National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Growth Factors

Version 1.2025 — October 11, 2024

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Hematopoietic Growth Factors

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 1.2025 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 3.2024 include:

Global

- FDA-approved biosimilar footnote language updated throughout: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

MGF-A 1 of 5

- Examples of Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia (>20%)
  - Hodgkin Lymphoma
    - ◊ Regimen added: BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone)
  - Ovarian Cancer
    - ◊ Regimen added: Carboplatin/docetaxel

MGF-A 2 of 5

- Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia (10%–20%)
  - Breast Cancer
    - ◊ Regimen added: Sacituzumab govitecan-hziy
  - Ovarian Cancer
    - ◊ Carboplatin/docetaxel removed from this page and added to high risk (MGF-A 1 of 5)

MGF-A 3 of 5

- References have been updated.

MGF-B 1 of 2

- G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery
  - Bullet 5 modified: Caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation. *Randomized data have indicated a detrimental effect on toxic deaths with the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) during concurrent chemoradiotherapy. This was not observed in a more recent secondary analysis of the CONVERT trial, in which prophylactic G-CSF was allowed. The risks and benefits of G-CSF versus dose reduction or delay during modern chemoradiotherapy are uncertain at this time.*
  - Footnote c added: Non-cytotoxic targeted therapeutics should be excluded from 24-hour recommendation.
  - Footnote f added: Pegfilgrastim administration increases bone marrow and spleen fluorodeoxyglucose (FDG) uptake, which may impact PET/CT assessment and interpretation.
  - Footnote g modified: Rarely (1.7%–6.9%), there is a failure to inject that requires further medical attention. *Individuals with on-body injectors should avoid MRIs.*

MGF-B 2 of 2

- References have been updated.

TGF-1

- Assessment
  - Suspected chemotherapy induced thrombocytopenia (CIT)
    - ◊ Bullet 2, sub-bullet 7 modified: Radiation- *or chemotherapy*-induced myelosuppression

TGF-2

- Footnote c modified: Insufficient data are available to support use of TPO-RAs other than romiplostim for CIT outside of a clinical trial. *Retrospective studies have evaluated other TPO-RA agonists, including avatrombopag, but there are insufficient data from these studies to recommend these agents. Additional prospective studies are needed to determine safety, efficacy, and benefits of TPO-RA agonists.*

Continued

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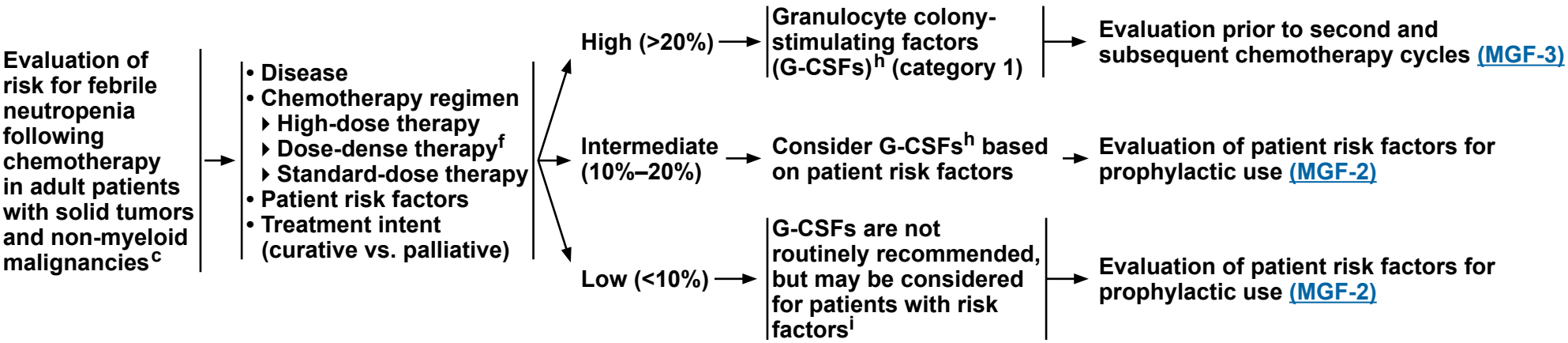
Updates in Version 1.2025 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 3.2024 include:

ANEM-B 1 of 2
- Parenteral Iron Preparations
  - Ferumoxytol (in select cases)
    - Dosing regimen added: 1020 mg IV single dose over 15–30 min

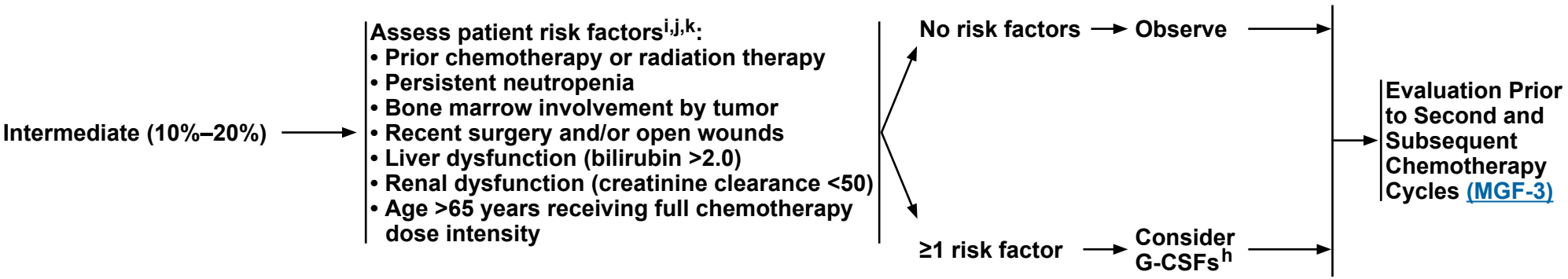
ANEM-B 2 of 2
- References have been updated.

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



[a] The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.
[b] Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with myeloid growth factors (MGFs) as clinically indicated, unless precluded by trial specifications.
[c] For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes; in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia; in chronic myeloid leukemia (CML), see the NCCN Guidelines for Chronic Myeloid Leukemia; in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), see the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. For use of growth factors in other cancer types, refer to the appropriate Guidelines.
[d] There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (MGF-A) and patient risk factors (MGF-2).
[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 hour; and neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 hours. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[f] In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.
[g] Toxicity Risks with MGFs (MGF-C).
[h] G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).
[i] G-CSFs may be considered for patients receiving low-risk regimens who have 2 or more patient-related risk factors (MGF-2). Use of G-CSF in this setting is based on clinical judgment.

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



[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 hour; and neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 hours. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[h] G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[i] G-CSFs may be considered for patients receiving low-risk regimens who have 2 or more patient-related risk factors. Use of G-CSF in this setting is based on clinical judgment.

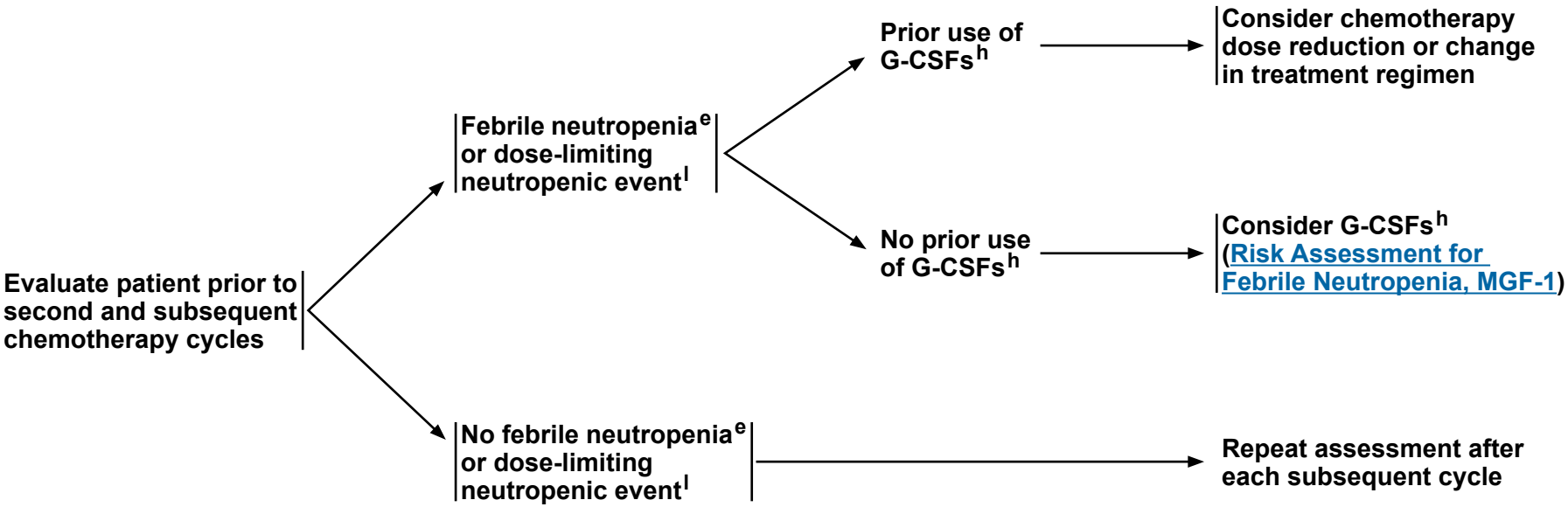
[j] Other possible patient risk factors for febrile neutropenia may include poor performance status or human immunodeficiency virus (HIV) infection (in particular, patients with low CD4 counts). The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory patients with cancer receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoietic cell transplant (Lyman GH, et al. Crit Rev Oncol Hematol 2014;90:190-199).

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

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

EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



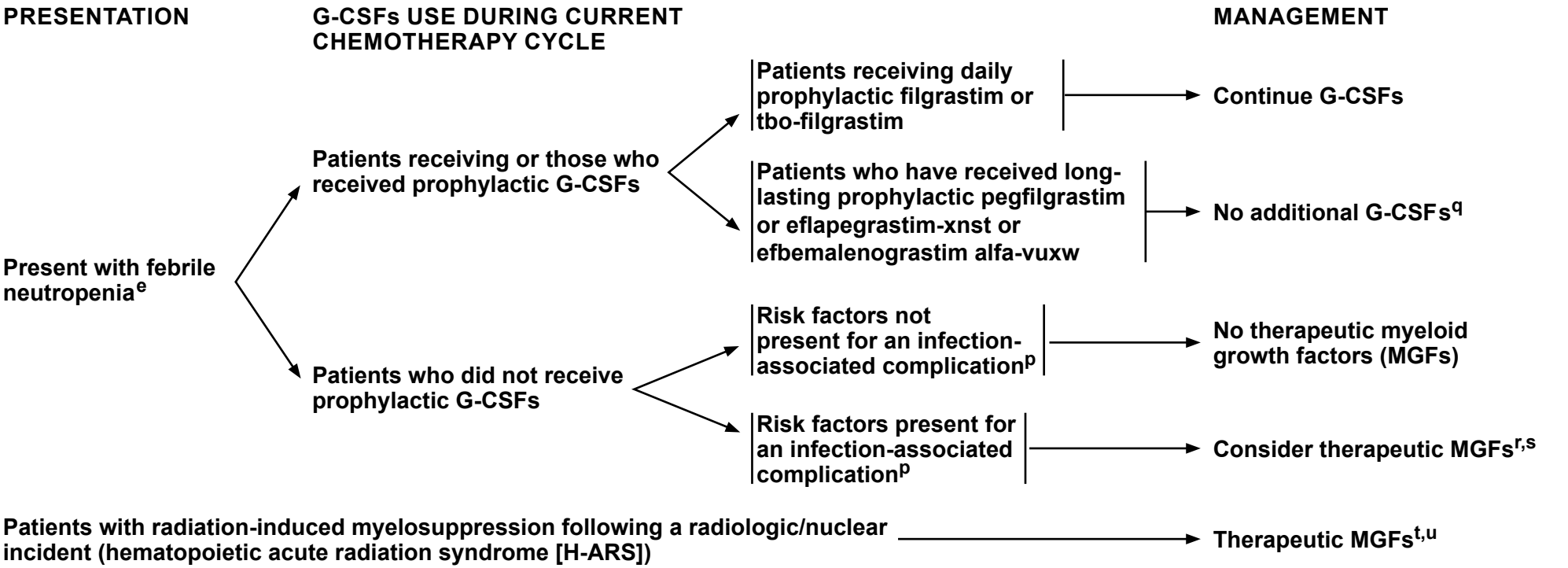
[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 hour; and neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 hours. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[h] G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[l] Dose-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.

THERAPEUTIC USE OF MGFs[e,m,n,o]



Patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]) → **Therapeutic MGFs[t,u]**

[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 hour; and neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 hours. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

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

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

[o] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

[p] Risk factors/possible indications for therapeutic MGFs include sepsis syndrome, age >65 years, absolute neutrophil count [ANC] <100/mcL, neutropenia expected to be >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.

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

[r] See Discussion for further details. Pegfilgrastim (or biosimilars), eflapegrastim-xnst, and efbemalenograstim alfa-vuxw have only been studied for prophylactic use. Filgrastim (or biosimilars), tbo-filgrastim, or sargramostim may be used therapeutically with initial dosing and discontinued at time of neutrophil recovery.

[s] Filgrastim (or biosimilars) or tbo-filgrastim: daily dose of 5 mcg/kg; sargramostim: used in clinical trials at a dose of 250 mcg/m^2 per day. Continue therapeutic MGFs until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.

[t] Therapeutic options include filgrastim (or biosimilars), tbo-filgrastim, pegfilgrastim (or biosimilars), sargramostim, eflapegrastim-xnst, and efbemalenograstim alfa-vuxw.

[u] Farese AM, et al. Drugs Today (Barc) 2015;51:537-548.

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

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 Type are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the risk assessment (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) (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 (NCCN Guidelines for ALL)

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

Bone Cancer
- VAIA (vincristine, doxorubicin, ifosfamide, dactinomycin)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7,b]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,c] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[11-13]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[14]
- Escalated BEACOPP[d] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[15]
- BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone)[16]

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin Lymphomas
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[18]
- ICE (ifosfamide, carboplatin, etoposide)[a,19,20]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[21,22]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[23]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[24]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[25]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[26,27]
- Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, prednisone)[28]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[29]

Multiple Myeloma
- DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide)[30] ± bortezomib (VTD-PACE)[31]

Ovarian Cancer
- Topotecan[a,32]
- Docetaxel[33]
- Carboplatin/docetaxel[34]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[35]
- Doxorubicin[a,36]
- Ifosfamide/doxorubicin[37]

Small Cell Lung Cancer[e]
- Topotecan[38]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[39]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[40]

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

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

[b] Growth factor support may not be needed during the paclitaxel portion and can be safely avoided in a large percentage of patients.

[c] Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

[d] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with MGFs (MGF-C).

[e] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

References

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

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 Type 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) (MGF-1).**
- **In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.**

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel[43]

Breast Cancer
- Docetaxel[a,44,45]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,46]
- Paclitaxel every 21 days[a,47]
- Sacituzumab govitecan-hziy[48,49]

Cervical Cancer
- Cisplatin/topotecan[50,51]
- Paclitaxel/cisplatin[a,50]
- Topotecan[52]
- Irinotecan[53]

Colorectal Cancer
- FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)[f,54-56]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,57]

Non-Hodgkin Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,58]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[59,60] including regimens with pegylated liposomal doxorubicin[61,62]
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[63]
- Cisplatin/vinorelbine[64]
- Cisplatin/docetaxel[63,65]
- Cisplatin/etoposide[66]
- Carboplatin/paclitaxel[a,g,67]
- Docetaxel[65]

Pancreatic Cancer
- FOLFIRINOX[h] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Prostate Cancer
- Cabazitaxel[i,68]

Small Cell Lung Cancer[e]
- Etoposide/carboplatin[69]

Testicular Cancer
- BEP[d] (bleomycin, etoposide, cisplatin)[70-72]
- Etoposide/cisplatin[73]

Uterine Sarcoma
- Docetaxel[74]

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

[d] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with MGFs (MGF-C).

[e] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for ES-SCLC.

[f] There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (MGF-A) and patient risk factors (MGF-2).

[g] If carboplatin dose is area under the curve ≥6 and/or patient is of Japanese ancestry.

[h] A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[41] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSFs were administered to 42.5% of patients who received FOLFIRINOX).[42] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

[i] The published results for cabazitaxel have an 8% rate of febrile neutropenia but neutropenic deaths were reported. Primary prophylaxis with G-CSFs is recommended in patients with high-risk clinical features, and should be considered in all patients receiving a dose of 25 mg/m^2.

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

References

CHEMOTHERAPY REGIMEN REFERENCES

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

[1] Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638-2646.
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Note: All recommendations are category 2A unless otherwise indicated.

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

G-CSFs FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY[a]

- **Filgrastim (category 1) or tbo-filgrastim[b] (category 1)**
  - **Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir absolute neutrophil count (ANC) recovery to normal or near-normal levels by laboratory standards.**
  - **Start the next day[c] or up to 3–4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.[d,e,1]**
- **Pegfilgrastim[f,2] (category 1)**
  - **One dose of 6 mg**
    - ◊ **Based on clinical trial data, pegfilgrastim can be administered the day after myelosuppressive chemotherapy (category 1).[3] There are data for and against same-day dosing,[c] but the U.S. Food and Drug Administration (FDA)-approved dosing schedule is still recommended.[4-9]**
    - ◊ **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,10-16]**
    - ◊ **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.**
- **Eflapegrastim-xnst[17,18]**
  - **Administer 13.2 mg subcutaneously once per chemotherapy cycle.**
  - **Administer approximately 24 hours[c] after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy.**
- **Efbemalenograstim alfa-vuxw[19]**
  - **Administer 20 mg subcutaneously once per chemotherapy cycle.**
  - **Administer approximately 24 hours[c] after cytotoxic chemotherapy. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.**
- **Caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation.[20] Randomized data have indicated a detrimental effect on toxic deaths with the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) during concurrent chemoradiotherapy. This was not observed in a more recent secondary analysis of the CONVERT trial, in which prophylactic G-CSF was allowed. The risks and benefits of G-CSF versus dose reduction or delay during modern chemoradiotherapy are uncertain at this time.[21]**
- **Subcutaneous route is preferred for all G-CSFs listed above.**
- **For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

Toxicity Risks with MGFs (MGF-C)

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] Tbo-filgrastim is a human G-CSF approved by the FDA through an original biologic license application. All of these G-CSFs 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.
[c] Non-cytotoxic targeted therapeutics should be excluded from 24-hour recommendation.
[d] Studies suggest that shorter durations of G-CSFs may be less efficacious.
[e] Neutrophil counts should be monitored, as indicated, appropriate to the setting.
[f] Pegfilgrastim administration increases bone marrow and spleen fluorodeoxyglucose (FDG) uptake, which may impact PET/CT assessment and interpretation.
[g] Rarely (1.7%–6.9%), there is a failure to inject that requires further medical attention. Individuals with on-body injectors should avoid MRIs.

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

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

TOXICITY RISKS WITH MGFs[a]

Filgrastim, Pegfilgrastim, and Tbo-filgrastim[b,c,d,e]

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

Eflapegrastim-xnst and Efbemalenograstim alfa-vuxw[b,e]

- **Warnings:**
  - **Splenic rupture**
  - **Acute respiratory distress syndrome**
  - **Serious allergic reactions, including anaphylaxis**
  - **Sickle cell crisis (only in patients with sickle cell disease)**
  - **Glomerulonephritis**
  - **Leukocytosis**
  - **Thrombocytopenia**
  - **MDS and AML in patients with breast and lung cancer**
  - **Capillary leak syndrome**
  - **Aortitis**

Sargramostim[b,d]

- **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, gastrointestinal (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), high cholesterol**

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] Full prescribing information for specific product information.
[c] Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars.
[d] The toxicities listed are from the prescribing information and are based on studies from different patient populations. For filgrastim, tbo-filgrastim, and biosimilars, 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 IV route of administration and may differ from those of subcutaneous administration.
[e] G-CSFs are not recommended for use within 14 days after receipt of chimeric antigen receptor (CAR)-modified T cells due to concern for exacerbation of cytokine release syndrome. Use after that time period can be considered for treatment of neutropenia.
[f] See Discussion for details.
[g] Lyman et al reported an increase in absolute and relative risk of AML/MDS of 0.41% and 1.92, respectively, related to G-CSFs. Overall mortality was decreased. See Discussion for details and references.
[h] Available data support use of naproxen and other nonsteroidal anti-inflammatory drugs (NSAIDs) or loratadine. See Discussion for more details.

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

USE OF THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RA) IN PATIENTS WITH CANCER

PRESENTATION	ASSESSMENT	MANAGEMENT
Suspected chemotherapy-induced thrombocytopenia (CIT)[a]	Evaluate for other potential causes of thrombocytopenia as indicated • First check ▸ Complete blood count (CBC) with differential, including evaluation for other cytopenias ▸ Blood smear morphology, including evaluation for platelet clumping • Then consider other potential etiologies, including: ▸ Nutritional deficiencies ▸ Medications and supplements suppressing platelet production ▸ Infection (including viral reactivation) ▸ Disseminated intravascular coagulation (DIC) ▸ Immune thrombocytopenia ▸ Heparin-induced thrombocytopenia (HIT) ▸ Radiation- or chemotherapy-induced myelosuppression ▸ Bone marrow involvement by underlying malignancy ▸ Hematologic malignancy (including therapy-related myeloid neoplasia) ▸ Hemolytic anemia ▸ Consumption of platelets secondary to blood loss ▸ Antiphospholipid syndrome (APLS) ▸ Hypersplenism ▸ Paroxysmal nocturnal hemoglobinuria (PNH) ▸ Thrombotic microangiopathies (TMAs) such as thrombotic microangiopathic anemia, thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS)	Treat underlying cause(s) as indicated CIT → Consider • Platelet transfusion per Association for the Advancement of Blood & Biotherapies (AABB) guidelines • Chemotherapy dose reduction or change in treatment regimen • Clinical trial of TPO-RA[b] • Romiplostim[b,c,d,e,f]
Thrombocytopenia post-hematopoietic cell transplant[a,g]	• Evaluate for other potential causes of thrombocytopenia as indicated, including examples above, as well as primary or secondary graft failure, graft-versus-host disease (GVHD), relapse of hematologic malignancy, and transplant-associated TMA (TA-TMA)	Treat underlying cause(s) as indicated Primary or secondary failure of platelet recovery without other clear underlying causes → Consider • Platelet transfusion per AABB guidelines • Clinical trial of TPO-RA[b] • Eltrombopag[h]

Known MDS → NCCN Guidelines for Myelodysplastic Syndromes

Known myeloid malignancy or ALL → Treat underlying disease per NCCN Guidelines

Footnotes and References on TGF-2

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

USE OF THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RA) IN PATIENTS WITH CANCER
FOOTNOTES AND REFERENCES

Footnotes

[a] Definitions used in several studies include thrombocytopenia (platelets <100,000/mcL) for ≥3 to 4 weeks following last chemotherapy administration and/or following delays in chemotherapy initiation related to thrombocytopenia.[1,2]

[b] In patients for whom a TPO-RA is being considered for management of CIT, participation in clinical trials is strongly encouraged whenever possible.

[c] Insufficient data are available to support use of TPO-RAs other than romiplostim for CIT outside of a clinical trial.[3] Retrospective studies have evaluated other TPO-RA agonists, including avatrombopag, but there are insufficient data from these studies to recommend these agents. Additional prospective studies are needed to determine safety, efficacy, and benefits of TPO-RA agonists.

[d] The primary purpose of TPO-RAs for CIT is to maintain dose schedule and intensity of chemotherapy when such benefit is thought to outweigh potential risks. Romiplostim dosing strategies include weekly dosing beginning at 2–4 mcg/kg, increased no more than 1–2 mcg/kg per week to target platelet count 100,000–150,000/mcL.[1,2] Maximum dose is 10 mcg/kg weekly per prescribing information.[4]

[e] It is uncertain whether use of TPO-RAs for CIT increases the risk of venous thromboembolism (VTE) in patients with cancer.[1,2,5,6] Caution is warranted.

[f] Insufficient data are available to support routine use of TPO-RAs for CIT in pediatric patients.

[g] Several reports have separately examined use of TPO-RA in patients with prolonged thrombocytopenia following hematopoietic cell transplantation, including patients with secondary failure of platelet recovery.[7,8] Clinical trial participation is encouraged whenever possible for such patients.

[h] Eltrombopag has been evaluated with efficacy in patients with prolonged thrombocytopenia post-allogeneic transplant and poor graft function.[9-14]

References

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

HEMOGLOBIN CONCENTRATION TO PROMPT AN EVALUATION OF ANEMIA

EVALUATION OF ANEMIA[a,b,c]

Hemoglobin (Hb) ≤11 g/dL or ≥2 g/dL below baseline[d] →

- **CBC with indices**
- **Blood smear morphology**

→

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

- **First check**
  - **Reticulocyte count[e] and mean corpuscular volume (MCV)**
- **Then consider**
  - **Hemorrhage (consider upper and lower endoscopic evaluation)**
  - **Hemolysis (ie, direct antiglobulin test, DIC panel, haptoglobin, indirect bilirubin, lactate dehydrogenase [LDH])**
  - **Nutritional (ie, iron, total iron-binding capacity, ferritin, B_{12}, folate)[f]**
  - **Inherited (ie, prior history, family history)**
  - **Renal dysfunction (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2)**
  - **Treatment-induced myelosuppression**
  - **Hormone dysfunction (ie, hypogonadism, adrenal dysfunction, hyper/hypothyroidism)**
  - **Anemia of chronic inflammation (ie, CRP and erythrocyte sedimentation rate [ESR])**
- **Evaluation of Iron Deficiency (ANEM-4)**

→ **Treat as indicated**

→ **No cause identified** → **Risk Assessment and Indications for Transfusion (ANEM-2)**

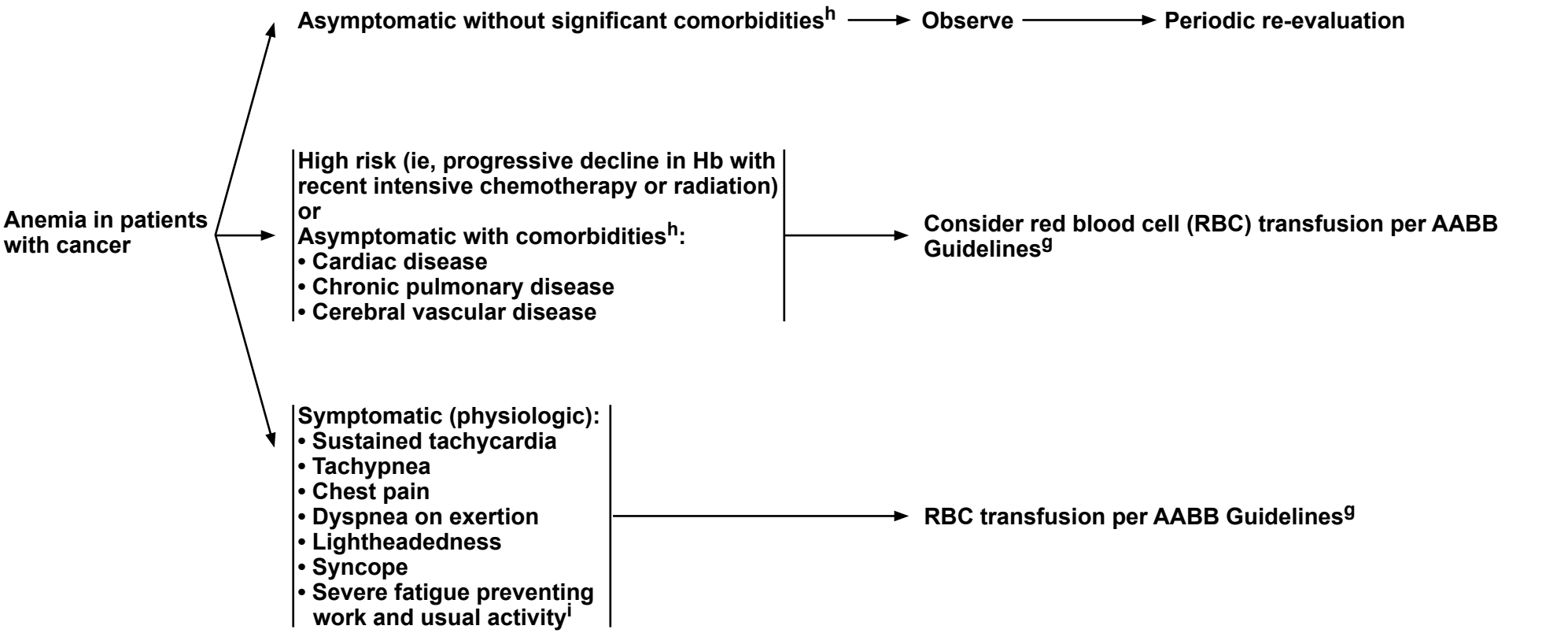
MDS → **NCCN Guidelines for Myelodysplastic Syndromes**

Myeloid malignancies or ALL → **Treat underlying disease per NCCN Guidelines for Treatment by Cancer Type**

[a] The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.
[b] This is a basic evaluation for possible causes of anemia.
[c] Trilaciclib may be used as a prophylactic option to decrease the incidence of anemia and red blood cell (RBC) transfusions when administered before platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for ES-SCLC. Use of trilaciclib in this setting is a category 2B recommendation.
[d] Consideration of gender in evaluation of anemia is relevant since women have a lower baseline Hb than men. See Discussion for more details.
[e] Correct reticulocyte count for degree of anemia. See Discussion.
[f] The 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 (TSAT). Fasting is preferred when testing for serum iron and total iron-binding capacity.

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

RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING[g]



See Discussion for comparison of risks and benefits of ESA use versus RBC transfusion

See Special Categories in Considering ESA Use (ANEM-3)

[g] The AABB has made recommendations regarding appropriate indications for RBC transfusion. See Discussion for details.
[h] Degree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating RBC transfusion.
[i] Fatigue (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.

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

SPECIAL CATEGORIES IN CONSIDERING ERYTHROPOIESIS-STIMULATING AGENT (ESA) USE

Cancer and chronic kidney disease (moderate to severe) → **Consider ESAs by FDA dosing/dosing adjustments[j,m,n,o]** →

Patient undergoing palliative treatment[k] →

Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia[k] →

Consider based on patient preferences:
- **ESAs by FDA dosing/dosing adjustments[j,m,n]**
  or
- **RBC transfusion per AABB Guidelines**
  or
- **Clinical trial**

→ **Evaluation of Iron Deficiency (ANEM-4)**

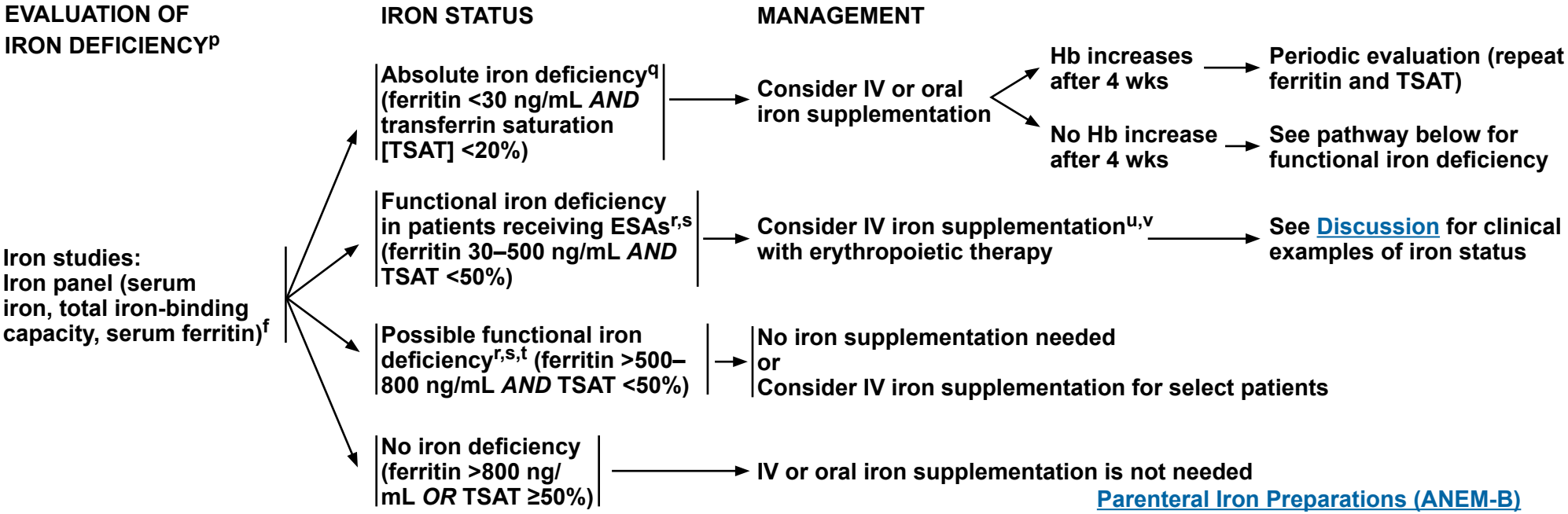
Select patients who refuse blood transfusions → **Consider ESAs by FDA dosing/dosing adjustments[j,m,n]** Management of Cancer- and Chemotherapy-Induced Anemia for Patients Who Refuse Blood Transfusions (ANEM-C) →

- **Patients with cancer not receiving therapy**
- **Patients receiving non-myelosuppressive therapy**
- **Patients receiving myelosuppressive chemotherapy with curative intent[l]**
  (Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin lymphomas, testicular cancer, early-stage non-small cell lung cancer, and small cell lung cancer)

→ **There is not enough evidence to support ESA use in these patient populations; therefore, ESAs are not recommended at this time**

[j] Optimal response to ESAs depend on adequate iron storage and availability.
[k] For comparison of risks and benefits of ESA use versus RBC transfusion, see Discussion.
[l] A few studies suggest that patients with small cell lung cancer on myelosuppressive chemotherapy may not have an increase in mortality when receiving ESAs (Nagel S, et al. Clin Lung Cancer 2011;12:62-69.)
[m] Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-A).
[n] Patients with previous risk factors for thrombosis are at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate and counsel patients regarding 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. (Nagel S, et al. Clin Lung Cancer 2011;12:63-69; Gergal Gopalkrishna Rao SR, et al. Cureus 2021;13:e17835) (NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease).
[o] The Hb 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.

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



[f] The 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 TSAT. Fasting is preferred when testing for serum iron and total iron-binding capacity.

[p] ESAs work optimally in patients who have adequate iron stores; thus, determination of iron stores and management of iron storage status is necessary.

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

[r] In 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.

[s] Only one of six studies (Henry DH, et al. Oncologist 2007;12:231-242) of IV iron therapy in patients with cancer provided a TSAT guideline for monitoring.

[t] Although 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.

[u] IV 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).

[v] Although 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.

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

ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (1 of 5)[a-f]

INITIAL DOSING	TITRATION FOR NO RESPONSE*
PACKAGE INSERT DOSING SCHEDULE	
Epoetin alfa 150 units/kg 3 times per wk by subcutaneous injection	→ Increase dose of epoetin alfa to 300 units/kg 3 times per wk by subcutaneous injection
or	
Epoetin alfa 40,000 units every wk by subcutaneous injection	→ Increase dose of epoetin alfa 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	
ALTERNATIVE REGIMENS[g]	
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[3]	→ 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[7]	→ Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection[4]
or	
Epoetin alfa 80,000 units every 2 wks by subcutaneous injection[5]	
or	
Epoetin alfa 120,000 units every 3 wks by subcutaneous injection[6]	

TITRATION FOR RESPONSE

- 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.
- For Hb target limits, refer to ANEM-A 3 of 5.

Footnotes and References (ANEM-A 2 of 5)
Erythropoietic Therapy - Adverse Effects (ANEM-A 3 of 5)

* No response is defined as Hb increase <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.
** Data indicate that darbepoetin alfa 300 mcg is equivalent in terms of efficacy to darbepoetin alfa 500 mcg for initial dosing.[7]

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

ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 of 5)

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

Footnotes

[a] The 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 GR, 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.

[b] Less-frequent dosing regimens of darbepoetin or epoetin alfa could be considered as an alternative to dose reduction.

[c] The 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.

[d] IV 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).

[e] See prescribing information for perioperative deep vein thrombosis (DVT) prophylaxis.

[f] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

[g] There are no data on alternative dosing schedules for epoetin alfa-epbx.

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[4] Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every 3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006;98:273-284.

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Erythropoietic Therapy - Dosing and Titration (ANEM-A 1 of 5)

Erythropoietic Therapy- Adverse Effects (ANEM-A 3 of 5)

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

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.[1-7,10] 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/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers. 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,[8-11] two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.[12,13]**
- **Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.[14-16]**
- **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 Discussion for comparison of risks and benefits of ESA use versus RBC transfusion).**
- **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)

References (ANEM-A 5 of 5)

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

ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 of 5)

Thrombosis

- Early trials of recombinant human erythropoietin reported that a high-target hematocrit (42 ± 3%) was found to have an increased number of vascular events (arterial and venous).
- EPO has a thrombogenic potential independent of Hb levels.[17] 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. (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.[8,11-13,18] The absolute risk of venous thromboembolism (VTE) was 7.5% in patients treated with ESAs compared to 4.9% in control patients.[8]
- 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.[19]

Hypertension

- Blood pressure should be controlled in all patients prior to initiating therapy with erythropoietic drugs and must be monitored regularly in treated patients.
- Hb level should be monitored to decrease the risk of hypertension (Titration for Response ANEM-A 1 of 5).

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

- Given that cases of PRCA related to anti-EPO antibodies have been reported rarely but with increased incidence with some preparations of recombinant EPOs (rEPOs), PRCA should be suspected whenever a response to rEPO is lost. It is important to report these cases to the FDA along with information on which biosimilar or innovator molecule is involved.[20-22]

References (ANEM-A 5 of 5)

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

ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 of 5)

ADVERSE EFFECTS REFERENCES

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

PARENTERAL IRON PREPARATIONS[1-6,a]
RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran[8,b]	Ferric Gluconate[10,b]	Iron Sucrose[13,b]	Ferric Carboxymaltose[16-19,b]	Ferumoxytol[20-22,b,c] (in select cases)	Ferric Derisomaltose[b]
Test dose[d]	Test dose required: 25 mg slow IV push over 1–2 min. If tolerated, follow with 75 mg IV bolus for total dose of 100 mg	Test dose not required	Test dose not required	Test dose not required	Test dose not required	Test dose not required
Dosage[7,e]	100 mg IV over 5 min[3] • Repeated dosing once weekly for 10 doses to total of 1000 mg or • Total dose infusion given over several hours[9,f] ▸ Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h[3]	125 mg IV over 60 min[2,4,5,11] • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommended based on published trial results[11] • Total treatment course = 1000 mg	Total treatment recommended = 1000 mg • Various dosing schedules have been tested. For additional details about dosing, see prescribing information[14,15]	750 mg IV for patients weighing ≥50 kg (110 lb) • 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 lb) • 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 or 1020 mg IV single dose over 15–30 min[23-25]	1000 mg IV over ≥20 min for patients weighing ≥50 kg (110 lb) • Single dose • Total treatment course = 1000 mg or 20 mg/kg body weight IV over ≥20 min for patients <50 kg (110 lb) • Single dose • Total treatment course not to exceed 1000 mg
Routes	IV; intramuscular (IM) (not recommended)	IV	IV	IV	IV	IV

[a] Five[2-6] of six[11] 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.

[b] Examples 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.

[c] 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. Ferumoxytol has not been prospectively evaluated in patients with cancer- or chemotherapy-induced anemia. Ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.[12]

[d] Premedications prior to IV iron should not be routinely used unless there is a history of allergy to more than one drug, an allergic diathesis or asthma, and a history of inflammatory arthritis, wherein both parenteral and oral iron have been shown to exacerbate symptoms. If warranted, premedications should be given before any test doses.

[e] For additional details about iron dosing, see prescribing information.

[f] Dose (mL) = 0.0442 (desired Hb - observed Hb) x LBW + (0.26 x LBW). Dose (mg) = Dose (mL) x 50 mg/mL; LBW = lean body weight (kg); Hb = hemoglobin (g/dL). If dose exceeds 1000 mg, remaining dose may be given after 4 weeks if inadequate Hb response.

References

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

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

MANAGEMENT OF CANCER- AND CHEMOTHERAPY-INDUCED ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSIONS[1-8]

- 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 B_{12} supplementation
  - Evaluate and correct baseline coagulation abnormalities
  - In patients with high clinical suspicion of folate and vitamin B_{12} deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using 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
  - 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]

References

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

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

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

ABBREVIATIONS

AABB	Association for the Advancement of Blood & Biotherapies
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APLS	antiphospholipid syndrome
BFI	Brief Fatigue Inventory
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CBC	complete blood count
CIT	chemotherapy-induced thrombocytopenia
CLL/SLL	chronic lymphocytic leukemia/ small lymphocytic lymphoma
CML	chronic myeloid leukemia
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ES-SCLC	extensive-stage small cell lung cancer
ESA	erythropoiesis-stimulating agent
ESR	erythrocyte sedimentation rate
FACT	Functional Assessment of Cancer Therapy
FDG	fluorodeoxyglucose
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
H-ARS	hematopoietic acute radiation syndrome
HIT	heparin-induced thrombocytopenia
Hb	hemoglobin
HIV	human immunodeficiency virus
HUS	hemolytic uremic syndrome
IND	Investigational New Drug Application
LDH	lactate dehydrogenase
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MGF	myeloid growth factor
NSAID	nonsteroidal anti-inflammatory drug
PNH	paroxysmal nocturnal hemoglobinuria
PRCA	pure red cell aplasia
RBC	red blood cell
rEPO	recombinant EPO
TA-TMA	transplant-associated thrombotic microangiography
TMA	thrombotic microangiography
TPO-RA	thrombopoietin receptor agonists
TSAT	transferrin saturation
TTP	thrombotic thrombocytopenic purpura
VTE	venous thromboembolism

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Hematopoietic Growth Factors

Discussion

This discussion corresponds to the NCCN Guidelines for Hematopoietic Growth Factors.
Last updated: October 11, 2024

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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 (CSFs) are hematopoietic growth factors that regulate the growth and differentiation of progenitor cells towards different myeloid lineages (granulocytes, red blood cells [RBCs], or platelets). Myeloid growth factors (MGFs), such as granulocyte colony-stimulating factors (G-CSF), are primarily used to reduce the incidence of febrile neutropenia (FN) in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy. Erythropoiesis-stimulating agents (ESAs), including epoetin alfa and darbepoetin alfa, are primarily used to manage cancer- and chemotherapy-induced anemia (CIA). Thrombopoietin receptor agonists (TPO-RAs), including romiplostim, are a class of platelet growth factors that can be used to manage chemotherapy-induced thrombocytopenia (CIT).[2] Management and prevention of FN, CIA, and CIT are integral parts of supportive care for many patients undergoing cancer treatment.

FN is defined as an absolute neutrophil count (ANC) of <500 neutrophils/mcL, or <1000 neutrophils/mcL with an anticipated decline to ≤500 within the next 48 hours, accompanied by a single oral temperature of ≥38.3°C or ≥38.0°C for a duration of over 1 hour.[3] FN is a major dose-limiting toxicity of many chemotherapy regimens. Patients who develop FN often require prolonged hospitalization and treatment with broad-spectrum antibiotics.[4] Development of FN increases treatment costs and can prompt dose reductions or treatment delays, which may compromise clinical outcome.[5] Additionally, a study found correlations between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.[6]

These guidelines focus on the two primary MGFs that have the most clinical applicability: G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF). For simplicity, the term “MGF” will be used when data support both G-CSF and GM-CSF. Pharmacologic 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 are: filgrastim, filgrastim-sndz, tbo-filgrastim, filgrastim-aafi, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-fpgk, eflapegrastim-xnst, and non-PEGylated efbemalenograstim alfa-vuxw.[7] Filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-fpgk, and pegfilgrastim-bmez were approved as biosimilars which allows their use for the same indications as the originator products. Tbo-filgrastim was approved by the FDA in an original biologic license application and therefore has a more restricted indication.[7] Several studies have demonstrated similar outcomes with the use of tbo-filgrastim compared to filgrastim for FN prevention. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.[8] Tbo-filgrastim was equivalent to filgrastim and superior to placebo in reducing the duration of severe neutropenia and FN incidence. Two other randomized studies in patients with lung cancer and non-Hodgkin lymphoma (NHL) receiving chemotherapy reported similar efficacy and toxicity for tbo-filgrastim and filgrastim.[9,10] A meta-analysis of these three trials concluded that tbo-filgrastim and filgrastim are similarly efficacious in reducing FN incidence.[11] Pharmacokinetic and pharmacodynamic profiles are alike in studies performed in healthy volunteers.[12,13] Tbo-filgrastim has demonstrated low immunogenicity in patients with cancer who are receiving chemotherapy, with no evidence for the development of neutralizing antibodies or immunogenic adverse events.[14]

The only FDA-approved GM-CSF is sargramostim, although some clinical trials have used the GM-CSF molgramostim. Molgramostim is not currently FDA approved; it is not recommended by the Panel due to increased adverse events compared to sargramostim.[15] Sargramostim is

primarily used for FN treatment; prophylactic use is not recommended. MGFs are also indicated for patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS; any available product would be acceptable in this context])[16,17] and those with severe chronic neutropenia.

Anemia is characterized by a decrease in hemoglobin (Hb) concentration, RBC count, and/or hematocrit (Hct) to subnormal levels. The pathophysiologic origins of anemia can be grouped into three categories: 1) decreased production of functional RBCs; 2) increased destruction of RBCs; and 3) blood loss. The degree of anemia can be graded according to the anemia scale provided by the National Cancer Institute. Refer to the most recent updated version of the Common Terminology Criteria for Adverse Events (CTCAE) for the cut-offs for anemia grades. CIA occurs in 30% to 90% of patients with cancer.[18,19] CIA can be improved by transfusion with packed red blood cells (PRBCs) or ESAs administration, with or without iron supplementation, in select patients receiving myelosuppressive chemotherapy. Epoetin alfa, a recombinant human erythropoietin (rhEpo), was the first FDA-approved ESA for anemia treatment in patients receiving myelosuppressive chemotherapy.[7] A second-generation rhEpo, darbepoetin alfa, with a longer half-life than epoetin alfa, is also FDA-approved for this indication.[7] In 2018, the FDA approved epoetin alfa-epbx as the first epoetin alfa biosimilar, which allows its use for the same indications as the originator product.[7]

Thrombocytopenia is characterized by a low blood platelet count resulting in decreased blood clotting capability. Mild thrombocytopenia does not require treatment or intervention. Moderate thrombocytopenia (platelet counts <50,000/mcL) increases the risk of bleeding in patients on systemic anticoagulation and severe thrombocytopenia (platelet counts <10,000/mcL) increases the risk for spontaneous bleeding events. CIT is defined as platelet count <100,000/mcL for ≥3 to 4 weeks following the last chemotherapy administration and/or resulting in delays in chemotherapy initiation related to thrombocytopenia. CIT occurs in 15% to 25% of patients with cancer and can disrupt treatment.[20-22] TPO-RAs, such as romiplostim, activate the TPO receptor and increase platelet production.[20] Romiplostim and other TPO-RAs are widely used to treat immune thrombocytopenia; at present there are no FDA-approved treatments for CIT.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors are divided into three sections outlining the evaluation, prevention, and management of FN, CIT, and CIA. The purpose of these guidelines is two-fold: 1) to operationalize the evaluation, prevention, and treatment of FN, CIT, and CIA in adult patients with cancer, especially those who are receiving chemotherapy; and 2) to enable the patient and clinician to assess management options for FN, CIT, and CIA in the context of an individual patient condition.

These guidelines focus on adult patients with solid tumors and lymphoid malignancies. Use of hematopoietic growth factors in the treatment of myeloid disorders or leukemias is discussed in the NCCN Guidelines for Myelodysplastic Syndromes, NCCN Guidelines for Chronic Myeloid Leukemia, NCCN Guidelines for Acute Myeloid Leukemia, NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, and NCCN Guidelines for Hairy Cell Leukemia. Use of hematopoietic growth factors in the context of hematopoietic cell transplantation (HCT) is addressed separately in the NCCN Guidelines for Hematopoietic Cell Transplantation.

Guidelines Update Methodology

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

Literature Search Criteria

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; febrile neutropenia and cancer; filgrastim and cancer; pegfilgrastim and cancer; anemia and cancer; erythropoiesis stimulating agents and cancer; thrombocytopenia and cancer; and romiplostim and cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[23]

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; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Validation Studies; Multicenter Study; and Controlled Clinical Trials. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[24] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Biosimilars

The cost of biologics such as filgrastim, pegfilgrastim, and epoetin alfa has limited their accessibility for many patients. In 2009, the Biologics Price Competition and Innovation Act established an abbreviated licensure pathway for biosimilars with the goal of reducing expenses for costly biologic drugs.[25,26] In 2015, the FDA approved the first biosimilar, filgrastim-sndz.[27] The increased need for cost-effective hematopoietic growth factors has led to the rapid approval of additional biosimilars.

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 clinically meaningful differences in efficacy, safety, and purity.[28] FDA-approved biosimilars have the same amino acid sequence as the originator product; however, differences may be seen in the three-dimensional structure, glycosylation sites, isoform profiles, and level of protein aggregation.[28] Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biological activity, efficacy, and safety.[26,29] Since biosimilars are supported by limited clinical data at the time of approval, data must be extrapolated to support the use of biosimilars for additional indications of the originator product. Scientific justification is required for extrapolation, including mechanism-of-

action studies in each indication as well as pharmacokinetic, immunogenicity, and toxicity assessments in different patient populations.[30] If overall safety and efficacy are equivalent, biosimilars may be approved for the same indications and can be substituted for the originator product.

Switching between the biosimilar and the originator product without the intervention of a health care provider is permitted if a biosimilar is designated as interchangeable.[28] Concerns regarding interchangeability include enhanced immunogenicity, compromised safety, and diminished efficacy. Although the FDA has not designated any biosimilars as interchangeable, limited data suggest that patients can alternate between the biosimilar and the originator biologic without any clinically meaningful differences regarding efficacy or safety.[31] Another concern is the potential for product drift that may arise during the manufacturing process of biologics and biosimilars that could result in differences in efficacy and safety over time. Continued post-marketing surveillance of all biologic products is necessary for long-term monitoring. To maintain pharmacovigilance of specific products, health care providers should be aware of the FDA's nomenclature for biosimilars (originator biologic name followed by a random four-letter suffix). It should be noted that tbo-filgrastim was approved as an original biologic in the United States, and therefore has a more restricted indication than filgrastim biosimilars.

The FDA's approval of biosimilars is 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. Based on the review, the NCCN Guidelines recommend FDA-approved biosimilars as appropriate substitutes for originator filgrastim, pegfilgrastim, and epoetin alfa.

Filgrastim Biosimilars

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim. The approval of filgrastim-sndz was based on data demonstrating highly similar protein structure to filgrastim with near-identical pharmacokinetics, pharmacodynamics, and immunogenicity in healthy volunteers and patients with cancer.[32-34] Filgrastim-sndz has an identical mass, size, charge, and hydrophobicity as the originator product.[32] Pharmacokinetic and pharmacodynamic modeling have further confirmed the same mechanism of action (ie, G-CSF receptor binding).[33] A potential concern regarding immunogenicity exists with biosimilars based on the originator filgrastim biologics and the nature of filgrastim as an unglycosylated protein; however, immunogenicity is anticipated to be low to nonexistent with filgrastim biosimilars. A limited clinical study of healthy volunteers or patients with cancer found filgrastim-sndz binding antibodies in 3% of the study population (11 of 333 individuals).[35] Further analysis of these patients showed no evidence of neutralizing antibodies, suggesting that there is no increased risk of immunogenic adverse events or reduction in efficacy.[34] Phase III trials in patients with breast cancer receiving myelosuppressive chemotherapy (TAC; docetaxel, doxorubicin, and cyclophosphamide) showed no clinically meaningful differences in efficacy, safety, or immunogenicity between filgrastim and filgrastim-sndz, even when the two biologics were alternated in subsequent chemotherapy cycles.[31,36] Several retrospective studies report similar efficacy between prophylactic use of filgrastim-sndz and filgrastim during chemotherapy-induced neutropenia.[37-40]

In July 2018, the FDA approved a second biosimilar, filgrastim-aafi, for the same indications as filgrastim. A phase III randomized equivalence study in 279 patients receiving docetaxel/doxorubicin chemotherapy for breast cancer found that filgrastim-aafi is bioequivalent to filgrastim in terms of efficacy and safety and with similar incidence of FN, treatment-related bone pain, and mean time to neutrophil recovery.[41] The prospective, non-

interventional, longitudinal VENICE study observed the tolerability, safety, and efficacy of filgrastim-aafi in 386 patients with cancer receiving chemotherapy.[42] The study concluded that filgrastim-aafi was effective and well-tolerated in both primary and secondary prophylactic settings.[42] 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 in to reference filgrastim in both the prophylactic and therapeutic settings.[43,44]

Pegfilgrastim Biosimilars

In 2018, the FDA approved biosimilars, pegfilgrastim-jmdb and pegfilgrastim-cbqv, for the same indications as pegfilgrastim based on data showing highly similar pharmacokinetics, pharmacodynamics, and safety in healthy volunteers.[45-47] Pegfilgrastim-jmdb is analytically and functionally analogous to pegfilgrastim, with similar structure, molecular mass, physicochemical characteristics, and G-CSF receptor binding affinity.[48,49] A phase I randomized equivalence trial in healthy volunteers concluded that compared to pegfilgrastim, pegfilgrastim-jmdb had similar pharmacokinetics, pharmacodynamics, and safety profiles.[45] In a multicenter, randomized, phase III efficacy and safety trial, compared to patients with breast cancer receiving myelosuppressive chemotherapy with reference pegfilgrastim, patients receiving pegfilgrastim-jmdb showed no difference in the duration of severe neutropenia, time to ANC nadir, duration of post-nadir recovery, or treatment-related adverse events.[50] Pegfilgrastim-jmdb shows low immunogenic potential in healthy volunteers and in patients with cancer receiving myelosuppressive chemotherapy.[51] There are limited comparative studies of pegfilgrastim-cbqv. A multicenter randomized crossover study with 122 healthy volunteers showed that compared to pegfilgrastim, pegfilgrastim-cbqv has a similar safety profile and bioequivalent pharmacokinetics and pharmacodynamics.[46,47] No serious treatment-related adverse events were observed with pegfilgrastim-cbqv use.

In late 2019, the FDA approved the third biosimilar, pegfilgrastim-bmez, for the same indications as pegfilgrastim. In healthy volunteers, pegfilgrastim-bmez showed similar pharmacokinetics and pharmacodynamics to pegfilgrastim with no clinically meaningful differences in safety, tolerability, or immunogenicity.[52] Two randomized phase III trials (PROTECT-1 and PROTECT-2) demonstrated equivalent efficacy and safety between pegfilgrastim-bmez and pegfilgrastim in patients with breast cancer receiving myelosuppressive chemotherapy.[53,54] In PROTECT-1, patients with breast cancer who were randomized to receive pegfilgrastim-bmez or pegfilgrastim had equivalent duration of severe neutropenia during cycle 1 of chemotherapy (difference = .07 days; 95% CI, -0.12–0.26).[54] This was confirmed in PROTECT-2, which reported a difference of 0.16 days in the duration of severe neutropenia between patients receiving pegfilgrastim-bmez or pegfilgrastim (95% CI, -0.40–0.08).[53] Compared to pegfilgrastim, pegfilgrastim-bmez had similar safety and tolerability across both trials, with no significant difference in reported adverse events.[55]

In September 2022, the FDA approved pegfilgrastim-fpgk. Pegfilgrastim-fpgk showed bioequivalent pharmacokinetics and pharmacodynamics to pegfilgrastim in healthy volunteers, with no clinically meaningful differences in safety, tolerability, or immunogenicity.[56,57]

Epoetin Alfa Biosimilars

In May 2018, the FDA approved the first epoetin alfa biosimilar, epoetin alfa-epbx, for anemia associated with administration of myelosuppressive chemotherapy, chronic kidney disease (CKD), or HIV treatment, or to prevent the need for RBC transfusions in patients undergoing surgery. Analytical studies and clinical pharmacology data from healthy volunteers show that epoetin alfa and epoetin alfa-epbx have similar protein structure, stability, pharmacokinetics, and pharmacodynamics.[58] In two randomized

phase III clinical trials in patients with anemia secondary to CKD, epoetin alfa and epoetin alfa-epbx showed similar efficacy, safety, and mechanism of action.[58] Additionally, the results of three independent studies in patients with CKD and healthy volunteers showed similar rates and titers of anti-drug antibodies for both products, indicating that there is no clinically meaningful difference in immunogenicity risk for epoetin alfa-epbx as compared to epoetin alfa. Although there are limited data on the efficacy of epoetin alfa-epbx in treating CIA, two studies concluded that there were no clinically meaningful differences in efficacy or safety between epoetin alfa-epbx and epoetin alfa in the treatment of anemia in patients with CKD.[59,60] Therefore, the FDA approved extrapolation of epoetin alfa-epbx for the treatment of anemia in patients undergoing treatment with myelosuppressive chemotherapy, as well as all other indications for the originator product.

Management of Neutropenia

Benefits of MGFs

The NCCN Guidelines recommend MGF use based on therapeutic efficacy and clinical benefit. Prophylactic use of MGFs is known to reduce FN incidence, duration, and severity, decrease the subsequent rates of infection and hospitalization, and improve the delivery of full dose-intensity chemotherapy on schedule in patients with various cancers.[61-89] In a meta-analysis of 13 studies (1518 patients) by Clark et al, the prophylactic use of MGFs resulted in a clear reduction in infection-related mortality (odds ratio [OR], 0.51; 95% CI, 0.26–1.00; $P = .05$), 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; $P < .0001$).[86] In a systematic review of 17 randomized trials including 3493 patients with solid tumors and lymphoma, primary prophylaxis with G-CSF (defined as G-CSF administration within 5 days of beginning chemotherapy) reduced the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; $P < .001$).[88] The review showed a significant improvement with an average difference in the relative dose intensity (RDI) of chemotherapy of 8.4% between patients treated with G-CSF (mean RDI = 95.1%) and patients who did not receive G-CSF (mean RDI = 86.7%) ($P = .001$).[88] 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 G-CSF use. This survival advantage was confirmed in a systematic review of 25 randomized controlled trials that involved >12,000 patients undergoing chemotherapy with or without G-CSF support.[89] 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.

An increasing number of studies have assessed the financial implications of MGF use. Based on data analyzed in 2004, the rising cost of inpatient hospitalization resulted in a reduction of FN risk threshold from 40% to ~20% for prophylactic G-CSF use.[90] For example, if the risk of FN is >20% in a given patient, the overall costs of treatment are substantially reduced with prophylactic G-CSF. While the MGF addition to treatment regimens inevitably raises drug costs, it may equate to substantial savings in comparison to the costs of hospitalization and subsequent FN treatment. Pharmacoeconomic models of MGF use have reflected these clinical observations by simulating sequential chemotherapy regimens to account for FN risk on a per-cycle basis, and by accounting for chemotherapy dose reductions and consequent survival losses.[91] Economic analyses of MGFs have yielded mixed results depending on the usage context.[92-96] Selective use of MGFs in patients at an increased risk for neutropenic complications may also enhance cost-effectiveness.[90,97] Additionally, the use of biosimilars represent a new opportunity for cost containment in oncology care, as biosimilars are typically more affordable than their originator products.[26,98-101]

Risks of MGFs

The risks and benefits of G-CSF vs. dose reduction or delay during modern chemoradiotherapy are uncertain at this time. While MGFs may result in improved outcomes, they are also associated with toxicities. The listed toxicities are from the FDA package inserts (see the full inserts for specific products), which are based on studies from different patient populations. For filgrastim, tbo-filgrastim, and filgrastim biosimilars, the toxicities are based on studies in patients with non-myeloid malignancies. For sargramostim, the toxicities are based on studies in patients with leukemia or who are undergoing transplant. The listed toxicities may reflect the IV route of administration, which may differ from those of subcutaneous administration. Not all the toxicities are seen with each preparation, but similar toxicities are expected with filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars.

Bone Pain

The adverse event consistently associated with prophylactic G-CSF is mild to moderate bone pain, which occurs in 10% to 30% of patients.[79,102-105] Data for G-CSF–related bone pain treatment is limited to case series, reviews, and small randomized trials. These studies support the use of naproxen 500 mg, two times per day (BID) or other similar nonsteroidal anti-inflammatory drugs (NSAIDs) for 5 to 7 days after G-CSF administration.[103,106] However, NSAID use may not be appropriate for all patients with ongoing chemotherapy receiving G-CSF support due to comorbidities, side effects, drug-drug interactions, and drug-disease interactions.[106] Additionally, some patients may experience bone pain that is unresponsive to NSAIDs.[103] As an alternative, loratadine 10 mg daily or a similar anti-histamine can be used for 5 to 7 days after G-CSF administration.[107-110] Some studies have suggested that reducing the pegfilgrastim dose may be effective in managing G-CSF–related bone pain without increasing FN risk.[111-113] However, this strategy may not be feasible since pegfilgrastim comes in a pre-filled, non-graduated syringe designed and FDA-labeled for single-patient use. Therefore, use of reduced-dose pegfilgrastim is not currently recommended by the Panel for management of G-CSF–related bone pain.

Splenic Rupture

Rare cases of splenic rupture have been reported with G-CSF use, some of which are fatal.[114-120] 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.

Bleomycin-Induced Pulmonary Toxicity

The risk of bleomycin-induced pulmonary toxicity may be higher in patients treated with G-CSF. In a retrospective study of 141 patients with Hodgkin lymphoma receiving ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy, bleomycin-induced pulmonary toxicity was observed in 26% of patients receiving G-CSF compared with 9% of patients who did not receive it (P = .014).[121] Two studies have shown that ABVD can be safely administered at full dose without G-CSF support.[122,123] Due to the risk of pulmonary complications, G-CSF use in conjunction with the most common chemotherapy regimens, ABVD and Stanford V, is not recommended in patients with classical Hodgkin lymphoma. The toxicity potential for patients following BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is less clear, although bleomycin is given every 3 weeks in this regimen as opposed to every 2 weeks in ABVD. G-CSF support is

recommended for patients with Hodgkin lymphoma receiving the escalated BEACOPP regimen due to the high incidence of toxicity and treatment delays.

AML and MDS

Epidemiologic studies suggest an increased risk for development of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) following MGF administration; however, this has not been observed in individual randomized trials.[114,124-126] A meta-analysis by Lyman et al 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) of G-CSF-related AML/MDS development.[89] Although this meta-analysis could not determine whether the risk for AML/MDS is secondary to G-CSF or related to higher total doses of chemotherapy, overall mortality decreased with the addition of G-CSF support. An updated meta-analysis and systematic literature review by Lyman et al largely reached 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.[127] Analyses of the SEER database also show a slightly elevated risk of developing AML/MDS in patients receiving G-CSF support.[126,128] However, these studies should be interpreted with caution since they cannot exclude the possibility that G-CSFs were used in cases that were more likely to progress into AML/MDS, regardless of adjuvant therapy use.

Other Toxicities

Some patients may develop allergic reactions to G-CSF that involves the skin, respiratory system, or cardiovascular system. Other potential toxicities include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.[129] Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease receiving G-CSF, but not in patients with sickle cell trait.[130-132] Two case reports also found significant toxicity following G-CSF administration in patients with amyloidosis.[133,134]

Adverse events have also been reported with GM-CSF use. Adverse reactions, including mild myalgias, facial flushing, low-grade fever, headache, nausea, and dyspnea, were seen in 65% of patients with advanced malignancy following GM-CSF administration, although they were not severe and were reversible.[135] A side-effect study of GM-CSF, completed several years later, reported mild-to-moderate adverse events in 20% to 30% of patients, and attributed this decline to improved dosing and delivery.[136] Although uncommon, severe side effects have also been reported with GM-CSF use; <1% of patients develop blood clots, which may lead to pulmonary embolism or stroke in rare cases.[7,137,138] There have also been reports of capillary leak syndrome, a condition in which fluids move from the vascular system into the interstitial space, resulting in hypotension and reduced blood flow to internal organs.[7,139-141] While this is more common with GM-CSF use, it has also been reported to occur with G-CSF use.[142,143]

Data regarding the safety of MGF administration following infusion of chimeric antigen receptor (CAR)-modified T cells are limited and institutional practices vary widely.[144-146] The FDA label for tisagenlecleucel recommends avoiding MGFs, particularly GM-CSF, during the first 3 weeks after cell infusion or until cytokine release syndrome (CRS) has resolved.[7] Although data are not provided to support this recommendation, it is likely based on the potential of GM-CSF to promote antigen-presenting cell function that may exacerbate CRS severity or incidence.[144,147] More studies are needed to determine the safety of MGFs in patients undergoing CAR T-cell therapies due to the high rates of neutropenic complications and the potential for promotion of CRS with MGF use.

Prophylactic Use of MGFs

Risk Assessment

The risk of developing FN is related to the treatment regimen, delivered dose intensity, and patient-specific risk factors. FN risk should be evaluated prior to the first and each subsequent cycle of chemotherapy. Risk assessment should include 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 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 those in the intermediate-risk group based on patient-specific risk factors. Patients in the low-risk group should generally not receive prophylactic G-CSF.

There is currently no consensus nomogram for FN risk assessment. While the NCCN Panel outlines criteria to aid FN risk assessment, independent clinical judgment should be exercised based on the individual patient's situation. The NCCN Panel recommends that patients receiving cytotoxic chemotherapy as part of a clinical trial be evaluated for prophylactic use of G-CSF based on both regimen-specific and patient-specific risk factors, unless precluded by trial specifications.

Chemotherapy Regimens and Risk for FN

The Panel considers chemotherapy regimens for which clinical trial data show an incidence of FN >20% in patients who have not received prior chemotherapy as high risk. The addition of monoclonal antibodies to chemotherapy regimens has the potential to increase FN risk. Of particular concern is rituximab, an anti-CD20 monoclonal antibody mainly used in the treatment of CD20+ hematologic malignancies, with known independent potential to cause severe neutropenia. Rituximab is associated with prolonged, delayed-onset neutropenia with and without chemotherapy.[148]

The algorithm lists common chemotherapy regimens associated with high or intermediate risk of developing FN based on published data. These lists are not comprehensive and are meant to serve as examples only. 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. The Panel emphasizes that chemotherapy regimen is only one component of risk assessment and needs to be combined with patient-specific risk factors to estimate the overall risk of FN.

Patient Risk Factors for Developing FN

Patient-specific risk factors are important in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk.[149] For example, many regimens for breast and lung cancers are associated with an intermediate risk of neutropenic complications. The presence of patient-specific risk factors may elevate the overall risk to a high-risk category, where prophylactic G-CSFs are more routinely recommended. Even a low-risk regimen may warrant G-CSF use in a patient with one or more clinical risk factors.

An important patient-specific risk factor for FN development is age (>65 years; see NCCN Guidelines for Older Adult Oncology).[150-155] Other identified risk factors that might prompt the use of prophylactic G-CSF include prior exposure to chemotherapy or radiation therapy (RT), persistent neutropenia, tumor involving the bone marrow, poor performance status, recent surgery and/or open wounds, renal or liver dysfunction, and HIV infection.[156] Chronic immunosuppression in the post-transplant setting (including organ transplant) may also warrant G-CSF use. 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 in 3760 patients with cancer beginning chemotherapy.[157] This model and its associated risk factors have been retrospectively validated both internally and externally in an independent patient population.[158] In the future, external validation of other proposed FN risk assessment models and novel patient-specific risk factors may improve identification of individuals at high risk of developing FN.[97,159-162]

Patients at High Risk for FN

The Panel recommends prophylactic G-CSF use if a patient's risk of developing FN is >20% (category 1). The American Society of Clinical Oncology (ASCO) and European Organization for Research and Treatment of Cancer (EORTC) guidelines have also adopted the 20% threshold for considering routine prophylactic MGF support.[163,164] This consistent recommendation is based on several large randomized trials that show primary G-CSF prophylaxis, when the risk of FN without prophylaxis is >20%, results in a significant reduction in FN incidence.[88,165] A phase III, randomized, placebo-controlled trial in patients with breast cancer receiving docetaxel and cyclophosphamide found that FN incidence was significantly lower in patients who received prophylactic G-CSF compared to those who received placebo (1.2% vs. 68.8%, respectively; $P < .001$).[165] Patients in the G-CSF group also had lower rates of hospitalization and antibiotic use. In individuals with diffuse large B-cell lymphoma (DLBCL), 13.8% and 8% of patients who received Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), respectively, had grade 3 or 4 febrile neutropenia.[166] In these studies, 90.1% and 93.2% of patients treated with Pola-R-CHP and R-CHOP, respectively, also received prophylactic G-CSF.[166] Prophylactic G-CSF use was associated with a 46% reduction in the RR of developing FN in a systematic review of 17 randomized controlled trials involving 3493 patients with solid tumors or malignant lymphoma receiving systemic chemotherapy.[88]

The Panel recognizes that different circumstances exist in which patients treated with relatively non-myelosuppressive 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 have high-risk features, 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 one or more risk factors 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, G-CSF use is a difficult decision and requires careful discussion between the physician and patient. If the increased risk for FN is due to patient-specific 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, 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.[90,167,168] However, prophylactic G-CSF use may be

appropriate if the individual is receiving therapy with curative intent and is at significant patient-specific risk of developing FN.

Evaluation Prior to Subsequent Chemotherapy Cycles

After the first cycle of chemotherapy, the patient should be evaluated prior to each subsequent cycle to determine FN risk category. 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 as planned for the current cycle, this patient is now considered to be at high risk for FN. Prophylactic G-CSF support should be considered for such patients who have not received prior G-CSF. In patients who received 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 before a decision is made regarding prophylactic G-CSF use.

Dosing and Administration

Prophylactic G-CSFs are given the next day or 3 to 4 days after chemotherapy. The Panel clarified that non-cytotoxic targeted therapies are excluded from this 24-hour recommendation. Filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars are FDA-approved options for FN prophylaxis in patients with solid tumors receiving myelosuppressive chemotherapy. Sargramostim is not recommended in this setting. Caution should be exercised when administering prophylactic G-CSF in patients receiving concurrent chemotherapy and radiation.[169] Randomized data have indicated a detrimental effect on toxic deaths with the use of GM-CSF during concurrent chemoradiotherapy. This was not observed in a more recent secondary analysis of the CONVERT trial, in which prophylactic G-CSF was allowed.[170] For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Filgrastim and Filgrastim Biosimilars

Subcutaneous administration of filgrastim, tbo-filgrastim, or filgrastim biosimilars is a category 1 recommendation for FN prevention. Initial doses are administered the next day or up to 3 to 4 days after completion of myelosuppressive chemotherapy. A daily dose of 5 mcg/kg is administered until post-nadir ANC recovery 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 and appropriate to the setting. The NCCN Panel recommends treatment of patients through post-nadir recovery since studies show shorter durations of G-CSF treatment to be less efficacious.[171]

Pegfilgrastim and Pegfilgrastim Biosimilars

Pegfilgrastim and pegfilgrastim biosimilars are pegylated versions of filgrastim designed to have a longer half-life and allow for a single administration of 6 mg. Based on clinical trial data, pegfilgrastim or pegfilgrastim biosimilars can be administered the day after myelosuppressive chemotherapy (category 1).[172,173] Administration up to 3 to 4 days after myelosuppressive chemotherapy is also reasonable based on trials of filgrastim. The rationale for not giving same-day pegfilgrastim is the potential neutropenic exacerbation caused by hematopoietic progenitor stimulation (by active cytotoxic chemotherapy) in dividing cells, which can cause progenitor loss.[174,175] A systematic literature review evaluating the relative merits of next-day versus same-day pegfilgrastim found that delivery at least 24 hours after myelosuppressive chemotherapy improved patient outcomes across a variety of tumor types.[172] A 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.[176] Another retrospective study found that 50% of all FN episodes requiring hospitalization occurred among patients with cancer who either did not receive or received pegfilgrastim on the same day as chemotherapy.[171] An observational study in Korea found that administration of secondary prophylactic pegfilgrastim 24 hours after chemotherapy in patients with breast cancer reduced FN incidence from 11.8% to 1.6%.[177] A large-scale retrospective analysis in 53,814 patients receiving intermediate- or high-risk chemotherapy found significantly higher FN incidence in patients administered prophylactic pegfilgrastim either the same day or 4 to 5 days after chemotherapy compared to those receiving pegfilgrastim on days 1 to 3 following chemotherapy.[178] In a direct comparative study, Kaufman et al showed that in individuals with breast cancer with ongoing TAC treatment, 33% of patients who received same-day pegfilgrastim had FN events compared to only 11% of patients who received pegfilgrastim the next day.[179] A similar trend was seen in a prospective, randomized trial in patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like therapy for NHL, where same-day pegfilgrastim was associated with enhanced myelosuppression.[180]

In contrast, some retrospective analyses found no statistically significant difference in FN rates among patients administered pegfilgrastim the next day versus the same day as chemotherapy.[181-184] In a retrospective analysis of 297 patients (64% had breast cancer and 24% had lymphoma) treated with dose-dense chemotherapy, 6% of patients in the same-day pegfilgrastim group and 6.7% in the next-day group experienced one or more episode of FN in cycle 1 (P = .814).[184,185] Across all cycles, 9.3% in the same-day group and 8.9% in the next-day group experienced one or more episode of FN (P = .910). In a single-institution retrospective review of 69 patients who received pegfilgrastim the same day as chemotherapy, there were no reported FN cases.[182] A retrospective review of 93 patients concluded that pegfilgrastim can be safely administered the same day as chemotherapy in patients with lymphoma receiving CHOP-like chemotherapy.[183] Although there are data for and against same-day pegfilgrastim administration, the FDA-approved dosing schedule of next-day administration is recommended.

The NCCN Panel recognizes that some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize travel burdens on patients traveling long distances. Travel burden in addition to patients' prior knowledge and prescribing practices can impact G-CSF administration.[186-188] An alternative for patients who cannot return to the clinic for next-day administration is an FDA-approved 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).[189] However, this on-body delivery device is currently only available for use with originator pegfilgrastim and not pegfilgrastim biosimilars. Failure to inject, which requires further medical attention, is rare (1.7%–6.9%).[189-192] The Panel suggests that physicians be aware that on-body injectors may not be acceptable or safe for patients who require an MRI study during the period of wear.[193]

The Panel has also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle lengths. In general, there should be at least 12 days between pegfilgrastim administration and the next chemotherapy cycle. If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment. Pegfilgrastim use, during chemotherapy given every 3 weeks in phase III clinical trials, is a category 1 recommendation.[65,194] Pegfilgrastim use is a category 2A recommendation, based on phase II studies, for chemotherapy regimens given every 2 weeks.[195-200] There are insufficient data to support pegfilgrastim use for weekly regimens; therefore, pegfilgrastim should not be used. The Panel extends these recommendations to pegfilgrastim biosimilars. The Panel notes that pegfilgrastim can increase fluorodeoxyglucose (FDG) uptake in bone

marrow/spleen and therefore advises careful assessment and interpretation of PET/CT scans after pegfilgrastim administration.[201]

Therapeutic Use of MGFs

There is less evidence supporting the therapeutic use of MGFs for FN. While there are clinical benefits to G-CSF therapy for FN, such as shorter time to neutrophil recovery and shorter length of hospitalization, it remains unclear whether these benefits translate into a survival advantage.[86,202] The NCCN Panel recommends that patients presenting with FN who are receiving or have previously received prophylactic filgrastim, tbo-filgrastim, or filgrastim biosimilars should continue G-CSF. No studies address the therapeutic use of filgrastim for FN in patients who have already received prophylactic pegfilgrastim or a pegfilgrastim biosimilar. However, since pegfilgrastim and pegfilgrastim biosimilars are long-acting,[203] those who have received these agents prophylactically should not be treated with additional G-CSF. Pharmacokinetic data following treatment with pegfilgrastim demonstrate high levels during neutropenia and suggest that additional G-CSF use may not be beneficial.[204] However, additional G-CSF support may be considered in patients with prolonged neutropenia (beyond 12–14 days) as the pegylated products are unlikely to endure beyond this window.

The NCCN Panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome for patients presenting with FN who have not received prophylactic G-CSF. Features associated with poor outcome 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 FN episode(s). Therapeutic MGF use should be considered if risk factors are present. Filgrastim, tbo-filgrastim, filgrastim biosimilars, or sargramostim may be administered in the therapeutic setting. Pegfilgrastim, pegfilgrastim biosimilars, eflapegrastim-xnst, and efbemalenograstim alfa-vuxw have only been studied prophylactically and are not recommended for therapeutic use at this time.[205,206]

Filgrastim, pegfilgrastim, and sargramostim are also FDA-approved for the treatment of patients with radiation-induced myelosuppression following a radiologic/nuclear incident (H-ARS).[16,207] The Panel also recommends use of tbo-filgrastim, eflapegrastim-xnst, efbemalenograstim alfa-vuxw, or filgrastim/pegfilgrastim biosimilars as appropriate options 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 increase survival.[208] According to U.S. Department of Health and Human Services Radiation Emergency Medical Management guidance, MGF initiation should be strongly considered for patients who received ≥2 Gy whole body exposure or significant partial body exposure and have an ANC ≤500 cells/mm^3 and will likely have prolonged periods of significant neutropenia.[208] Patients who have trauma and/or burns have worse clinical outcomes compared to radiation exposure alone, which can impact cytokine administration.[208] Most of the data that support MGF use in this setting are derived from animal studies and case reports concerning patients involved in radiation accidents.[209-218]

Dosing and Administration

Filgrastim, tbo-filgrastim, filgrastim biosimilars, and sargramostim are the recommended MGFs for FN treatment in select patients who are high risk as outlined above who have not received prophylactic G-CSF. Filgrastim, tbo-filgrastim, and filgrastim biosimilars should be given at a daily dose of 5 mcg/kg and sargramostim should be given at a daily dose of 250 mcg/m^2. Treatment should continue through post-nadir recovery. For patients presenting with H-ARS, filgrastim, tbo-filgrastim, or filgrastim biosimilars should be given at a daily dose of 10 mcg/kg; pegfilgrastim and pegfilgrastim biosimilars should be given as a single dose of 6 mg; and sargramostim should be given at a daily dose of 250 mcg/m^2.[208] MGFs

should be administered as soon as possible after acute radiation exposure.

Severe Chronic Neutropenia

These guidelines focus on the management of neutropenia in the cancer setting; therefore, severe chronic neutropenia 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.[219] 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). Patients with congenital neutropenia 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 severe congenital neutropenia are at risk for myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, who require higher G-CSF doses, 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 Thrombocytopenia

Use of Thrombopoietin Receptor Agonists in Patients with Cancer

Thrombocytopenia is common in patients with cancer and can lead to chemotherapy delays or dose reductions that disrupt treatment.[20-22] Platelet transfusion only offers temporary improvement in platelet count and is often unreliable and impractical to continue for extended periods.[21] TPO is the main growth factor responsible for the stimulation of platelet production. TPO-RAs, such as romiplostim, bind to and activate the TPO receptor, thereby increasing platelet production.[20] Romiplostim is FDA-approved to treat immune thrombocytopenia. Although romiplostim is widely used to treat CIT; there are no FDA-approved agents for treating CIT. Retrospective studies have evaluated other TPO-RA agonists, including avatrombopag; however, the Panel emphasizes that there are insufficient data from these studies to recommend any of these agents.[220] No overall survival (OS) or progression-free survival (PFS) benefits have been demonstrated with these agents and thus far no randomized trials have been conducted to address survival benefits. Additional prospective studies are needed to determine safety, efficacy, and benefits of TPO-RA agonists. Whenever possible, participation in clinical trials is strongly encouraged. The subcommittee on Hemostasis and Malignancy from the International Society on Thrombosis and Haemostasis (ISTH) has similar recommendations and emphasizes the need to optimize study design including selection criteria in managing CIT.[221]

Patients with suspected CIT should be evaluated for other potential etiologies such as nutritional deficiencies, medications/supplements that suppress platelet production, infections (including viral reactivation), immune thrombocytopenia, heparin-induced thrombocytopenia (HIT), radiation-or chemotherapy-induced myelosuppression, hematologic malignancy, consumption of platelets secondary to blood loss, and thrombotic microangiopathies, among others and treated accordingly. A

CBC with differential and blood smear for morphologic evaluation, including evaluation for platelet clumping and other cytopenias, should be performed. If CIT is diagnosed, consider platelet transfusion per Association for the Advancement of Blood & Biotherapies (AABB) guidelines, chemotherapy dose reduction or change in regimen, enrollment in a clinical trial of TPO-RAs, or treatment with romiplostim. The primary purpose of using TPO-RAs for CIT is to maintain chemotherapy dose schedule and intensity. In patients for whom a TPO-RA is being considered for CIT management, participation in clinical trials is encouraged whenever possible. Romiplostim dosing strategies include weekly dosing beginning at 2 to 4 mcg/kg, increased by no more than 1 to 2 mcg/kg per week to target platelet count 100,000 to 150,000/mcL.[20,21] Maximum dose is 10 mcg/kg weekly per prescribing information.

Studies of romiplostim to manage CIT have been limited to case series and small single-center studies that have shown that romiplostim is effective in increasing platelet counts in patients with solid tumors.[21,222,223] Romiplostim use in non-myeloid hematologic malignancies has not been evaluated. In a multicenter retrospective analysis (*N* = 173), 71% of patients with solid tumors had response to romiplostim.[21] A case series of 20 patients with solid tumors and CIT reported that romiplostim treatment improved platelet counts in all patients, which allowed chemotherapy resumption.[223] In a phase II randomized trial in patients with solid tumors and CIT, 93% of patients treated with romiplostim experienced correction of their platelet count and thus CIT within 3 weeks compared with 12.5% of patients who did not receive romiplostim ($P < .001$).[20] However, data suggest that TPO-RAs used for CIT may increase the risk of venous thromboembolism (VTE) in patients with cancer.[20,21,222,223] Therefore, caution is warranted.

Several reports have examined the efficacy of TPO-RAs in patients with prolonged thrombocytopenia following HCT, including those patients with secondary failure of platelet recovery.[224,225] Patients with thrombocytopenia post-HCT should be evaluated for other potential causes of thrombocytopenia mentioned above as well as primary or secondary graft failure, graft-versus-host disease (GVHD), relapse of hematologic malignancy, and transplant-associated thrombotic microangiopathy (TA-TMA). Patients with primary or secondary failure of platelet recovery without another clear underlying cause should be considered for platelet transfusion per AABB guidelines. Clinical trial participation is encouraged whenever possible.

Eltrombopag has been shown to be efficacious in patients with prolonged thrombocytopenia post-allogeneic transplant and poor graft function.[226-231] Eltrombopag is FDA-approved for patients with chronic immune thrombocytopenia or severe aplastic anemia. In a phase II randomized trial in 60 patients with post-HCT thrombocytopenia, a significantly higher proportion of patients in the eltrombopag arm achieved a platelet count of ≥50,000/μL compared with the placebo arm (21% vs. 0%; $P = .046$). However, OS, PFS, relapse rate, and non-relapse mortality were similar in the two arms.

TPO-RA lusutrombopag has been suggested to have activity for thrombocytopenia in patients with cancer or thrombocytopenia post-HCT. Lusutrombopag is currently FDA-approved for thrombocytopenia management in patients with chronic liver disease who are scheduled to undergo a medical or dental procedure. The efficacy of lusutrombopag was assessed in an integrated analysis of data from two phase III trials that compared lusutrombopag to placebo in 270 patients with chronic liver disease and hepatocellular carcinoma (HCC). Treatment with lusutrombopag reduced the need for platelet transfusions, increased platelet counts for 3 weeks, and reduced the number of bleeding events compared with placebo in patients with HCC secondary to chronic liver disease.[232] Although these reports are promising, outside of a clinical

trial setting, insufficient data are available to support use of TPO-RA other than romiplostim and eltrombopag for treatment of CIT.

During the pandemic, when many institutions decided to limit platelet transfusions to patients with active bleeding or a numerical value <10 K/mcL, the Panel convened a voluntary subcommittee to provide guidance for more optimal use of growth factors.[233] Prophylactic antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) can be used for those with platelet counts <10 K/mcL when platelets are unavailable due to blood supply shortage, or in patients who are alloimmunized who do not have suitable human leukocyte antigen–matched units available. The Panel recommends holding antifibrinolytics when endogenous platelet counts are >30 K/mcL and in patients with embolic strokes, active thromboembolism, and urinary tract bleeding.

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.[234] Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, nutritional deficiencies, hereditary disease, renal insufficiency, hormone dysfunction, chronic inflammation, or a combination of these factors.[235,236] The malignancy itself can lead to or exacerbate anemia in a number of ways.[237] 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 highly prevalent among patients with cancer at initial presentation, especially in patients with lung cancer.[19,238-240]

Many chemotherapy agents cause myelosuppression, which contribute to anemia.[240] Chemotherapeutic agents induce anemia by directly impairing hematopoiesis in the bone marrow, including disruption of RBC precursor production.[237] Additionally, the nephrotoxic effects of some cytotoxic agents (eg, platinum-containing agents) can result in decreased erythropoietin production by the kidneys.[237] RT to the skeleton has also been associated with hematologic toxicity. In a retrospective analysis of 210 patients with primary central nervous system tumors receiving craniospinal RT, approximately one-third of patients developed grade 3/4 hematologic toxicities including anemia.[241] Newer modalities such as immunotherapies may also produce anemia, although data are limited.[242-245] Clinicians should become familiar with the adverse effects of immunotherapy drugs, including hematologic toxicities, and be watchful for other less-documented clinical conditions as these therapies become more prevalent in cancer care.

The myelosuppressive effects of certain 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. In the European Cancer Anaemia Survey (ECAS), the rate of anemia (Hb level <12 g/dL) increased from 19.5% in cycle 1 to 46.7% by cycle 5.[239] 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 CIA risk include nadir Hb level, the time to 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.[237]

Initial Evaluation of Anemia

Given the wide variation in Hb levels among healthy subjects, a universal “normal” value is difficult to define. The NCCN Panel recommends that an

Hb level ≤11 g/dL should prompt an evaluation of anemia in patients with cancer. A decrease by ≥2 g/dL below baseline is also cause for concern and assessment. Importantly, clinicians should consider gender differences in Hb as part of the initial evaluation of anemia, since women typically have a lower baseline Hb level than men.[246] 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 al[234]). The overall goals of evaluation are to characterize the anemia and identify any underlying comorbidities that can be potentially modified 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 examination 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. Pallor may also 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.[247] The above clinical manifestations are not sensitive or 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 anemia evaluation: morphologic and kinetic. A complete evaluation should use 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 medications[248] 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 B_{12}) or inadequate absorption of B_{12} 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 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 (immature RBCs) 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 = Reticulocyte count (%) x [(observed Hct)/(expected Hct)], where the expected Hct is equal to 45%.

Reticulocytes normally persist in circulation for 24 hours before becoming erythrocytes. However, as anemia increases younger reticulocytes are

released from the marrow, thus remaining in circulation for 2 to 3 days before becoming erythrocyte. This results in false high RI values. The reticulocyte production index (RPI) is an adjusted index that takes this into account and is calculated by the following formula: RPI = RI x (1/RMT), where RMT is the reticulocyte maturation time (RMT) constant determined by the observed Hct (see Table 1).

- Low RI/RPI ratio (<1) indicates decreased RBC production, suggesting iron deficiency, B_{12}/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 patient with anemia.

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

- Nutritional deficiency—low iron and elevated total iron-binding capacity (TIBC) and/or low vitamin B_{12} 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—consider upper and lower endoscopic evaluation.
- Hemolysis—direct antiglobulin test positive, disseminated intravascular coagulation panel positive, low haptoglobin levels, elevated indirect bilirubin, and elevated lactate dehydrogenase (LDH).
- Renal dysfunction—glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 consecutive months.
- Inherited anemia—personal and/or family history.
- Sideroblastic anemia—sideroblasts present in bone marrow biopsy.
- Hormone dysfunction—hypogonadism, adrenal dysfunction, and hyper/hypothyroidism.
- Chronic inflammation—increased C-reactive protein level and/or erythrocyte sedimentation rate.[249]
- Treatment-induced myelosuppression

Any cause of anemia that is independent of cancer or chemotherapy 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 patient with anemia 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 with or without iron supplementation may be warranted for long-term anemia management in patients with high risk or in patients with no symptoms but with comorbidities.

Red Blood Cell Transfusion

The decision to offer PRBC transfusion should not be made based on whether the Hb level of the patient has reached a certain threshold or “trigger.” Instead, the NCCN Panel outlines three general recommendations: 1) observation and periodic re-evaluation are appropriate for patients who are asymptomatic without significant comorbidities; 2) transfusion can be considered for patients with high risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation) or patients who are asymptomatic with comorbidities (eg, cardiac disease, chronic pulmonary disease, cerebral vascular disease); and 3) transfusion should be performed for patients with symptoms (physiologic). Physiologic symptoms warranting PRBC transfusion include sustained tachycardia, tachypnea, chest pain, dyspnea on exertion,

lightheadedness, syncope, or severe fatigue preventing work and usual activities.

The clinical manifestations are associated with anemia onset, severity, and duration, as well as other factors influencing tissue demands for oxygen. Symptoms are likely to be more pronounced when anemia onset is acute; whereas physiologic adjustments that compensate for lower oxygen-carrying capacity of blood can occur with gradual anemia onset. 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 clinical judgment of the physician. For example, even when a patient with anemia 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) and 128 to 240 mL of pure RBCs.[250]

Benefits and Risks of Red Blood Cell Transfusion

Benefits of Red Blood Cell Transfusion

The major benefit of PRBC transfusion, offered by no other anemia treatment, is the quick increase in Hb and Hct levels and thus a rapid improvement in anemia-related symptoms. Hence, PRBC transfusion is the best option for patients who require immediate correction of anemia. Transfusion of 1 unit (~300 cc) of PRBCs has been estimated to an average increase in Hb level by 1 g/dL or in Hct level by 3% in an adult who is not experiencing simultaneous blood loss.[250,251] 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.

Risks of Red Blood Cell Transfusion

Risks associated with PRBC transfusion include transfusion-related reactions (eg, hemolytic, non-hemolytic, febrile, lung injury), transfusion-associated circulatory overload (TACO), and bacterial contamination. 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.[252,253] Bacterial infection was the most common form, and occurred as frequently as 1 in 3000 random-donor samples before the mandate of bacterial screening in 2004.[253] Since the screening implementation, fewer than 10 deaths from bacterial sepsis per year have been reported in patients receiving PRBC transfusion. Additionally, pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse event.[254,255]

Red Blood Cell Transfusion Goals and Basic Principles

The overall goal of PRBC transfusion is to treat or prevent deficiencies in the blood oxygen-carrying capacity and improve oxygen delivery to tissues. In 2016, based on a systematic review of randomized controlled trials, the AABB published clinical practice guidelines evaluating Hb

thresholds for RBC transfusion.[256] AABB recommendations include: 1) using an Hb level of 7 g/dL as a threshold for adult patients who are hospitalized and 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 is lack of evidence to provide specific recommendations for individuals with cancer. The NCCN Panel agrees 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 symptoms, cancer course and treatment, comorbidities, and patient preference.

Prior to transfusion, PRBCs must be crossmatched to confirm compatibility with ABO and other antibodies with the recipient. There is no evidence to support routine premedication with acetaminophen or an antihistamine to prevent allergic and febrile non-hemolytic transfusion reactions.[257,258] 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 reassessed after each transfusion. When considering PRBC transfusion, refer to the 2016 AABB clinical practice guidelines.[259]

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 patients from using blood products. For these 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 used to reduce anemia, including minimizing blood loss,[260-264] ESA use,[263,265,266] or substitute blood products.[260,263,265-268] Strategies to reduce blood loss include batching routine laboratory testing, using pediatric blood collection tubes, minimizing phlebotomy, and returning discard in a closed system.[260-264] Additionally, daily folic acid and vitamin B_{12} supplementation should be considered prior to initiating myelosuppressive chemotherapy. Nutritional sufficiency for iron, folate, and vitamin B_{12} should be evaluated and deficiencies corrected. Iron deficiency should be corrected using IV iron. Baseline coagulation abnormalities should also be fully evaluated and corrected prior to myelosuppressive treatment.

Most data regarding the use of ESAs in patients who refuse blood transfusions are from published case reports and small cohort series involving individuals who are Jehovah's Witnesses. These types of reports carry inherent bias and vary significantly in reporting outcomes, regimens, and dosing.[265] Overall there is scarcity of data regarding individuals who are Jehovah's Witnesses with CIA. A 2008 analysis of 14 case reports of individuals who are Jehovah's Witnesses 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 duration varied widely among included studies.[269] Additional case reports on individuals who are Jehovah's Witnesses, including three involving patients with cancer, have shown similar results on ESAs effectiveness in increasing Hb levels.[270-276] In one case report, a 57-year-old Jehovah's Witness diagnosed with CIA, secondary to aggressive NHL, was administered darbepoetin alfa once per week, which increased Hb levels from 7.5 to 11.5 g/dL within 1 month and enabled completion of intensive chemotherapy.[270] Although there is a lack of prospective data, ESAs should be considered given that there is no option for transfusion.[263,265] However, ESAs are not recommended for patients with cancer who are not receiving therapy, patients receiving non-myelosuppressive chemotherapy, and patients receiving myelosuppressive chemotherapy with curative intent. If ESAs are prescribed off-label for these indications, patients should be made aware

of the off-label use along with potential increased risks of thrombosis and tumor progression. It should be noted that ESA therapy impact on Hb level may not be evident for several days after administration. Therefore, in cases of severe, life-threatening anemia, pure oxygen (400 mmHg, S_AO_2 = 1.0) by mechanical ventilation can be used to increase blood oxygenation.[277]

Although not FDA-approved, clinicians may access investigational blood substitute products, also known as Hb-based oxygen carriers (HBOCs), for single-patient compassionate use under the FDA's Expanded Access program.[260,263,265-268,278] 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.[265] Despite these benefits, few products have advanced to phase III trials and none have produced a significant decrease in the need for transfusions (in patients who accept transfusion support). HBOCs have been associated with serious adverse reactions.[268] 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.[279] However, with compassionate use in emergent settings, HBOCs have successfully treated individuals with severe anemia who are Jehovah's Witnesses.[267,280-284] A case series evaluation has suggested that delay in receipt of HBOCs is independently associated with mortality in patients who refuse blood transfusions. Therefore, clinicians should consider starting the regulatory process for HBOC procurement early in the treatment course.[285] While HBOCs may represent a lifesaving modality in severe anemia in patients who refuse blood transfusions, further evaluation of these products in clinical trials is needed.

Erythropoietic Therapy

ESAs stimulate erythropoiesis in patients with low RBC levels, although not all patients have diseases that respond to ESA therapy. In a study involving 2192 patients with cancer receiving ESA therapy, 65% of patients showed an Hb increase of ≥1 g/dL.[286] Unlike transfusion, which immediately boosts Hb level; ESAs can take weeks to elicit an Hb response, but they are effective at maintaining a target Hb level with repeated administration. Iron studies (serum iron, TIBC, and serum ferritin) should accompany ESA therapy to monitor the development of iron deficiency.

Benefits of ESA Therapy

The main goals of ESA therapy are gradual improvement in anemia-related symptoms and avoidance of transfusion. In a randomized, placebo-controlled study, epoetin alfa increased Hb levels (2.2 vs. 0.5 g/dL; $P < .001$) and reduced transfusion requirements (24.7% vs. 39.5%; $P = .0057$) in patients with anemia receiving chemotherapy.[287] In a randomized phase III study, patients with lung cancer 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.[288] The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review that analyzed 20,102 patients undergoing treatment for cancer with concomitant ESA therapy.[289] A decreased RR for transfusion was observed in patients receiving ESAs (RR, 0.65; 95% CI, 0.62–0.68).[289] Of the patients treated with ESAs, 25 out of 100 subsequently received a transfusion versus 39 out of 100 patients in the untreated group. This equated to a one-unit reduction of transfusion in patients treated with ESA. The first meta-analysis found that more patients with CIA 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) when treatment was

initiated at Hb ≤10 g/dL.[290] Transfusions were also less common in patients receiving darbepoetin alfa (HR, 0.58; 95% CI, 0.44–0.77).

Risks of ESA Therapy

ESA-associated toxicities include increased thrombotic events, possible decreased survival, and shortened time to tumor progression. When considering ESAs, the risks of ESA therapy including the potential for tumor growth, increased mortality, blood clots, and hypertension should be discussed with patients.

Possible Increased Mortality and Tumor Progression

The FDA has made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa, including the addition of black-box warnings, since their approval in 2007. These strengthened FDA restrictions were based on the results of eight 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).[291-298] Of the eight studies, four investigated ESAs in patients who received chemotherapy, two studies involved patients receiving RT alone, and two studies involved patients receiving neither chemotherapy nor RT. All eight 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 ESA use when targeting Hb levels >12 g/dL.[289,299-302] Data from the Cochrane Database also reported increased mortality associated with ESA use in patients when targeting Hb levels >12 g/dL.[289] 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 <10 g/dL resulted in fewer thromboembolic events and reduced mortality.[302]

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.[303,304] Pharmacovigilance trials have also reported no adverse effects on survival in patients with CIA receiving ESAs.[305,306] 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.[307] In this study, no impact on event-free survival (EFS) (darbepoetin alfa, 89.3% vs. no darbepoetin alfa, 87.5%; $P_{\text{log-rank}} = 0.55$) or OS (darbepoetin alfa, 95.5% vs. no darbepoetin alfa, 95.4%; $P_{\text{log-rank}} = 0.77$) was observed with ESA use. In the AGO-ETC trial, which included 1284 patients with high-risk breast cancer, epoetin alfa resulted in improved Hb levels and decreased transfusions without an impact on relapse-free survival or OS.[308] Additionally, data from randomized studies showed no increase in mortality in patients receiving chemotherapy for small cell lung cancer when ESAs were given as indicated in the prescribing label.[309-311] A systematic review also showed no major change in OS with ESA therapy in patients with cancer.[312] While these data suggest that although ESA use may not be associated with decreased survival or increased disease progression as previously thought, data from additional prospective trials designed and powered to measure survival of patients with cancer are needed to guide clinicians on optimal ESA use.

Thromboembolism

Increased thromboembolic events, including VTE, are associated with ESA therapy in patients with cancer.[289,299,301-304,312] The cause of VTE in patients with cancer is complex with increased baseline risk related to both the malignancy itself and to the chemotherapy regimen used (see NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease).[313-316] Risk factors for VTE in patients with cancer include but are not limited to 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.[317] Patients with risk factors may be more susceptible to thrombosis with ESA use. Therefore, risk factors should be evaluated individually before administrating ESA therapy. The NCCN Panel recommends physicians to be on alert for signs and symptoms of thromboembolism in patients with cancer receiving ESAs.

In an analysis of phase III trials comparing ESAs with placebo for CIA treatment, the absolute risk of VTE was 7.5% in patients treated with ESAs compared with 4.9% in patients in the control group.[299] 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).[318] 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 patients with all three conditions: anemia, CKD and cancer.[319] It is important to note that the thrombotic potential of ESAs is independent of Hb levels.[320]

Hypertension

A Cochrane review reported an increased risk for hypertension with ESA use in patients with cancer (RR, 1.30; 95% CI, 1.08–1.56).[289] A systematic review also reported increased hypertension risk in patients with cancer receiving ESAs.[312] 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 ESA use to decrease the risk of hypertension.

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) related to anti-EPO antibodies have been reported rarely but with increased incidence in specific preparations of recombinant EPOs (rEPOs); PRCA should be suspected whenever a response to rEPO is lost. It is important to report these cases to the FDA along with information on which biosimilar or innovator molecules are involved.[7,321,322]

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.[7] The FDA made this determination based on the results of 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 be discontinued once the chemotherapy course is complete. 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.[309-311] Additionally, ESAs are not recommended for use in patients with cancer who are not receiving therapy or in patients receiving non-myelosuppressive therapy. Patients undergoing palliative treatment may be considered for ESA therapy, PRBC 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. If ESAs are utilized, physicians are advised to use the lowest dose necessary to eliminate symptoms and avoid transfusion.

CKD is an independent indication for ESA therapy. Increased risks of mortality and adverse cardiovascular outcomes are associated with ESA

use in patients with CKD and Hb levels >11 g/dL in controlled clinical trials.[318-320,323-325] Hence, the FDA label mandates individualized dosing to reduce the need for PRBC transfusions. Since almost one-third of patients with end-stage renal disease are also diagnosed with cancer, they represent a unique subgroup who require personalized ESA administration based on careful risks and benefits evaluation (reviewed by Bennett et al[326]). In a study comparing darbepoetin alfa to placebo, a significant increase in cancer-related death occurred in patients with CKD, pre-existing cancer at baseline and who were treated with ESA therapy (P = .002).[318] Additionally, data from Seliger et al 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.[319] ESAs should be tried to be avoided in patients with CKD not receiving active therapy for a malignancy, while those receiving palliative chemotherapy can receive carefully dosed ESAs to treat severe anemia over transfusion. If 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.

Dosing Schedules

The NCCN Panel recommends epoetin alfa, epoetin alfa-epbx, or darbepoetin alfa. Head-to-head comparisons for superiority between epoetin alfa versus darbepoetin alfa have been inconclusive.[302,327,328] 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[287,329] or 40,000 units once weekly[294,297,298,330] administered by subcutaneous injection. Other dosing ranges and schedules of epoetin alfa may be considered, including an extended dose of 80,000 units administered every 2 weeks[331] and a dose of 120,000 units administered once every 3 weeks.[332]

Although darbepoetin alfa doses were initially administered at 2.25 mcg/kg every week,[288,292,333] studies have tested 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 anemia and non-myeloid malignancies showed that the percentage of patients achieving the target Hb level (≥11 g/dL) was higher in the weekly arm compared to those receiving darbepoetin alfa every 3 weeks (84% vs. 77%).[333] Dosing once every 3 weeks was further refined in two studies that reduced the dose to 300 mcg. Initially, a multicenter study of 1493 patients showed that 79% of patients receiving the lower dose achieved a target Hb level ≥11 g/dL,[334] which was confirmed in a phase II randomized trial of head-to-head comparison with 500 mcg. In this study, the proportion of patients who achieved target Hb levels (≥11 g/dL) was similar between those receiving 300 mcg versus 500 mcg darbepoetin alfa (75% vs. 78%, respectively).[335] Alternative dosing schedules for darbepoetin alfa include a fixed weekly dose of 100 mcg[288] and a fixed dose of 200 mcg every 2 weeks.[336] The NCCN Panel recommends these alternative regimens to support the delivery of the lowest ESA dose possible while maintaining maximum efficacy.

Response Assessment and Dose Titration

To determine whether the initial dose should be reduced, escalated, or withheld, response to ESA therapy should be assessed. 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 for increasing RBC numbers. Hb levels 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, ESA dose should be increased according to the algorithm for patients receiving chemotherapy who show no response (defined as Hb

increase <1 g/dL that remains <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 Cochrane Database review concluded that adding iron to ESA therapy offers superior hematopoietic response, reduces the risk of transfusions, improves Hb levels, and appears to be well tolerated.[337] 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% compared to ESAs alone.[338] 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 also have anemia.[339] Iron studies, including serum iron, TIBC, and serum ferritin, should be performed prior to ESA treatment to rule out absolute iron deficiency that may respond to oral or IV iron monotherapy. Serum iron and TIBC levels may be falsely elevated by diet (reviewed in Collings et al[340]); therefore, fasting is recommended to provide more accurate measurements. Transferrin saturation (TSAT) should be calculated from these values using the following formula:

- TSAT = (serum iron level x 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.[234] 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 is beneficial. The reference interval for serum ferritin depends on laboratories, 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 chronic inflammatory states, 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. A meta-analysis showed that treatment with both ESA and iron showed a greater increase in Hb, Hct, RBC count, and hematopoietic response rate in patients with CIA and treated with both ESA and oral iron compared to oral iron alone.[341] 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.[342] 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.*

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 inflammation. Functional iron deficiency is defined in these guidelines as ferritin levels between 30 and 500 ng/mL and TSAT levels <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 (see *Intravenous Versus Oral Iron* below). 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 to maintain optimal erythropoiesis.[343,344] 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 TSAT levels <50% and a ferritin level of 500 to 800 ng/mL. Although clinical trials suggest that these patients 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 patients with possible functional iron deficiency. Administration of IV iron to these patients should be individualized with the goal of avoiding 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 patients with iron-deficient anemia, there are situations in which IV iron therapy is a valuable option: 1) CIA in many patients may not respond to oral iron; 2) oral iron cannot be given due to intolerance; and 3) patients may require higher iron doses than achievable with oral iron.[345] Evidence from several 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.[346-351] In 2011, a trial published by Steensma et al challenged these results.[352] 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 did not confer any benefit in terms of Hb response, transfusion requirement, or quality of life compared to oral iron or placebo. However, the lack of response to IV iron may have been attributable to problems with the study design, including a suboptimal IV iron dosing regimen and a high proportion of participant dropouts.[353] Indeed, reanalysis of study data indicated that trial participants who received at least 80% of the planned IV iron dosage had Hb response rates similar to participants in other IV iron trials.[354] It should be noted that patients with a baseline TSAT level <20% have a higher response rate to IV iron supplementation when given with an ESA. As the TSAT level increases from 20% to 50%, the response rate to IV iron is diminished and the time to response is prolonged. Hence, for patients with TSAT levels between 20% to 50%, the decision to offer IV iron should be reserved for those in whom the benefits are likely to outweigh the risks. Studies on

parameters that make patients more or less likely to benefit from IV iron and alternative IV iron dosing schedules are needed.

None of the studies on iron supplementation in conjunction with ESAs provide instruction on how or when to re-dose iron after the initial cumulative dose has been given. Generally, repeating iron studies is 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, repeating iron studies can be considered for anemia that does not respond to iron supplementation 4 to 6 weeks after administration of the total intended dose.[348,352] If evidence of iron overload exists, 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%.[347-349]

Since most studies show that IV iron is superior to oral iron, the Panel recommends that IV iron supplementation be used in most clinical circumstances. Low-molecular-weight iron dextran, ferric gluconate, iron sucrose, ferric carboxymaltose, ferumoxytol, and ferric derisomaltose are the recommended IV iron preparations. Common adverse events following FDA-approved doses of IV iron include hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness.[355-357] Dosage details for administering IV iron therapy are listed in the algorithm.

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).[346] 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 including headaches, dizziness, nausea, vomiting, and diarrhea occurred with high-molecular-weight iron dextran.[358] Therefore, low-molecular-weight iron dextran is the recommended iron dextran preparation.[359] Test doses are required for iron dextran (25 mg slow IV push over 1–2 minutes; if tolerated, followed by 75 mg IV bolus for a total dose of 100 mg).[346] Premedication should occur prior to test dose administration since reactions to the IV iron dextran test dose may be severe. 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.

Ferric Gluconate

In a multicenter trial, 187 patients with CIA on chemotherapy and epoetin alfa were randomized to receive no iron, oral ferrous sulfate three times daily, or weekly IV ferric gluconate.[349] 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.[350] 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 patients with non-myeloid malignancies and CIA undergoing chemotherapy, patients were treated with darbepoetin alfa with or without IV ferric gluconate every 3 weeks for 16 weeks.[347] Erythropoietic responses were improved in the IV ferric gluconate arm. Significantly, this was the first study to show IV iron associated with fewer RBC transfusions in patients with cancer (9% vs. 20%; $P = .005$).

Iron Sucrose

A randomized controlled trial involving 64 patients with gynecologic cancers compared the efficacy of IV iron sucrose to oral ferrous fumarate for primary anemia prevention (ie, patients did not present with anemia).[360] In this study, patients received a single dose of 200 mg iron sucrose after each chemotherapy infusion course for 6 cycles. The number of patients requiring blood transfusion was double in the oral iron group compared to the IV iron sucrose group (56.3% vs. 28.1%; *P* = .02). Even when patients required transfusion in the IV iron sucrose group, they received a lower 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.[348] Although an oral iron arm was not included, IV iron sucrose resulted in a higher mean change in Hb level from baseline (2.76 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 IV iron group.

Ferric Carboxymaltose

An observational study by Steinmetz et al[361] evaluated the use of ferric carboxymaltose with and without an ESA in patients with cancer. In 233 patients treated with ferric carboxymaltose alone, a median Hb increase of 1.4 g/dL (range, 1.3–1.5 g/dL) was observed with an overall increase in >11 g/dL median Hb levels within 5 weeks of treatment.[361] Similar results were seen in patients receiving concomitant treatment with ferric carboxymaltose and an ESA (1.6 g/dL increase; range, 0.7–2.4 g/dL; n = 46). Another 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 vs. 1.4 g/dL, respectively) over a 3-month period.[362] A retrospective analysis of 303 patients with gastrointestinal cancers and anemia found that IV administration of ferric carboxymaltose resulted in a significant increase in Hb levels, with a median change between baseline and follow-up Hb of 0.5 g/dL (interquartile range [IQR]: -0.1–1.6).[363] In the randomized clinical IVICA trial, including 116 patients with anemia and colorectal cancer, preoperative administration of ferric carboxymaltose showed higher Hb levels after surgery compared to oral ferrous sulfate (11.9 vs. 11.0 g/dL; *P* = .002).[364] A follow-up study indicated that patients who received ferric carboxymaltose had significantly improved quality-of-life scores, as measured by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) subscale, compared to patients who received oral iron.[365] In patients with colon cancer and anemia, preoperative treatment with ferric carboxymaltose was shown to significantly reduce RBC transfusion requirements (9.9% vs. 38.7%; *P* < .001) and length of hospital stay (8.4 ± 6.8 vs. 10.9 ± 12.4 days to discharge; *P* < .001) compared to those not receiving IV iron.[366]

Ferric carboxymaltose is associated with severe phosphate deficiency that is often asymptomatic.[367-371] Lack of awareness of this complication causes delayed time to diagnosis and results in significant morbidity.[367] Therefore, patients receiving ferric carboxymaltose should be closely monitored for hypophosphatemia.

Ferumoxytol

Ferumoxytol is colloidal iron oxide indicated for the treatment of iron-deficiency anemia in patients with CKD or intolerance or poor response to oral iron.[322,372,373] However, ferumoxytol has not been prospectively evaluated in patients with CIA.[321] In a phase III trial involving patients with anemia due to various causes, 81.1% of patients treated with ferumoxytol had an Hb increase ≥2.0 g/dL at week 5 compared to only 5.5% of patients given placebo (*P* < .0001).[322] Only a small percentage of patients in this study had cancer (n = 39).[322] A positive trend, not significant, was observed in ferumoxytol in patients with cancer compared with placebo (ferumoxytol, 51.7% vs. placebo, 30.0%; *P* < .2478).[322] In a randomized phase III study of patients with iron-deficiency anemia that did not responded to oral iron, a similar percentage of patients had a ≥2 g/dL

increase in Hb from baseline to week 5 in the ferumoxytol and iron sucrose groups (84% with ferumoxytol vs. 81.4% with iron sucrose).[373] However, these results were not observed in the cancer subgroup (n = 31), potentially due to the small sample size. A post-hoc analysis of pooled data, in a subgroup of 98 patients with cancer, from these two trials found that ferumoxytol and iron sucrose administration resulted in a significant increase in Hb from baseline compared to placebo (1.8 g/dL, $P < .0001$ and 1.9 g/dL, $P = .002$, respectively).[321]

It should be noted that ferumoxytol may cause interference with MRI, causing potential false interpretation of organ iron overload.[374] 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.

Ferric Derisomaltose

Ferric derisomaltose is indicated for the treatment of iron-deficiency anemia in patients with CKD or an intolerance or poor response to oral iron. Ferric derisomaltose increased Hb levels similar to iron sucrose in two randomized phase III trials in patients with iron-deficiency anemia.[375,376] The FERWON-IDA trial demonstrated that a single 1000-mg dose of IV ferric derisomaltose resulted in a significant rapid hematologic response in the first 2 weeks, swift reduction in fatigue, and a similar safety profile compared to repeated doses of iron sucrose.[375] The FERWON-NEPHRO trial in patients with iron-deficiency anemia and CKD demonstrated that compared to iron sucrose, ferric derisomaltose induced a similar 8-week hematologic response, lower rates of hypersensitivity reactions, and a significantly lower incidence of cardiovascular adverse events.[376] Additionally, the PHOSPHARE trials demonstrated that the incidence of hypophosphatemia was significantly lower following ferric derisomaltose treatment compared to ferric carboxymaltose.[377] The phase III PROFOUND trial analyzed the safety and efficacy of ferric derisomaltose for the treatment of iron-deficiency anemia in 350 patients with cancer.[378] Results showed that ferric derisomaltose was equivalent to oral iron sulfate in increasing Hb concentration from baseline to week 4. Ferric derisomaltose resulted in a faster onset of Hb response and a higher proportion of patients treated with oral iron experienced adverse drug reactions. Hypophosphatemia was reported at similar but low frequencies in the two groups.

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 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 398,000/µL. She does not have CKD. Serum folate, vitamin B_{12} 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 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.[346]

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 helpful. Iron would be beneficial in this patient as these laboratory values 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. However, 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 and therefore an ESA should be considered first. Concomitant IV iron can be considered as it may increase the percentage of patients whose anemia responds 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 iron replete and unlikely to benefit from iron therapy. In this scenario, an ESA may be considered. ESA use induces functional iron deficiency by increasing iron utilization without the compensatory ability to mobilize stored iron in a timely manner. Therefore, iron repletion can be initiated if 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.

Tables

Table 1. 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

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