, an Hb increase of ≥ 1 g/dL was attained in 65% of patients.³⁴⁴ Unlike transfusion, which immediately boosts the Hb level, ESAs can take weeks to elicit an Hb response, but they are effective at maintaining a target Hb level with repeated administration.

Benefits of ESA Therapy

A gradual improvement in anemia-related symptoms and avoidance of transfusion are the main goals of ESA therapy. Use of ESAs has been demonstrated to decrease transfusion requirements in patients with cancer undergoing chemotherapy. In a randomized, placebo-controlled study, epoetin alfa was shown to reduce transfusion requirements (24.7% vs. 39.5%, $P = .0057$) and increase Hb levels (2.2 g/dL vs. 0.5 g/dL, $P < .001$) in patients with anemia receiving chemotherapy.³⁴⁵ In a randomized phase III study, lung cancer patients with Hb ≤ 11 g/dL receiving chemotherapy and darbepoetin alfa required fewer transfusions (27% vs.

52%; 95% CI, 14%–36%; $P < .001$) than patients receiving chemotherapy and placebo.³⁴⁶ The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review that enrolled a total of 20102 patients undergoing treatment for cancer with concomitant ESA therapy.³⁴⁷ A decreased RR for transfusion was observed in patients receiving ESAs (RR, 0.65; 95% CI, 0.62–0.68).³⁴⁷ Of the patients treated with ESAs, 25 out of 100 subsequently received a transfusion versus 39 out of 100 patients in the untreated group, equating to a one-unit reduction in transfusion in ESA-treated patients. The first patient-level meta-analysis evaluating the efficacy of darbepoetin alfa treatment when initiated at Hb ≤ 10 g/dL in patients with CIA found that more patients who received darbepoetin alfa than placebo achieved an Hb increase of ≥ 1 g/dL (fixed-effects HR = 2.07; 95% CI, 1.62–2.63) or ≥ 2 g/dL (HR = 2.91; 95% CI, 2.09–4.06).³⁴⁸ Transfusions were also less common in these patients (HR = 0.58; 95% CI, 0.44–0.77).

Risks of ESA Therapy

ESA use has associated toxicities, including increased thrombotic events, possible decreased survival and shortened time to tumor progression. When considering ESAs, discuss the risks of ESA therapy with patients including the potential for tumor growth, death, blood clots, and serious heart problems. It should be reiterated that ESAs are not recommended for patients with cancer treated with curative intent outside of a clinical trial.

Risk for Thromboembolism

Increased thromboembolic events, including VTE, have been associated with ESA therapy in patients with cancer. The thrombotic potential of ESAs is independent of Hb levels.³⁴⁹ The cause of VTE is complex with a heightened baseline risk related to both the malignancy itself and to the chemotherapy regimen used (see [NCCN Guidelines for Cancer-](#)

[Associated Venous Thromboembolic Disease](#)).³⁵⁰⁻³⁵³ Other risk factors for VTE in patients with cancer include prior history of VTE, inherited or acquired mutations, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, prolonged immobility, steroid use, and comorbidities such as hypertension.³⁵⁴ Patients with risk factors for thrombosis may be at a higher risk for thrombosis with the use of ESAs. Therefore, risk factors should be evaluated in each patient before administration of ESA therapy.

Results from several meta-analyses have established a significant association between ESA usage and increased risk of thrombotic events, with an increased RR ranging from 1.48 to 1.69.^{347,355-359} In an analysis of phase III trials comparing ESAs with placebo or standard of care for the treatment of anemia in patients with cancer, the absolute risk of VTE was 7.5% in patients treated with ESAs compared with 4.9% in control patients.³⁵⁵ Additionally, an increased risk of stroke was associated with darbepoetin alfa in a clinical trial of patients with CKD (RR, 1.92; 95% CI, 1.38–2.68; absolute risk; 5% vs. 2.6% in the placebo group).³⁶⁰ ESA use was also associated with a significantly increased risk of stroke (OR, 1.83; 95% CI, 1.26–2.65) in a retrospective case-controlled study of CKD patients with cancer.³⁶¹

The increased risk for thromboembolism in patients with cancer receiving ESA therapy is specified in the black-box warnings included in the FDA labels. The NCCN Panel cautions physicians to be alert to the signs and symptoms of thromboembolism in patients with cancer receiving ESAs.

Possible Increased Mortality and Tumor Progression

Since their approval in 2007, the FDA has made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa,^{16,17} including the addition of black-box warnings. These strengthened FDA restrictions were based on the results of 8 randomized studies that individually showed a decrease in OS and/or locoregional

disease control with ESA usage in breast, cervical, head and neck, lymphoid, non-myeloid, and non-small cell lung cancers (NSCLCs).³⁶²⁻³⁶⁹ Of the 8 studies, 4 investigated ESAs in patients who underwent chemotherapy, 2 studies involved patients receiving RT alone, and 2 studies involved patients receiving neither chemotherapy nor RT. All 8 trials had an off-label target Hb level >12 g/dL. Additional meta-analyses of randomized controlled trials have confirmed worsened health outcomes associated with the use of ESAs when targeting Hb levels >12 g/dL.^{347,355,357,359,370} Data from the Cochrane Database also reported increased mortality associated with ESA use in patients when targeting Hb >12 g/dL.³⁴⁷ It should be noted that the risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL. Data from a systematic review by the Agency for Healthcare Research and Quality (AHRQ) showed that delaying ESA treatment until Hb is <10 g/dL resulted in fewer thromboembolic events and a reduced mortality.³⁵⁷

Recent studies suggest that use of ESAs may be deleterious when used in patients with metastatic breast cancer. A randomized phase III noninferiority study by Leyland-Jones et al compared epoetin alfa versus best supportive care for the treatment of CIA in 2098 women with metastatic breast cancer and Hb ≤11 g/dL.³⁷¹ The primary endpoint of progression-free survival (PFS) was the same in both groups (7.4 months; HR, 1.089; 95% CI, 0.988–1.200). Median OS was 17.2 months in the epoetin alfa group compared to 17.4 months in the best standard of care group (HR, 1.057; 95% CI, 0.949–1.177) and median time to tumor progression was 7.5 months in both groups (HR, 1.094; 95% CI, 0.991–1.209). The authors conclude that transfusions should remain the preferred treatment for anemia in patients with metastatic breast cancer. This assertion has been contested by other investigators.³⁷²⁻³⁷⁴

The association between increased mortality and ESA therapy has been debated in other meta-analyses, including two studies reporting no

statistically significant effect of ESAs on mortality or disease progression.^{356,358} Pharmacovigilance trials have also reported no adverse effects on survival in patients with CIA receiving ESAs.^{375,376} Several prospective trials have reported similar outcomes. The phase III WSG-ARA trial that included 1234 patients with early-stage breast cancer receiving adjuvant ESA therapy evaluated survival as the primary endpoint.³⁷⁷ In this study, no impact on event-free survival (EFS) (darbepoetin alfa, 89.3% vs. no darbepoetin alfa, 87.5%; $P_{\log\text{-rank}} = 0.55$) or OS (darbepoetin alfa, 95.5% vs. no darbepoetin alfa, 95.4%; $P_{\log\text{-rank}} = 0.77$) was observed with the use of ESAs. Additionally, data from two randomized studies showed no increase in mortality in patients receiving chemotherapy for small cell lung cancer when ESAs were given according to the prescribing label.^{378,379} In the AGO-ETC trial, which included 1284 high-risk breast cancer patients, epoetin alfa resulted in improved Hb levels and decreased transfusions without an impact on relapse-free or OS.³⁸⁰ In another trial involving 873 patients with ovarian cancer, administration of ESAs did not have a negative impact on survival after adjustment of prognostic factors. The authors suggest that ESAs may appear to be associated with shorter survival in univariate analyses because factors prognostic for ESA use are also prognostic for PFS. While these data suggest that use of ESAs may not be associated with decreased survival or increased disease progression as previously thought, additional prospective trials designed and powered to measure survival of patients with cancer are needed to provide clinicians with data to guide optimal use of ESAs.

Risk for Hypertension/Seizures

Seizures have been reported in patients with chronic renal failure receiving ESAs.¹⁶ Additionally, an increased risk for hypertension with ESA usage in patients with cancer was reported by a Cochrane review (RR, 1.30; 95% CI, 1.08–1.56).³⁴⁷ Blood pressure should be controlled in all patients prior to initiating ESA therapy and must be monitored regularly throughout

treatment. Hb levels should be monitored before and during the use of ESAs to decrease the risks of hypertension and seizures.

Risk for Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count and loss of bone marrow erythroblasts caused by the development of neutralizing antibodies against erythropoietin. A marked rise in incidence (197 cases) of PRCA was observed between 1998 and 2004, though over 90% of cases occurred with an epoetin alfa product used outside of the United States.^{381,382} Causation was attributed to formulations without human serum albumin, subcutaneous administration, and use of uncoated rubber stoppers.³⁸³ Interventions, designed accordingly to address these issues, reduced the incidence of PRCA by 83%. In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia, resulting in a class label change for all ESAs.^{16,17} Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa in patients with chronic renal failure.³⁸³ Therefore, patients who develop a loss of response to ESAs should be evaluated for possible PRCA, and if present, all ESA drugs should be discontinued.³⁸¹

Considerations for the Use of ESAs

In 2017, the FDA determined that the ESA Risk Evaluation and Mitigation Strategy (REMS) program is no longer necessary to ensure that the benefits of ESA therapy outweigh its risks of shortened OS and/or increased risk of tumor progression or recurrence in patients with cancer.³⁸⁴ The FDA made this determination based on an evaluation of the results of the REMS Assessments and additional FDA analyses.

For patients with cancer, the black box warning on the revised FDA label states that ESAs should only be used to treat CIA and should be discontinued once the chemotherapy course is complete.¹⁶ As discussed previously, randomized trial data suggest that ESAs may promote tumor growth in an off-target manner. For this reason, the FDA states that these agents should not be used when the treatment intent is curative. This includes primary and adjuvant chemotherapy for malignancies such as early-stage breast cancer, NSCLC, lymphomas, and testicular cancer, among others. An exception to this may be small cell lung cancer, for which there are trials demonstrating no negative impact on survival or disease progression with ESA use.^{378,379} Additionally, ESAs are not recommended for use in patients with cancer who are not receiving therapy, patients receiving non-myelosuppressive therapy, or patients receiving myelosuppressive therapy in whom the anemia can be managed by transfusion. Patients undergoing palliative treatment may consider ESA therapy, transfusion, or participation in a clinical trial, depending on their preferences and personal values. The NCCN Panel recognizes that it is not always clear whether a chemotherapy regimen is considered curative. Under these circumstances, if no other cause of anemia has been identified, physicians should first consider PRBC transfusion or clinical trial enrollment, if available, for anemia management. Upon the decision to use an ESA, physicians are advised to use the lowest dose necessary to eliminate symptoms and avoid transfusion.

CKD is an independent indication for ESA therapy. Adverse events occurring with the use of ESAs in these patients appear to be associated with high doses and/or high-target Hb levels. Hence, the FDA label mandates individualized dosing to reduce the need for PRBC transfusions. Controlled clinical trials have associated increased risks of mortality and adverse cardiovascular outcomes with ESA use in CKD patients when targeted to Hb levels >11 g/dL.^{349,360,361,385-387} In the study by Pfeffer et al³⁶⁰ comparing darbepoetin alfa to placebo, a significant increase in cancer-

related death was seen in CKD patients with pre-existing cancer at baseline treated with ESA therapy ($P = .002$). However, another study of patients with stages 4 and 5 CKD did not find an increased incidence of cancer in patients receiving ESAs.³⁸⁵ Additionally, data from Seliger et al³⁶¹ indicated that ESA treatment in patients with CKD was not associated with an overall increased risk for stroke, except in the subpopulation diagnosed with cancer.³⁶¹ Since almost one-third of patients with end-stage renal disease are also afflicted with cancer, they represent a unique subgroup that requires personalized use of ESAs based on very careful evaluation of risks and benefits (reviewed by Bennett et al³⁸⁸). For example, CKD patients not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor carefully dosed ESAs over transfusion to treat severe anemia. In the scenario where the patient with CKD has a curable solid tumor, ESAs should not be administered during chemotherapy. However, they may be used with caution after chemotherapy is complete, keeping in mind the possibility of recurring disease. Risk for thrombosis must be taken into account as part of the risk-benefit ratio.

Dosing Schedules

Epoetin alfa, epoetin alfa-epbx, and darbepoetin alfa are recommended equivalently by the NCCN Panel. Head-to-head comparisons of epoetin alfa versus darbepoetin alfa are inconclusive with regard to the superiority of one agent over the other.³⁸⁹⁻³⁹¹ Recommended dosing schedules for patients receiving chemotherapy are summarized in the algorithm. The panel recommends two initial dosing schedules for epoetin alfa and epoetin alfa-epbx: 150 units/kg 3 times weekly^{345,392} and 40,000 units once weekly^{365,368,369,393} administered by subcutaneous injection (see *Erythropoietic Therapy – Dosing, Titration, and Adverse Effects* in the algorithm). Other dosing ranges and schedules of epoetin alfa may be considered, including an extended dose of 80,000 units administered

every 2 weeks³⁹⁴ and a dose of 120,000 units administered once every 3 weeks.³⁹⁵

Although darbepoetin alfa doses were initially administered at 2.25 mcg/kg every week,^{346,363,396} there has been interest in implementing either fixed doses or higher doses at decreased frequency. A randomized trial comparing weekly dosing at 2.25 mcg/kg versus fixed dosing at 500 mcg every 3 weeks in 705 patients with non-myeloid malignancies and an Hb level <11 g/dL showed that the percentage of patients achieving the target Hb level (≥ 11 g/dL) was higher in the weekly arm compared to patients receiving darbepoetin alfa every 3 weeks (84% vs. 77%).³⁹⁶ Dosing once every 3 weeks was further refined in 2 studies, which reduced the dose to 300 mcg. Initially, a multicenter study of 1493 patients showed that 79% of patients receiving this dose achieved a target Hb level ≥ 11 g/dL.³⁹⁷ A head-to-head comparison with 500 mcg in a phase II randomized study further confirmed the efficacy of 300 mcg. In this study, no difference in the proportion of patients who achieved target Hb levels (≥ 11 g/dL) was seen between those receiving 300 mcg versus 500 mcg darbepoetin alfa (75% vs. 78%, respectively).³⁹⁸ Alternative dosing schedules for darbepoetin alfa include a fixed weekly dose of 100 mcg³⁴⁶ and a fixed dose of 200 mcg every 2 weeks.³⁹⁹ In addition to the dosing schedules on the package insert, the NCCN Panel recommends these alternative regimens to support the delivery of the lowest ESA dose possible while maintaining maximal efficacy. Iron studies (serum iron, TIBC, and serum ferritin) should accompany ESA therapy to monitor the development of iron deficiency (See *Iron Monitoring and Supplementation* below for more information).

Response Assessment and Dose Titration

Response to ESA therapy is assessed to determine whether the initial dose should be reduced, escalated, or withheld. Decisions related to ESA dose adjustment are based on the goal of maintaining the lowest Hb level

sufficient to avoid transfusion. ESAs require at least 2 weeks of treatment before there is an increase in the number of RBCs. Hb level should be measured weekly until stabilized. Dose reduction (generally 25% for epoetin alfa or epoetin alfa-epbx and 40% for darbepoetin alfa) should be implemented once Hb reaches a level sufficient to avoid transfusion or if the Hb level increases by ≥ 1 g/dL during a 2-week period.

Conversely, the ESA dose should be increased according to the algorithm (see *Erythropoietic Therapy – Dosing, Titration, and Adverse Effects*) for patients receiving chemotherapy who show no response (defined as Hb increase < 1 g/dL and remains below 10 g/dL) following 4 weeks of epoetin alfa or epoetin alfa-epbx treatment or following 6 weeks of darbepoetin alfa treatment. A subsequent response at 8 weeks may necessitate a dose escalation to avoid transfusion. Iron supplementation should be considered to improve response to ESA therapy. A recent Cochrane Database review concluded that the addition of iron to ESA therapy offers superior hematopoietic response, reduces the risk of transfusions, improves Hb levels, and appears to be well tolerated.⁴⁰⁰ A meta-analysis of randomized controlled trials also showed that the addition of parenteral iron reduces the risk of transfusions by 23% and increases the chance of hematopoietic response by 29% when compared with ESAs alone.⁴⁰¹ ESA therapy should be discontinued and PRBC transfusion should be considered in patients showing no response despite iron supplementation after 8 weeks of therapy. ESAs should also be discontinued when chemotherapy is completed or withdrawn.

Iron Monitoring and Supplementation

Iron Deficiency Evaluation and Definitions of Iron Status

Iron deficiency is reported in 32% to 60% of patients with cancer, most of whom are also anemic.⁴⁰² Iron studies, including serum iron, TIBC, and serum ferritin, should be performed prior to ESA treatment in order to rule out absolute iron deficiency, which may respond to oral or IV iron

monotherapy. Serum iron and TIBC levels may be falsely elevated by diet (reviewed in Collings et al⁴⁰³); therefore, fasting is recommended to provide more accurate measurements. Transferrin saturation should be calculated from these values using the following formula:

- $TSAT = (\text{serum iron level} \times 100) / TIBC$

Treatment for iron deficiency is guided by iron status, defined in these guidelines as absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. In the absence of a universal numerical definition of iron deficiency in relevant studies, the NCCN Panel recognizes that ferritin and TSAT values defining absolute and functional iron deficiencies represent moving targets.²⁷⁷ However, as general guidance, definitions and characteristics of each iron status group are discussed below.

Absolute Iron Deficiency

Absolute iron deficiency refers to the depletion of total body iron stores. It is characterized by low Hb, low serum iron, and high TIBC that result in a TSAT level $< 20\%$ and a ferritin level < 30 ng/mL. If the TSAT and ferritin parameters are discordant, a low ferritin value should take precedence in determining whether iron supplementation will be beneficial. The reference interval for serum ferritin depends on the specific laboratory used, but in general, the lower the level, the more probable that true iron deficiency is present. However, in the cancer setting, clinicians should be aware of a chronic inflammatory state, which may falsely elevate serum ferritin levels.

Although IV iron is preferred, either IV or oral iron products alone (without an ESA) are recommended for patients with cancer who develop absolute iron deficiency. Hb levels should increase after 4 weeks of treatment. Periodic evaluation of ferritin and TSAT levels is required as some patients, especially those with continued internal bleeding, may suffer a relapse. If the patient initially receives oral iron and the anticipated

response is not seen after 4 weeks, a trial of IV iron should be considered. If Hb is not improved after 4 weeks following IV iron supplementation, the patient should be evaluated for functional iron deficiency. Although data are conflicting in the literature, concerns exist regarding the possibility of IV iron promoting inflammation and bacterial growth.⁴⁰⁴ Hence, IV iron supplementation is not recommended for patients with an active infection.

For further discussion of absolute iron deficiency, see *Clinical Examples of Iron Status, case scenarios 1 and 2* below.

Functional Iron Deficiency

Functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production is deficient. This may occur when infection or inflammation blocks iron transport to the bone marrow, as seen in anemia of chronic disease (also known as anemia of chronic inflammation). Functional iron deficiency is defined in these guidelines as a ferritin level between 30 ng/mL and 500 ng/mL and a TSAT level <50%. IV iron supplementation with erythropoietic therapy should be considered for these patients. Although oral iron has been used more commonly, IV iron has superior efficacy and should be considered for supplementation in this setting. However, there are insufficient data to routinely recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency. Functional iron deficiency often arises following continued ESA use, resulting in a blunted erythropoietic response to anemia. Hence, iron supplementation will eventually be required in most patients in order to maintain optimal erythropoiesis.^{405,406}

For further discussion of functional iron deficiency, see *Clinical Examples of Iron Status, case scenario 3*.

Possible Functional Iron Deficiency

Possible functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production may

be deficient. These patients are defined by a TSAT level <50% and a ferritin level of 500 ng/mL to 800 ng/mL. Although clinical trials suggest that these patients may have functional iron deficiency, there are insufficient data to support the routine use of IV iron in this setting. The panel recommends no iron supplementation or the consideration of IV iron supplementation for select patients. Administration of IV iron to these patients should be individualized with the goal of avoiding allogeneic transfusion. ESA therapy is not recommended in this setting.

For further discussion of possible functional iron deficiency, see *Clinical Examples of Iron Status, case scenarios 4 and 5*.

No Iron Deficiency

Patients with ferritin values >800 ng/mL or a TSAT ≥50% are not iron deficient. These patients do not require iron supplementation or ESA therapy.

Intravenous Versus Oral Iron

Iron can be administered orally or intravenously. Although oral iron is appropriate for most iron-deficiency anemia patients, many patients with CIA either do not respond to oral iron, may be intolerant of oral iron, or may require higher iron doses than achievable with oral iron, making IV iron therapy a valuable option.⁴⁰⁷ Evidence from 5 published studies utilizing iron in conjunction with an ESA suggest that IV iron is superior to oral iron in improving Hb response rates in patients with CIA.⁴⁰⁸⁻⁴¹² Additionally, a recent study indicated that the addition of IV iron to ESA therapy for the treatment of CIA improved hematopoietic response, reduced the need for RBC transfusions, and increased Hb levels when compared to oral iron supplementation.⁴¹³ However, a trial published by Steensma et al challenged these positive results.⁴¹⁴ In this study, patients with CIA (n = 502) were randomized to receive IV iron, oral iron, or oral placebo in combination with ESA therapy. Initial analysis of the data led

the authors to conclude that IV iron failed to confer any benefit in terms of Hb response, transfusion requirement, or quality of life compared to oral iron or placebo. However, problems with the study design (including a suboptimal IV iron dosing regimen and a high proportion of participant dropouts) could explain the lack of response to IV iron observed in this study.⁴¹⁵ Another possible reason for the lack of response may have been that the mean baseline TSAT level for patients in the IV iron group was 22.5%, a value above what is considered to be associated with functional iron deficiency.^{414,415} Indeed, further analysis of study data indicated that even though the change in TSAT during the study period did not differ significantly between the 3 arms, median serum ferritin rose markedly in the IV iron group compared to the other cohorts, suggesting that the total body iron balance was substantially increased in the IV iron arm.⁴¹⁶ However, Steensma et al note that although this suggests that IV iron offers benefits to some patients, it is not yet clear which patients with CIA would benefit most from IV-administered iron. Therefore, developing clearer insight into the parameters that make patients more or less likely to respond to IV iron, as well as studies of alternative dose schedules of IV iron, are warranted.⁴¹⁶

It should be noted that patients with a baseline TSAT level <20% have a higher response rate to IV iron supplementation when given in addition to an ESA. As the TSAT level increases from 20% to 50%, the response rate is diminished, and the time to a response is prolonged. Hence, for patients with TSAT levels between 20% and 50%, IV iron should only be offered if benefits are likely to outweigh risks. None of the studies on iron supplementation in conjunction with ESAs provided instruction on how or when to re-dose iron after the initial cumulative dose has been given. Generally, repeat iron studies are not recommended within 3 to 4 weeks of administration. Clinicians may consider repeating iron studies when the MCV declines or hypochromic RBCs are seen on the peripheral blood smear. Additionally, repeat iron studies can be considered for patients with

anemia that fails to respond to iron supplementation 4 to 6 weeks after administration of the total intended dose.^{410,414} If evidence exists of iron overload, do not administer IV iron. Subsequent doses of iron should be withheld if the serum ferritin exceeds 800 ng/mL or if the TSAT exceeds 50%.⁴⁰⁹⁻⁴¹¹

Since the majority of studies show that IV iron is superior to oral iron, the panel recommends that IV iron supplementation be used in most circumstances. Low-molecular-weight iron dextran, ferric gluconate, and iron sucrose are the recommended IV iron preparations. Ferric carboxymaltose and ferumoxytol may be used in select cases. Common adverse events following FDA-approved doses of IV iron include hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness.⁴¹⁷⁻⁴¹⁹ Dosage details for administering IV iron therapy are listed in the algorithm (see *Recommendations for Administering Parenteral Iron Products*).

Low-Molecular-Weight Iron Dextran

A prospective, multicenter trial randomized 157 patients with CIA on epoetin alfa to receive: 1) no iron; 2) oral iron; 3) iron dextran IV bolus; or 4) iron dextran total dose infusion (TDI).⁴⁰⁸ Increases in Hb concentration were greater with IV iron dextran (groups 3 and 4) compared to oral iron or no iron ($P < .02$). Importantly, there was no difference between the oral and no iron groups ($P = .21$). Additionally, there was no statistically significant difference between groups 3 and 4 ($P = .53$), suggesting that lower, intermittent doses of IV iron dextran are equally as efficacious as TDI. Most adverse events associated with iron dextran, such as headaches, dizziness, nausea, vomiting, and diarrhea occurred with high-molecular-weight iron dextran.⁴²⁰ Therefore, the recommended iron dextran product is low-molecular-weight iron dextran.⁴²¹ Test doses are required for iron dextran (25 mg slow IV push). As reactions to the IV iron dextran test dose may be severe, pre-medication of the patient should

occur prior to administration of the test dose. Anaphylaxis-like reactions occur within minutes of the test dose but respond readily to IV epinephrine, diphenhydramine, and corticosteroids. It should be noted that patients may develop a reaction to IV iron dextran with later doses, and clinicians should be prepared to administer appropriate treatment. Delayed reactions to iron dextran may result in adverse events up to 24 to 48 hours following injection.⁴²²

Ferric Gluconate

In a multicenter trial, 187 patients with CIA on chemotherapy and epoetin alfa were randomized to receive no iron, oral ferrous sulfate 3 times daily, or weekly IV ferric gluconate.⁴¹¹ The Hb response rate (≥ 2 g/dL increase) was higher in the IV ferric gluconate arm (73%; $P = .0099$ vs. oral iron; $P = .0029$ vs. no iron) compared to the oral (45%; $P = .6687$ vs. no iron) or no iron (41%) arms. In another study, 149 patients with solid tumors and CIA were randomly assigned to receive weekly darbepoetin alfa with or without IV ferric gluconate.⁴¹² The IV ferric gluconate group showed a higher hematopoietic response rate compared to the no iron group (93% vs. 70%, respectively; $P = .0033$). In a study evaluating 396 CIA patients with non-myeloid malignancies undergoing chemotherapy, patients were treated with darbepoetin alfa with or without IV ferric gluconate every 3 weeks for 16 weeks.⁴⁰⁹ Both erythropoietic responses and time to reach the target Hb level were better in the IV ferric gluconate arm. Most significantly, this was the first study to associate IV iron with fewer RBC transfusions in patients with cancer (9% vs. 20%, $P = .005$). Prior to administration, test doses are recommended at physician discretion for patients receiving ferric gluconate based on the risk for reaction.

Iron Sucrose

A randomized controlled trial involving 64 patients with gynecologic cancers compared the efficacy of IV iron sucrose versus oral ferrous

fumarate for the “primary prevention” of anemia (ie, patients did not present with anemia).⁴²³ In this study, patients were given a single dose of 200 mg iron sucrose following each course of chemotherapy infusion for 6 cycles. The number of patients requiring a blood transfusion was double in the oral iron group compared to the IV iron sucrose group (56.3% vs. 28.1%; $P = .02$). Furthermore, patients receiving IV iron sucrose required fewer median number of PRBC units (0 vs. 0.5 units; $P = .05$). Another study randomized 67 patients with lymphoproliferative malignancies not undergoing chemotherapy to receive weekly ESA therapy with or without IV iron sucrose.⁴¹⁰ Although an oral iron arm was not included, IV iron sucrose resulted in a higher mean change in Hb level from baseline (2.76 g/dL vs. 1.56 g/dL, $P = .0002$) and a higher Hb level response rate (≥ 2 g/dL increase; 87% vs. 53%, $P = .0014$) compared to the no iron group. Prior to administration, test doses are recommended at physician discretion for patients receiving iron sucrose based on the risk for reaction.

Ferric Carboxymaltose

Ferric carboxymaltose is indicated for the treatment of anemia in adult patients with CKD or an intolerance or poor response to oral iron.⁴²⁴⁻⁴³⁰ It has also been evaluated for the treatment of iron-deficiency anemia in patients with gastrointestinal disorders,⁴³¹⁻⁴³⁴ chronic heart failure,⁴³⁵⁻⁴³⁷ and other chronic conditions.⁴³⁸⁻⁴⁴⁰ A recent phase III trial (FAIRY) randomized 454 patients with acute isovolemic anemia following gastrectomy for gastric cancer to receive IV ferric carboxymaltose or normal saline for 12 weeks.⁴⁴¹ At week 12, the percentage of Hb responders was significantly greater in the IV ferric carboxymaltose group versus the placebo group (92.2% vs. 54.0%; $P = .001$). Patients in the ferric carboxymaltose group also experienced significantly greater improvements in serum ferritin level (233.3 ng/mL vs. 53.4 ng/mL; $P = .001$) and TSAT level (35% vs. 19.3%; $P = .001$). An observational study from Steinmetz et al⁴⁴² evaluated the use of ferric carboxymaltose in patients with cancer. Of the 233 patients treated with doses ranging from

600 to 1500 mg, a median Hb increase of 1.4 g/dL (range, 1.3–1.5 g/dL) was observed with an overall increase in median Hb levels to >11 g/dL within 5 weeks of treatment.⁴⁴² A second observational study of 367 patients with solid tumors or hematologic malignancies also demonstrated improved median Hb levels following administration of ferric carboxymaltose alone or in combination with an ESA (1.3 g/dL vs. 1.4 g/dL, respectively) when measured over the 3-month observational period.⁴⁴³ Stable median Hb levels ≥11 g/dL were reached in patients without signs of iron overload.

These data suggest that ferric carboxymaltose may be an effective and well-tolerated treatment for CIA. However, ferric carboxymaltose has not been prospectively evaluated for the treatment of CIA, and therefore should only be considered when other parenteral iron preparations fail. In addition to the adverse events common to all parenteral iron preparations, ferric carboxymaltose has also been associated with severe phosphate deficiency.⁴⁴⁴⁻⁴⁴⁸ Prior to administration, test doses are recommended at physician discretion for patients receiving ferric carboxymaltose based on the risk for reaction.

Ferumoxytol

Ferumoxytol is a colloidal iron oxide that is indicated for the treatment of iron-deficiency anemia in patients with CKD or an intolerance or poor response to oral iron.^{248,449-451} However, there are no prospective data supporting the efficacy of ferumoxytol in patients with cancer. In a phase III trial involving patients with anemia due to various causes, 81.1% of patients treated with ferumoxytol achieved an Hb increase ≥2.0 g/dL at week 5 compared to only 5.5% of patients given placebo ($P < .0001$).⁴⁵¹ After 5 weeks, Hb levels ≥12 were seen in 50.5% of patients treated with ferumoxytol versus 2.0% of patients receiving placebo ($P < .0001$). While this study indicates that ferumoxytol is well tolerated and can effectively correct anemia, only a small percentage of patients in this study had

cancer ($n = 39$).⁴⁵¹ Although a positive trend in favor of ferumoxytol was demonstrated in the cancer subgroup compared with placebo (ferumoxytol, 51.7% vs. placebo, 30.0%; $P < .2478$), the difference was not statistically significant.⁴⁵¹ In a randomized phase III study of patients with iron-deficiency anemia that had not responded to oral iron, ferumoxytol was noninferior to iron sucrose as measured by the proportion of patients who had ≥2 g/dL increase in Hb from baseline to week 5 (84% with ferumoxytol vs. 81.4% with iron sucrose).⁴⁵⁰ However, noninferiority was not reached in the cancer subgroup ($n = 31$), potentially due to the small sample size. A recent post-hoc analysis of pooled data from these two trials found that both ferumoxytol and iron sucrose produced significant increases in Hb from baseline compared to placebo (1.8 g/dL, $P < .0001$ and 1.9 g/dL, $P = .002$, respectively) in a subgroup of 98 patients with cancer.⁴⁵²

It should be noted that ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.⁴⁵³ This is especially pertinent for populations at risk for serious organ-threatening iron deposition and should be a consideration when selecting the agent for iron supplementation. Prior to administration, test doses are recommended at physician discretion for patients receiving ferumoxytol based on the risk for reaction.

Clinical Examples of Iron Status

The following clinical scenarios illustrate how iron studies may guide iron supplementation and ESA treatment of patients with CIA.

Patient Case

A 59-year-old female with no significant past medical history presented to her primary care provider after acute onset of bloody stools in addition to a 2-month history of early satiety and 9 kg weight loss. Abdominal imaging revealed a colonic mass and mesenteric lesions. She was referred to an

oncologist. Biopsy of the mass demonstrated a poorly differentiated adenocarcinoma. Her oncologist has begun palliative treatment with FOLFOX plus bevacizumab, a myelosuppressive regimen. After 2 cycles of chemotherapy, her CBC results are as follows: Hb 8.8 g/dL, Hct 26.7%, MCV 73 fL, reticulocytes 0.8%, mean corpuscular Hb 25 pg, red cell distribution width 18.2%, and platelets 398000/μL. She does not have CKD. Serum folate, vitamin B₁₂ levels, indirect bilirubin, and serum LDH are within normal limits. Bleeding has ceased, but given her baseline anemia and red cell indices, iron studies have also been ordered. Five different scenarios are provided below to illustrate the potential management of this patient depending on various ferritin and TSAT combinations.

Scenario 1: Serum Ferritin 5 ng/mL & TSAT 4%

With a ferritin level <30 ng/mL and a TSAT level <20%, this patient has absolute iron deficiency and would benefit from iron repletion. Reducing transfusion requirements remains the goal of therapy. With a baseline Hb of 8.8 g/dL, imminent chemotherapy initiation, and very low iron stores, IV iron repletion is preferred. Oral iron may not supply bioavailable iron rapidly enough in certain patients.⁴⁰⁸

Scenario 2: Serum Ferritin 10 ng/mL & TSAT 22%

With low ferritin and normal TSAT levels, we can postulate that iron stores are becoming depleted. Iron is being mobilized, but signs of iron-restricted erythropoiesis are beginning to emerge. If the ferritin and TSAT levels are discordant, the low ferritin level should take precedence to determine if IV iron therapy would be beneficial to the patient. Iron would be beneficial in this patient as these laboratory values potentially reflect a transition from an iron-replete to an iron-deficient state. For the same reasons as discussed in scenario 1, IV iron is preferred over oral iron. It is also possible for TIBC to be low secondary to malnutrition, resulting in a normal

TSAT level despite definitive absolute iron deficiency. ESA use should be considered only after iron repletion.

Scenario 3: Serum Ferritin 580 ng/mL & TSAT 12%

With normal or elevated ferritin and low TSAT levels, we can assume that iron is either not bioavailable or that the ferritin level reflects an acute-phase response, potentially secondary to cancer-related inflammation (functional iron deficiency). Functional iron deficiency may cause iron-restricted erythropoiesis, and there is no ferritin threshold at which we can assume iron supply is adequate for erythropoiesis if the TSAT level is low. Thus, patients with ferritin levels >100 ng/mL could be treated with IV iron, as discussed in scenario 2. However, in this instance, an ESA should be considered first. This is because as the ferritin level moves across the spectrum from absolute iron deficiency to iron overload, the response to either an ESA or IV iron will diminish. Concomitant IV iron can be considered as it may increase the percentage of patients who respond to the ESA as well as reduce the time to response.

Scenario 4: Serum Ferritin 100 ng/mL & TSAT 30%

As the TSAT level increases from 20% to 50%, the percentage of patients with anemia that responds to iron decreases; therefore, this patient may not necessarily require IV iron until the TSAT level trends downward as a result of ESA use. If the anticipated response to ESA therapy is not realized by 4 to 6 weeks, consider repeating iron studies. If TSAT and/or ferritin levels decrease, consider giving IV iron. If iron studies remain unchanged, continue the ESA for a total of 8 weeks. Discontinue thereafter if lack of response persists and consider RBC transfusion.

Scenario 5: Serum Ferritin 500 ng/mL & TSAT 40%

These ferritin and TSAT parameters suggest that functional iron deficiency is unlikely. Therefore, this patient is unlikely to benefit from iron therapy



since she is iron replete. In this scenario, an ESA may be considered. ESA use induces functional iron deficiency by increasing iron utilization without the compensatory ability to mobilize storage iron in a timely manner. Therefore, iron repletion can be initiated if a response to ESA therapy is not seen and the patient remains transfusion-dependent. Of note, improved response is generally expected as the TSAT level decreases from 50% to 20%. Ultimately, clinical judgment must be used to determine whether the potential benefits of iron administration are likely to outweigh the risks.

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