



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Growth Factors

Version 2.2023 — March 6, 2023

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[NCCN Hematopoietic Growth Factors Panel Members](#) [Summary of the Guidelines Updates](#)

Management of Neutropenia

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

Management of Thrombocytopenia

- [Use of Thrombopoietin Receptor Agonists \(TPO-RA\) in Patients with Cancer \(TGF-1\)](#)

Management of Cancer- and Chemotherapy-Induced Anemia

- [Evaluation of Anemia \(ANEM-1\)](#)
- [Risk Assessment and Indications for Initial Transfusion in Acute Setting \(ANEM-2\)](#)
- [Special Categories in Considering Erythropoiesis-Stimulating Agent \(ESA\) Use \(ANEM-3\)](#)
- [Evaluation of Iron Deficiency \(ANEM-4\)](#)
- [Erythropoietic Therapy - Dosing, Titration, and Adverse Effects \(ANEM-A\)](#)
- [Parenteral Iron Preparations \(ANEM-B\)](#)
- [Management of Cancer- and Chemotherapy-Induced Anemia for Patients Who Refuse Blood Transfusions \(ANEM-C\)](#)

[Abbreviations \(ABBR-1\)](#)

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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](#).

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**Updates in Version 2.2023 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 1.2023 include:****[MGF-1](#) and [MGF-2](#)**

- Footnote i was revised and added to low risk for clarification: G-CSFs may be considered for patients receiving low-risk regimens ~~who have substantial patient risk factors~~ *who have 2 or more patient-related risk factors (see MGF-2). Use of G-CSF in this setting is based on clinical judgment.*

Updates in Version 1.2023 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 1.2022 include:**[MGF-1](#)**

- Overall febrile neutropenia risk, Low (<10%), modified: ~~No~~ G-CSFs *are not routinely recommended, but may be considered for patients with risk factors*

[MGF-2](#)

- Footnote k added: G-CSFs may be considered for patients receiving low-risk regimens who have substantial patient risk factors.

[MGF-4](#)

- Patients receiving or those who received prophylactic G-CSFs, modified: Patients who have received long-lasting prophylactic pegfilgrastim *or eflapegrastim-xnst*
- Footnote s modified: See Discussion for further details. Pegfilgrastim (or biosimilars) *and eflapegrastim-xnst* ~~has~~ 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.

[MGF-A 1 of 5](#)

- Examples of disease settings and chemotherapy regimens with a high risk for febrile neutropenia (>20%):
 - ▶ Colorectal Cancer:
 - ◊ Removed: FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)
 - ▶ Pancreatic Cancer
 - ◊ Removed: FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)
- Footnote removed: Rates of febrile neutropenia vary. Clinical judgment should be exercised as to which patient population needs growth factor support. There can be a high risk of febrile neutropenia in selected patients.
- Footnote removed: A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting 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). While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

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[Continued](#)

UPDATES

**Updates in Version 1.2023 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 1.2022 include:****MGF-A 2 of 5**

- Examples of disease settings and chemotherapy regimens with an intermediate risk for febrile neutropenia (10%-20%):
 - ▶ Colorectal Cancer:
 - ◊ Removed: FOLFOX (fluorouracil, leucovorin, oxaliplatin)
 - ◊ Added: FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)
 - ▶ Pancreatic Cancer
 - ◊ Added: FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)
- Footnote added: There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen ([See MGF-A](#)) and patient risk factors ([See MGF-2](#)).
- Footnote added: A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting 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). While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

MGF-A 4 of 5

- The reference pages were updated to reflect the changes in the algorithm.

MGF-B 1 of 2

- G-CSFs for prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery
 - ▶ Third bullet and subsequent bullets added: Eflapegrastim-xnst
 - ◊ Administer 13.2 mg subcutaneously once per chemotherapy cycle.
 - ◊ Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy.

MGF-B 2 of 2

- ▶ The reference pages were updated to reflect the changes in the algorithm.

MGF-C

- Toxicity risks with MGFs:
 - ▶ Filgrastim, Pegfilgrastim, and Tbo-filgrastim, 2nd bullet, 1st sub-bullet modified: ~~Cutaneous~~ *Rare: vasculitis, Sweet's syndrome*
 - ▶ The following bullets have been added:
 - ◊ Eflapegrastim-xnst
 - 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

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UPDATES

**Updates in Version 1.2023 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 1.2022 include:****TGF-2**

- Footnote d modified: 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/ mL. Maximum dose is 10 mcg/kg weekly per prescribing information. *There is limited data to support the use of high dose romiplostim (10 mcg/kg) initially as a rescue therapy in patients with severe, refractory immune thrombocytopenia.*
- The reference pages were updated to reflect the changes in the algorithm.

ANEM-3

- Footnote j added: Optimal response to ESAs depend on adequate iron storage and availability.

ANEM-4

- Footnote p added: ESAs work optimally in patients who have adequate iron stores, thus determination of iron stores and management of iron storage status is necessary.

ANEM-B 1 of 2

- Parenteral Iron Preparations
 - ▶ Iron sucrose, dosage, modified: ~~200 mg IV over 60 min (repeated every 2–3 wks) or 200 mg IV over 2–5 min, 5 times within 14 days Individual doses over 300 mg are not recommended~~
 - ◊ Bullet modified: ~~Total treatment course = 1000 mg~~ *Total treatment recommended = 1000 mg*
 - ◊ Bullet added: Various dosing schedules have been tested. For additional details about dosing, see prescribing information
 - ▶ Ferric Carboxymaltose (in select cases), modified: Ferric Carboxymaltose (~~in select cases~~)

ANEM-B 2 of 2

- The reference pages were updated to reflect the changes in the algorithm.

ABBR-1

- New page added: Abbreviations

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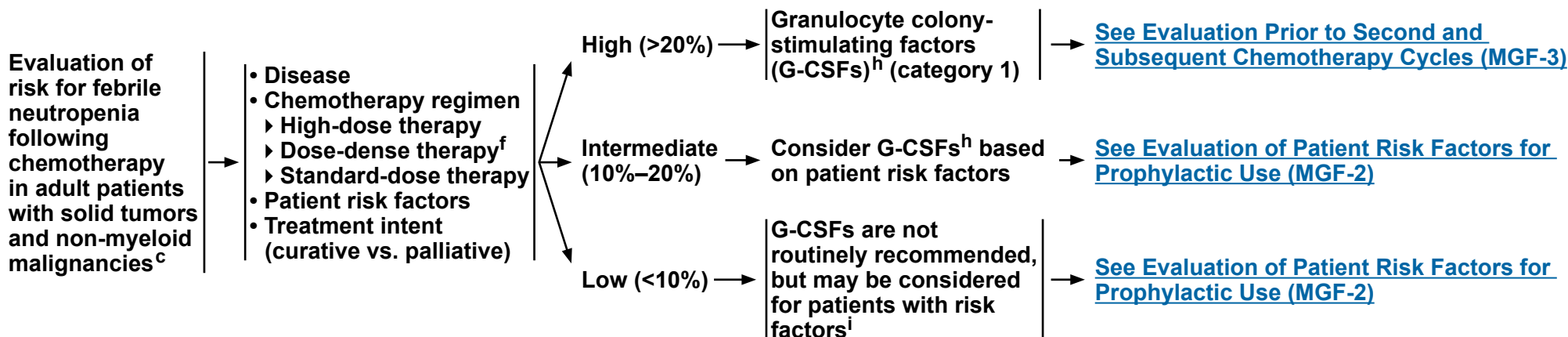
Hematopoietic Growth Factors

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

RISK ASSESSMENT^d FOR FEBRILE NEUTROPENIA^e

OVERALL FEBRILE NEUTROPENIA RISK

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



^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](#); and in chronic myeloid leukemia (CML), see the [NCCN Guidelines for Chronic Myeloid Leukemia](#).

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

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

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

^g [See Toxicity Risks with MGFs \(MGF-C\)](#).

^h [See 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 (see [MGF-2](#)). Use of G-CSF in this setting is based on clinical judgment.

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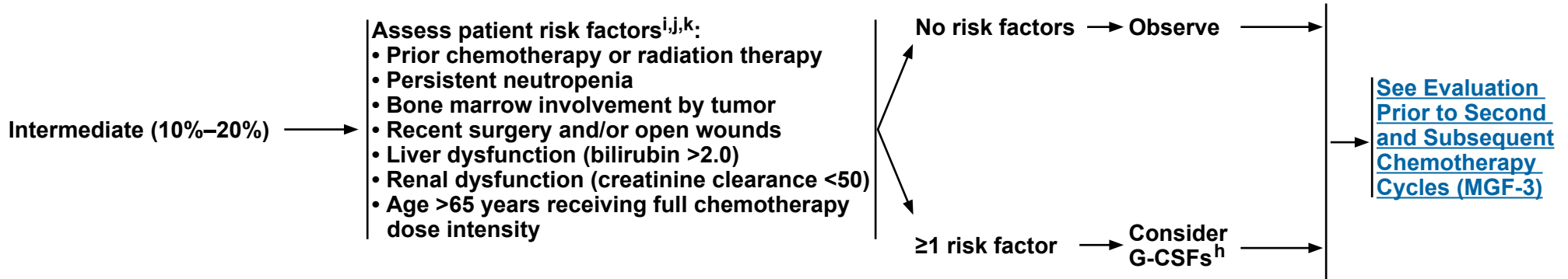
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Hematopoietic Growth Factors

OVERALL FEBRILE NEUTROPENIA^e RISK

PATIENT RISK FACTORS ASSESSMENT

PROPHYLACTIC USE OF G-CSFs FOR FEBRILE NEUTROPENIA



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

^h [See 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 cancer patients 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).

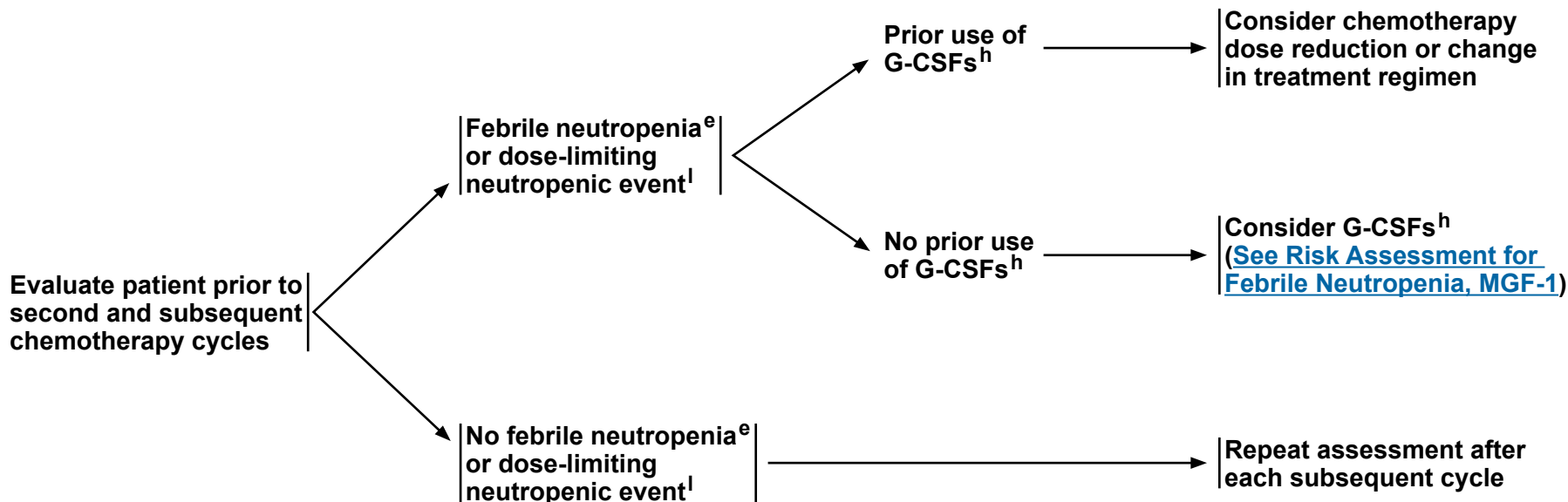
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EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



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

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

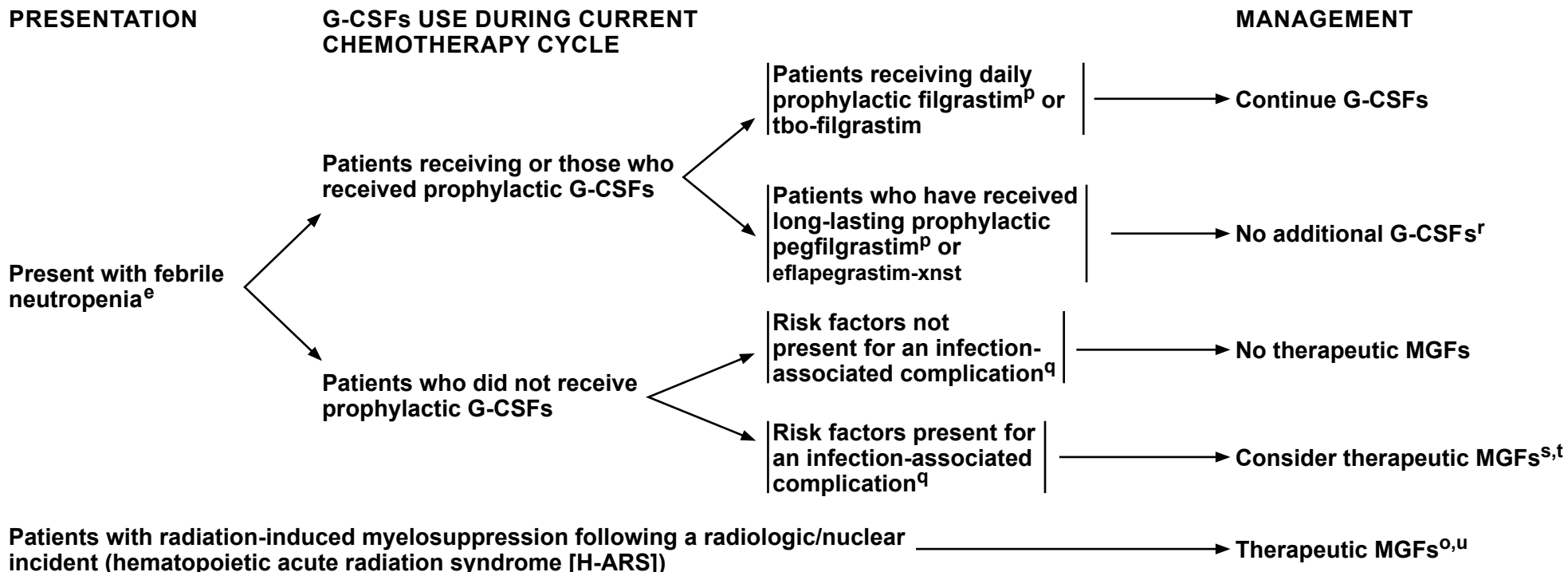
^l Dose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy.

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THERAPEUTIC USE OF MGFs^{e,m,n}



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

^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 Farese AM, et al. *Drugs Today (Barc)* 2015;51:537-548.

^p An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim.

^q 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.

^r 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.

^s [See Discussion](#) for further details. Pegfilgrastim (or biosimilars) and eflapegrastim-xnst 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.

^t Filgrastim (or biosimilars) or tbo-filgrastim: daily dose of 5 mcg/kg; Sargramostim: used in clinical trials at a dose of 250 mcg/m² per day. Continue therapeutic MGFs until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.

^u Therapeutic options include filgrastim (or biosimilars), tbo-filgrastim, pegfilgrastim (or biosimilars), and sargramostim.

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**EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)^a**

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

Acute Lymphoblastic Leukemia (ALL)

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

Bladder Cancer

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

Bone Cancer

- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)²
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)³
- Cisplatin/doxorubicin⁴
- 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

Kidney Cancer

- Doxorubicin/gemcitabine¹⁶

Non-Hodgkin Lymphomas

- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Dose-adjusted EPOCH^a (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)¹⁷
- ICE (ifosfamide, carboplatin, etoposide)^{a,18,19}
- Dose-dense CHOP-14^a (cyclophosphamide, doxorubicin, vincristine, prednisone)^{20,21}
- MINE^a (mesna, ifosfamide, mitoxantrone, etoposide)²²
- DHAP^a (dexamethasone, cisplatin, cytarabine)²³
- ESHAP^a (etoposide, methylprednisolone, cisplatin, cytarabine)²⁴
- HyperCVAD^a (cyclophosphamide, vincristine, doxorubicin, dexamethasone)^{25,26}

Melanoma

- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)²⁷

Multiple Myeloma

- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)²⁸ ± bortezomib (VTD-PACE)²⁹

Ovarian Cancer

- Topotecan^{a,30}
- Docetaxel³¹

Soft Tissue Sarcoma

- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)³²
- Doxorubicin^{a,33}
- Ifosfamide/doxorubicin³⁴

Small Cell Lung Cancer^e

- Topotecan³⁵

Testicular Cancer

- VeIP (vinblastine, ifosfamide, cisplatin)³⁶
- VIP (etoposide, ifosfamide, cisplatin)³⁷
- TIP (paclitaxel, ifosfamide, cisplatin)³⁷

[See 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 of Cancer by Site](#).

^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).

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References

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

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

Occult Primary - Adenocarcinoma

- Gemcitabine/docetaxel⁴⁰

Breast Cancer

- Docetaxel^{a,41,42}
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)^{a,43}
- Paclitaxel every 21 days^{a,44}

Cervical Cancer

- Cisplatin/topotecan⁴⁵⁻⁴⁷
- Paclitaxel/cisplatin^{a,47}
- Topotecan⁴⁸
- Irinotecan⁴⁹

Colorectal Cancer

- FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)^{e,50-52}

Esophageal and Gastric Cancers

- Irinotecan/cisplatin^{a,53}

Non-Hodgkin Lymphomas

- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)^{a,54}
- CHOP^a (cyclophosphamide, doxorubicin, vincristine, prednisone)^{55,56} including regimens with pegylated liposomal doxorubicin^{57,58}
- Bendamustine^a

Non-Small Cell Lung Cancer

- Cisplatin/paclitaxel⁵⁹
- Cisplatin/vinorelbine⁶⁰
- Cisplatin/docetaxel^{59,61}
- Cisplatin/etoposide⁶²
- Carboplatin/paclitaxel^{a,f,63}
- Docetaxel⁶¹

Ovarian Cancer

- Carboplatin/docetaxel⁶⁴

Pancreatic Cancer

- FOLFIRINOX^g (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Prostate Cancer

- Cabazitaxel^{h,65}

Small Cell Lung Cancerⁱ

- Etoposide/carboplatin⁶⁶

Testicular Cancer

- BEP^d (bleomycin, etoposide, cisplatin)⁶⁷⁻⁶⁹
- Etoposide/cisplatin⁷⁰

Uterine Sarcoma

- Docetaxel⁷¹

^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 of Cancer by Site](#).

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

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

^f If carboplatin dose is area under the curve ≥ 6 and/or patient is of Japanese ancestry.

^g A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting³⁸ 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).³⁹ While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

^h 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/m².

ⁱ 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.

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References

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**G-CSFs FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE
OF SCHEDULED DOSE DELIVERY**

- **Filgrastim^a (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 ANC recovery to normal or near-normal levels by laboratory standards.**
 - ▶ **Start the next day or up to 3–4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.^{c,d,1}**
- **Pegfilgrastim^a (category 1)**
 - ▶ **One dose of 6 mg**
 - ◊ **Based on clinical trial data, pegfilgrastim^a can be administered the day after myelosuppressive chemotherapy (category 1).² There are data for and against same-day dosing but the U.S. Food and Drug Administration (FDA)-approved dosing schedule is still recommended.³⁻⁸**
 - ◊ **There should be at least 12 days between the dose of pegfilgrastim^a and the next cycle of chemotherapy.**
 - ◊ **If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim^a 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).^{e,9-14}**
 - ◊ **Administration of pegfilgrastim^a 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^{15,16}**
 - ▶ **Administer 13.2 mg subcutaneously once per chemotherapy cycle.**
 - ▶ **Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy.**
- **Caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation.¹⁷**
- **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](#).**

[See Toxicity Risks with MGFs \(MGF-C\)](#)

^a An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim. [See Discussion](#) for more details.

^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 Studies suggest that shorter durations of G-CSFs may be less efficacious.

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

^e Rarely (1.7%–6.9%), there is a failure to inject that requires further medical attention.

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**TOXICITY RISKS WITH MGFS****Filgrastim, Pegfilgrastim, and Tbo-filgrastim^{a-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)**
- ▶ **MDS and AML^g**

• Precautions

- ▶ **Rare:** vasculitis, Sweet's syndrome
- ▶ **Immunogenicity**

• Adverse reactions

- ▶ **Bone pain^h**

Eflapegrastim-xnst^{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**

^a An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim.

^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 intravenous 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.

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), and high cholesterol**

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

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



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

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-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 such as thrombotic microangiopathic anemia (TMA), thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS)

Treat underlying cause(s) as indicated

CIT →

- Consider
- Platelet transfusion per American Association of Blood Banks (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 thrombotic microangiopathy (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

Known MDS →

[See NCCN Guidelines for Myelodysplastic Syndromes](#)

Known myeloid malignancy or ALL →

[Treat underlying disease per NCCN Guidelines](#)

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[See Footnotes and References on TGF-2](#)

**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 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

^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. There is limited data to support the use of high-dose romiplostim (10 mcg/kg) initially as a rescue therapy in patients with severe, refractory immune thrombocytopenia.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.

References

¹ Soff GA, Miao Y, Bendheim G, et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. *J Clin Oncol* 2019;37:2892-2898.

² Al-Samkari H, Parnes AD, Goodarzi K, et al. A multicenter study of romiplostim for chemotherapy-induced thrombocytopenia in solid tumors and hematologic malignancies. *Haematologica* 2021;106:1148-1157.

³ Al-Samkari H, Kolb-Sielecki J, Safina SZ, et al. Avatrombopag for chemotherapy-induced thrombocytopenia in patients with non-haematological malignancies: an international, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol* 2022;9:e179-e189.

⁴ Roumier M, Le Burel S, Audia S, et al. High dose romiplostim as a rescue therapy for adults with severe bleeding and refractory immune thrombocytopenia. *Am J Hematol* 2021;96:E43-E46.

⁵ Miao J, Leblebjian H, Scullion B, Parnes A. A single center experience with romiplostim for the management of chemotherapy-induced thrombocytopenia. *Am J Hematol* 2018;93:E86-E88.

⁶ Parameswaran R, Lunning M, Mantha S, et al. Romiplostim for management of chemotherapy-induced thrombocytopenia. *Support Care Cancer* 2014;22:1217-1222.

⁷ Mahat U, Rotz SJ, Hanna R. Use of thrombopoietin receptor agonists in prolonged thrombocytopenia after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2020;26:e65-e73.

⁸ Gao F, Zhou X, Shi J, et al. Eltrombopag treatment promotes platelet recovery and reduces platelet transfusion for patients with post-transplantation thrombocytopenia. *Ann Hematol* 2020;99:2679-2687.

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

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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 ([see Discussion](#)):

- First check
 - ▶ Reticulocyte count^e and mean corpuscular volume (MCV)
- Then consider
 - ▶ Hemorrhage (stool guaiac, endoscopy)
 - ▶ Hemolysis (ie, direct antiglobulin test [DAT], DIC panel, haptoglobin, indirect bilirubin, lactate dehydrogenase [LDH])
 - ▶ Nutritional (ie, iron, total iron-binding capacity, ferritin, B₁₂, folate)^f
 - ▶ Inherited (ie, prior history, family history)
 - ▶ Renal dysfunction (glomerular filtration rate [GFR] < 60 mL/min/1.73 m²)
 - ▶ Radiation-induced myelosuppression
 - ▶ Hormone dysfunction (ie, hypogonadism, adrenal dysfunction, hyper/hypothyroidism)
 - ▶ Anemia of chronic inflammation (ie, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR])
- [See Evaluation of Iron Deficiency \(ANEM-4\)](#)

Treat as indicated

No cause identified

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

MDS → [See NCCN Guidelines for Myelodysplastic Syndromes](#)

Myeloid malignancies or ALL → [Treat underlying disease per NCCN Guidelines](#)
[See NCCN Guidelines Table of Contents](#)

^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](#).

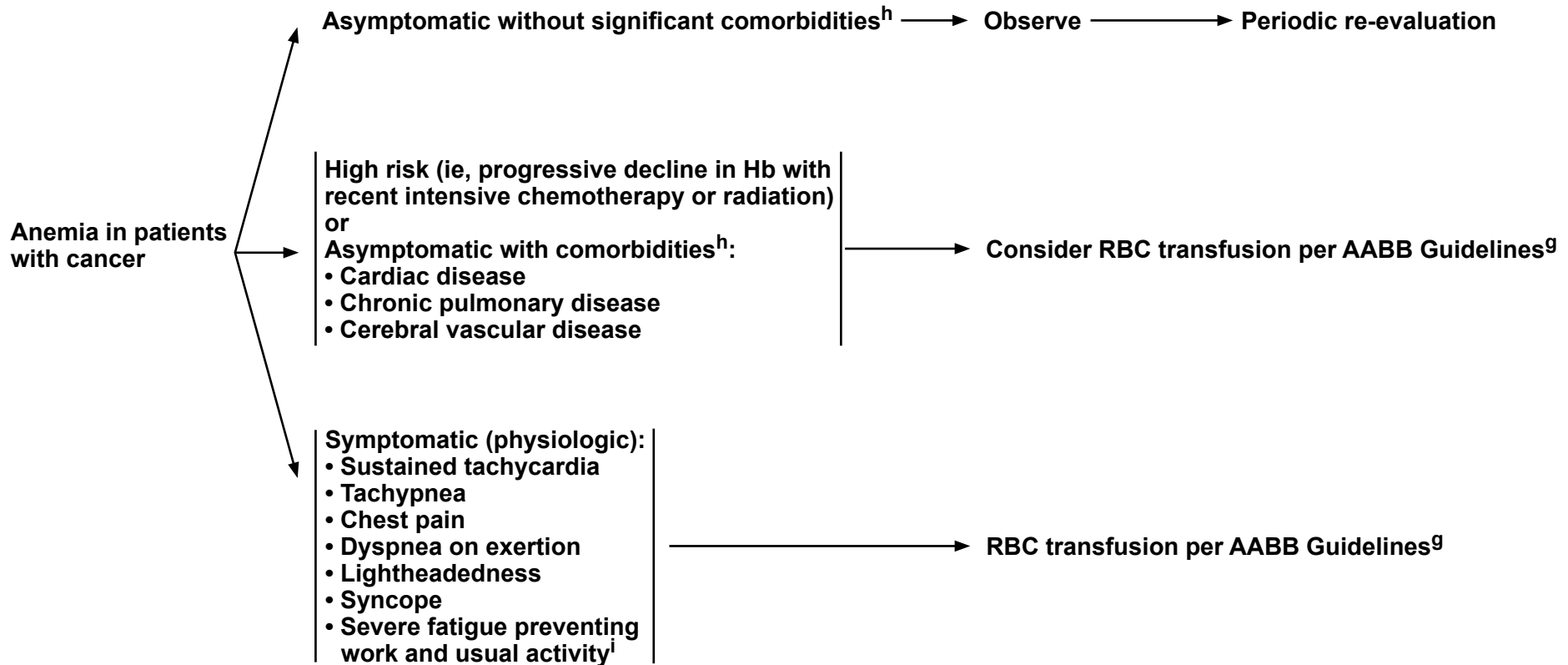
^f The ferritin value indicating iron deficiency is laboratory-specific. In general, the lower the level of ferritin, the higher the probability that the patient has true iron deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum 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.

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



[See Discussion for Comparison of Risks and Goals 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.

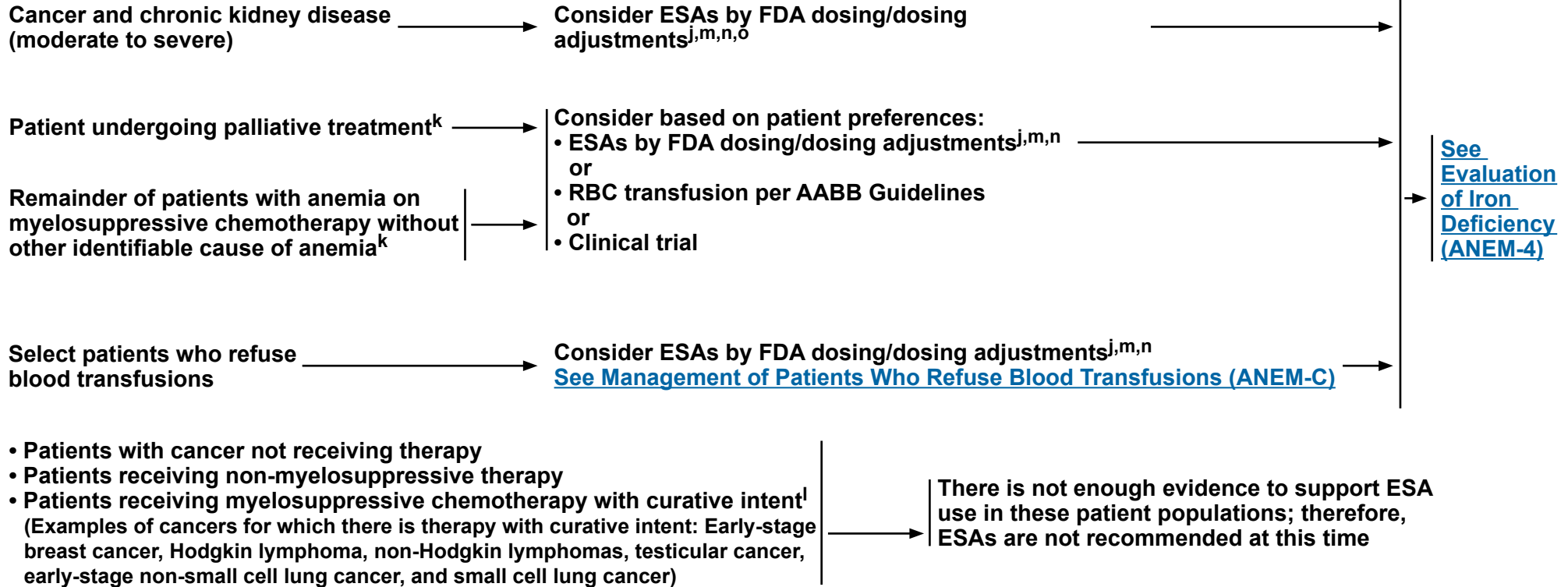
ⁱ Fatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI) are examples of standardized measures for assessing patient-reported fatigue.

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



^j Optimal response to ESAs depend on adequate iron storage and availability.

^k For comparison of risks and goals 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 [See 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 and Gergal Gopalkrishna Rao SR, et al. Cureus 2021;13:e17835) ([See 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](#).

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NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

EVALUATION OF IRON DEFICIENCY^p

IRON STATUS

MANAGEMENT

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

Absolute iron deficiency^q
(ferritin <30 ng/mL AND TSAT <20%)

Consider IV or oral iron supplementation

Hb increases after 4 wks
No Hb increase after 4 wks

Periodic evaluation (repeat ferritin and TSAT)

See pathway below for functional iron deficiency

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

Consider IV iron supplementation^{u,v,w} with erythropoietic therapy

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

Possible functional iron deficiency^{r,s,t} (ferritin >500–800 ng/mL AND TSAT <50%)

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

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

IV or oral iron supplementation is not needed

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

^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.

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

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

INITIAL DOSING

PACKAGE INSERT DOSING SCHEDULE

Epoetin alfa^f 150 units/kg 3 times per wk by subcutaneous injection →

Increase dose of epoetin alfa^f to 300 units/kg 3 times per wk by subcutaneous injection

or

Epoetin alfa^f 40,000 units every wk by subcutaneous injection →

Increase dose of epoetin alfa^f 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

TITRATION FOR NO RESPONSE**

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.

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 injection²

or

Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection³ →

Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection³

or

Darbepoetin alfa 300 mcg* fixed dose every 3 wks by subcutaneous injection⁷ →

Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection⁴

or

Epoetin alfa^f 80,000 units every 2 wks by subcutaneous injection⁵

or

Epoetin alfa^f 120,000 units every 3 wks by subcutaneous injection⁶

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

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

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

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

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**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 epoetin alfa.
- ^g There are no data on alternative dosing schedules for epoetin alfa-epbx.

References

- 1 Losem C, Koenigsmann M, Rudolph C. Biosimilar Retacrit® (epoetin zeta) in the treatment of chemotherapy-induced symptomatic anemia in hematology and oncology in Germany (ORHEO) - non-interventional study. *Onco Targets Ther* 2017;10:1295-1305.
- 2 Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 2002;94:1211-1220.
- 3 Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naïve patients and patients switched from epoetin alfa. *Pharmacotherapy* 2004;24:313-323.
- 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.
- 5 Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80 000 U Q2W) vs weekly dosing (40 000 U QW) in patients with chemotherapy-induced anemia. *Curr Med Res Opin* 2006;22:1403-1413.
- 6 Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol* 2006;24:1079-1089.
- 7 Auerbach M, Silberstein PT, Timothy Webb R, et al. Darbepoetin alfa 300 or 500 ug once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *Am J Hematol* 2010;85:655-663.

[See Erythropoietic Therapy - Dosing and Titration \(ANEM-A 1 of 5\)](#)[See Erythropoietic Therapy- Adverse Effects \(ANEM-A 3 of 5\)](#)**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 of 5)****Survival of Patients with Cancer**

- Studies have reported possible decreased survival in patients with cancer receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in patients receiving erythropoietic drugs for correction of anemia and target Hb levels of >12 g/dL.¹⁻⁸ One analysis in patients with cancer not receiving active therapy found decreased survival in patients treated with ESAs.⁶ Please refer to the FDA website for additional information: <https://www.fda.gov/drugs/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,⁹⁻¹² two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.^{13,14}
- Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.¹⁵⁻¹⁷
- The risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL.
- Additional prospective clinical trials designed and powered to measure survival of patients with cancer are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus RBC transfusion. ([See Discussion for comparison of risks and goals 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 \(ANEM-A 4 of 5\)](#)[See References \(ANEM-A 5 of 5\)](#)**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 of 5)****Thrombosis**

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

Hypertension

- 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. ([See Titration for Response ANEM-A 1 of 5](#))

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

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

[See References \(ANEM-A 5 of 5\)](#)**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 of 5)****ADVERSE EFFECTS REFERENCES**

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

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

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[References](#)



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.

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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.



ABBREVIATIONS

AABB	American Association of Blood Banks	Hb	hemoglobin
ALL	acute lymphoblastic leukemia	HIV	human immunodeficiency virus
AML	acute myeloid leukemia		
ANC	absolute neutrophil count	MDS	myelodysplastic syndromes
		MGF	myeloid growth factor
CBC	complete blood count		
CIT	chemotherapy-induced thrombocytopenia	PRCA	pure red cell aplasia
DIC	disseminated intravascular coagulation	RBC	red blood cell
ES-SCLC	extensive-stage small cell lung cancer	TPO-RA	thrombopoietin receptor agonists
ESA	erythropoiesis-stimulating agent	TSAT	transferrin saturation
G-CSF	granulocyte colony-stimulating factor	VTE	venous thromboembolism



NCCN Guidelines Version 2.2023 Hematopoietic Growth Factors

Discussion

This discussion corresponds to the NCCN Guidelines for Hematopoietic Growth Factors. Last updated on December 22nd, 2021.

Table of Contents

Overview.....	MS-2
Literature Search Criteria and Guidelines Update Methodology.....	MS-3
Biosimilars.....	MS-4
Management of Neutropenia.....	MS-7
Benefits of MGFs.....	MS-7
Risks of MGFs.....	MS-7
Prophylactic Use of MGFs.....	MS-10
Risk Assessment.....	MS-10
Chemotherapy Regimens and Risk for FN.....	MS-10
Patient Risk Factors for Developing FN.....	MS-10
Patients at High Risk for FN.....	MS-11
Patients at Intermediate Risk for FN.....	MS-11
Patients at Low Risk for FN.....	MS-12
Evaluation Prior to Subsequent Chemotherapy Cycles.....	MS-12
Dosing and Administration.....	MS-12
Therapeutic Use of MGFs.....	MS-14
Dosing and Administration.....	MS-14
Severe Chronic Neutropenia.....	MS-14
Management of Thrombocytopenia.....	MS-15
Use of Thrombopoietin Receptor Agonists in Patients with Cancer.....	MS-15
Management of Cancer- and Chemotherapy-Induced Anemia.....	MS-16

Etiology of Anemia Associated with Cancer and Myelosuppressive Chemotherapy.....	MS-16
Initial Evaluation of Anemia.....	MS-17
Approaches to Evaluation.....	MS-17
Red Blood Cell Transfusion.....	MS-19
Benefits and Risks of Red Blood Cell Transfusion.....	MS-19
Red Blood Cell Transfusion Goals and Basic Principles.....	MS-20
Patients with CIA Who Refuse Blood Transfusions.....	MS-20
Erythropoietic Therapy.....	MS-22
Benefits of ESA Therapy.....	MS-22
Risks of ESA Therapy.....	MS-22
Considerations for the Use of ESAs.....	MS-24
Dosing Schedules.....	MS-25
Response Assessment and Dose Titration.....	MS-25
Iron Monitoring and Supplementation.....	MS-26
Iron Deficiency Evaluation and Definitions of Iron Status.....	MS-26
Intravenous Versus Oral Iron.....	MS-27
Clinical Examples of Iron Status.....	MS-30
Tables.....	MS-32
References.....	MS-33



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 cells towards the myeloid and erythroid lineages. 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 the supportive care approach for many patients undergoing cancer treatment.

FN is defined as an absolute neutrophil count (ANC) of less than 500 neutrophils/mL, or an anticipated decline to ≤ 500 within the next 48 hours, accompanied by a single oral temperature of greater than or equal to 38.3°C or a temperature greater than or equal to 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 hospitalizations 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, correlations between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health, have been reported.⁶

These guidelines focus on the two MGFs that have shown the most promise for clinical use: G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF). For simplicity, the term “MGF” will be used when the data are supported by studies for both G-CSF and GM-CSF. Filgrastim, filgrastim-sndz, tbo-filgrastim, filgrastim-aafi, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are 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.⁷⁻¹⁴ Filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez were approved as biosimilars, allowing their use for the broader indications of the originator products (see *Biosimilars* below for more information). Tbo-filgrastim was approved by the FDA in an original biologic license application¹⁵ and therefore has a more restricted indication.⁹ The only FDA-approved GM-CSF is sargramostim, although some clinical trials have used the GM-CSF molgramostim. Molgramostim is not recommended by the panel due to increased adverse events compared to sargramostim¹⁶ as well as the lack of FDA approval. Sargramostim is primarily used for treatment of FN; 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])^{17,18} and those with severe chronic neutropenia.

Anemia is characterized by a decrease in hemoglobin (Hb) concentration, red blood cell (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 (Table 1). CIA is prevalent, occurring in 30% to 90% of cancer patients.^{19,20} Improvement of CIA can be achieved by transfusion with



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

packed red blood cells (PRBCs) or administration of ESAs, with or without iron supplementation, in select patients being treated with myelosuppressive chemotherapy. The first ESA approved by the FDA for the treatment of anemia in patients receiving myelosuppressive chemotherapy was epoetin alfa, a recombinant human erythropoietin (rhEpo).²¹ A second-generation rhEpo, darbepoetin alfa, with a longer half-life than epoetin alfa, has also been FDA-approved for this indication.²² In 2018, the FDA approved epoetin alfa-epbx as the first epoetin alfa biosimilar, allowing its use for the same indications as the originator product.^{23,24}

Thrombocytopenia is characterized by a low blood platelet count resulting in decreased blood clotting capability. Patients with thrombocytopenia are at an increased risk for bleeding. CIT, defined as platelet count less than 100,000/mcL for 3 to 4 weeks following the last chemotherapy administration and/or resulting in delays in chemotherapy initiation related to thrombocytopenia, occurs in 15% to 25% of cancer patients and can disrupt treatment.²⁵⁻²⁷ While mild thrombocytopenia does not require treatment or intervention, severe thrombocytopenia (platelet counts less than 10,000/mcL) can increase the risk for spontaneous bleeding events, and moderate thrombocytopenia (platelet counts less than 50,000/mcL) can increase the risk of bleeding for patients on systemic anticoagulation. TPO-RAs, such as romiplostim, activate the TPO receptor and can increase the production of platelets.²⁵ Although romiplostim and other TPS-RAs are widely used to treat immune thrombocytopenia, there is currently no FDA-approved treatment 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, respectively. 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's 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](#), the [NCCN Guidelines for Chronic Myeloid Leukemia](#), the [NCCN Guidelines for Acute Myeloid Leukemia](#), and the [NCCN Guidelines for Hairy Cell Leukemia](#). Use of hematopoietic growth factors in the context of hematopoietic cell transplantation (HCT) are addressed separately in the [NCCN Guidelines for Hematopoietic Cell Transplantation](#).

Literature Search Criteria and Guidelines Update Methodology

Prior to this update of the NCCN Guidelines® for Hematopoietic Growth Factors, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: myeloid growth factors and cancer; febrile neutropenia and cancer; filgrastim and cancer; pegfilgrastim and cancer; anemia and cancer; erythropoiesis stimulating agents and cancer; thrombocytopenia and cancer; 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.²⁸

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



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

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

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

Biosimilars

Biologics such as filgrastim, pegfilgrastim, and epoetin alfa are costly, which 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 expenditure for costly biologic drugs.^{29,30} The first drug granted FDA approval on the biosimilar pathway was filgrastim-sndz in 2015.³¹ The increased need for cost-effective hematopoietic growth factors has recently 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.³² 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 the level of protein aggregation.³² Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biological activity, efficacy, and safety.^{30,33} 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.¹⁵ 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.³² Concerns regarding interchangeability include enhanced immunogenicity, compromised safety, and diminished efficacy. Although there are no biosimilars designated as interchangeable by the FDA, limited data suggest that patients can alternate between the biosimilar and the originator biologic without any clinically meaningful differences regarding efficacy or safety.³⁴ 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 postmarketing surveillance of all biologic products is necessary for long-term monitoring of these agents. Health care providers should be aware of the FDA's nomenclature for biosimilars (originator biologic name followed by a random four-letter suffix), which is important for the pharmacovigilance of specific products.

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.⁹ Several studies have demonstrated similar outcomes with the use of tbo-filgrastim compared to filgrastim for the prevention of FN. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.³⁵ Tbo-filgrastim was equivalent to filgrastim and superior to placebo in reducing the duration of severe neutropenia and incidence of FN. Two other randomized studies in patients with lung cancer and non-Hodgkin lymphoma (NHL) receiving chemotherapy also report similar efficacy and toxicity for tbo-filgrastim and filgrastim.^{36,37} A meta-analysis of



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

these three trials concluded tbo-filgrastim to be non-inferior to filgrastim in reducing the incidence of FN.³⁸ Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.^{39,40} Tbo-filgrastim has demonstrated low immunogenicity in cancer patients receiving chemotherapy with no evidence for the development of neutralizing antibodies or immunogenic adverse events.⁴¹

Based on review of the data, the NCCN Guidelines recommend FDA-approved biosimilars as appropriate substitutes for originator filgrastim, pegfilgrastim, and epoetin alfa, respectively. 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.

Filgrastim Biosimilars

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim.^{8,31} The approval of filgrastim-sndz was based on review of data demonstrating highly similar protein structure to filgrastim with near-identical pharmacokinetics, pharmacodynamics, and immunogenicity in healthy volunteers and patients with cancer.^{8,42-44} Data have shown filgrastim-sndz to have identical mass, size, charge, and hydrophobicity to the originator product.⁴² Pharmacokinetic and pharmacodynamic modeling have further confirmed that the mechanism of action is the same and occurs through binding of the G-CSF receptor.⁴³ Clinical data leading to the approval of filgrastim-sndz were predominately based on data from healthy volunteers and data in patients with cancer in the prevention of chemotherapy-induced neutropenia. Although a potential concern regarding immunogenicity exists with biosimilars, immunogenicity is anticipated to be low to nonexistent with filgrastim biosimilars based on the lack of immunogenicity seen with the originator filgrastim biologics and the nature of filgrastim as an unglycosylated protein. In limited clinical

studies of healthy volunteers or patients with cancer, the incidence of antibodies binding to filgrastim-sndz reached 3% (11 of 333 patients).⁸ Further analysis of these patients showed no evidence of neutralizing antibodies, suggesting that there is no increased risk of immunogenic adverse events or reduction of efficacy.⁴⁴ A phase III trial of 218 patients with breast cancer receiving myelosuppressive chemotherapy with TAC (docetaxel, doxorubicin, and cyclophosphamide) showed no clinically meaningful differences regarding efficacy, safety, or immunogenicity between filgrastim and filgrastim-sndz, even in patients who alternated between the two in subsequent chemotherapy cycles.³⁴ A combined analysis of this and another phase III trial on the safety of filgrastim-sndz in patients with breast cancer concluded that filgrastim-sndz has a safety profile consistent with previous studies of reference filgrastim.⁴⁵ Several retrospective studies also report similar efficacy between filgrastim-sndz and filgrastim for prophylaxis of chemotherapy-induced neutropenia.⁴⁶⁻⁴⁹

In July 2018, the FDA approved a second filgrastim biosimilar, filgrastim-aafi, for the same indications as filgrastim.⁵⁰ A phase III randomized equivalence study in 279 patients receiving docetaxel/doxorubicin chemotherapy for breast cancer found filgrastim-aafi to be bioequivalent to filgrastim in terms of efficacy and safety, with similar incidence of FN, treatment-related bone pain, and mean time to neutrophil recovery.⁵¹ The prospective, non-interventional, longitudinal VENICE study, which observed the tolerability, safety, and efficacy of filgrastim-aafi in 386 patients with cancer receiving chemotherapy, concluded that filgrastim-aafi was effective and well-tolerated in both the primary and secondary prophylactic settings.⁵² The majority of patients (95.6%) experienced no change in chemotherapy dose or schedule due to FN and less than one-third (29.8%) of patients experienced one or more treatment-related adverse events. Two other non-interventional studies reached similar conclusions regarding the bioequivalence of filgrastim-aafi to reference filgrastim in both the prophylactic and therapeutic settings.^{53,54}



Pegfilgrastim Biosimilars

In 2018, the FDA approved the first pegfilgrastim 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.^{12,13,55-59}

Pegfilgrastim-jmdb has been shown to have high analytical and functional similarity to pegfilgrastim, with similar structure, molecular mass, physicochemical characteristics, and G-CSF receptor binding affinity.^{60,61} A phase I randomized equivalence trial concluded that pegfilgrastim-jmdb demonstrated similar pharmacokinetics, pharmacodynamics, and safety to pegfilgrastim in healthy volunteers.⁵⁵ In a multicenter randomized phase III efficacy and safety trial, patients with breast cancer receiving myelosuppressive chemotherapy with pegfilgrastim-jmdb support showed no difference in the duration of severe neutropenia, time to ANC nadir, duration of post-nadir recovery, or treatment-related adverse events compared to patients receiving reference pegfilgrastim.⁶² Pegfilgrastim-jmdb has also demonstrated low immunogenic potential in healthy volunteers and in patients with cancer receiving myelosuppressive chemotherapy.⁶³ Although data are limited, pegfilgrastim-cbqv was shown to have a similar safety profile and bioequivalent pharmacokinetics and pharmacodynamics to pegfilgrastim in 122 healthy volunteers in a multicenter randomized crossover study.^{56,57} No serious treatment-related adverse events were observed with the use of pegfilgrastim-cbqv.

In late 2019, the FDA approved the third pegfilgrastim biosimilar, pegfilgrastim-bmez, for the same indications as pegfilgrastim.^{14,64} Pegfilgrastim-bmez showed similar pharmacokinetics and pharmacodynamics to pegfilgrastim in healthy volunteers, with no clinically meaningful differences in safety, tolerability, or immunogenicity.⁶⁵ 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.^{66,67} In PROTECT-1, patients with breast cancer who were randomized to receive pegfilgrastim-bmez had equivalent duration of severe neutropenia during cycle 1 of chemotherapy as patients receiving pegfilgrastim (difference = .07 days; 95% CI, -0.12 to 0.26).⁶⁷ This was confirmed in PROTECT-2, which reported a difference in duration of severe neutropenia between patients receiving pegfilgrastim-bmez and those receiving pegfilgrastim for 0.16 days (95% CI, -0.40 to 0.08).⁶⁶ Pegfilgrastim-bmez also demonstrated highly similar safety and tolerability to pegfilgrastim across both trials, with no significant difference in adverse events reported.⁶⁸

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), treatment of HIV, or to prevent the need for RBC transfusions for patients undergoing surgery.^{23,24} Analytical studies and clinical pharmacology data from healthy volunteers have shown epoetin alfa-epbx to have highly similar protein structure, stability, pharmacokinetics, and pharmacodynamics to epoetin alfa.⁶⁹ Epoetin alfa-epbx was also shown to have similar efficacy, safety, and mechanism of action to epoetin alfa in two randomized phase III clinical trials involving patients with anemia secondary to CKD.⁶⁹ Additionally, the results of three independent studies conducted in patients with CKD and healthy volunteers showed similar rates and titers of anti-drug antibodies for both products, indicating 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.^{70,71} 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.²⁴

Management of Neutropenia

Benefits of MGFs

Many studies have shown that the prophylactic use of MGFs reduces the incidence, duration, and severity of FN; decreases the subsequent rates of infection and hospitalization; and improves the delivery of full dose-intensity chemotherapy on schedule in patients with various cancers.⁷²⁻¹⁰⁰ In a meta-analysis by Clark et al, which included 13 studies involving 1518 patients, 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; $P < .0001$) was observed with the prophylactic use of MGFs.⁹⁷ 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; $P < .001$) and significantly improved the relative dose intensity (RDI) of chemotherapy with an average difference in RDI of 8.4% between G-CSF–treated (mean RDI = 95.1%) and non-G-CSF–treated (mean RDI = 86.7) patients ($P = .001$).⁹⁹ This analysis also reported a substantial reduction in the risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; $P = .018$) and early death during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; $P = .002$) with use of G-CSF. This survival advantage was confirmed in a systematic review of 25 randomized controlled trials that involved greater than 12,000 patients undergoing chemotherapy with or without G-CSF support.¹⁰⁰ With an average follow-up of 5 years, G-CSF support was associated with a 3.4% reduction in absolute risk of mortality and an RR of 0.9 for all-cause mortality. Notably,

the degree of survival benefit correlated with the chemotherapy dose intensity received by the patient.

The recommendations in the NCCN Guidelines regarding the use of MGFs are based on therapeutic efficacy and clinical benefit. However, in addition to evaluating the clinical benefits of MGF therapy, an increasing number of studies have assessed the financial implications of their use. Based on data analyzed in 2004, the higher cost of inpatient hospitalization resulted in a change of the FN risk threshold on a pure cost basis from 40% to approximately 20% for the cost-saving use of G-CSF prophylaxis.¹⁰¹ Therefore, if the risk of FN is greater than 20% in a given patient, the overall costs of treatment are substantially reduced with G-CSF prophylaxis. While the addition of MGFs to treatment regimens inevitably raises drug costs, it may equate to substantial savings in comparison to the costs of hospitalization and subsequent treatment of FN. Recently developed pharmacoeconomic models of MGF use have reflected these clinical observations by modeling sequential chemotherapy regimens to account for FN risk on a per-cycle basis, and by accounting for chemotherapy dose reductions and consequent survival losses.¹⁰² Economic analyses of MGFs have yielded mixed results depending on the context of usage.¹⁰³⁻¹⁰⁷ Selective use of MGFs in patients at an increased risk for neutropenic complications may also enhance cost-effectiveness.^{101,108} Additionally, the use of biosimilars represents a new opportunity for cost containment in oncology care, as biosimilars are typically more affordable than their originator products.^{30,109-112}

Risks of MGFs

While MGFs may result in improved outcomes, they are also associated with toxicities (see *Toxicity Risks with Myeloid Growth Factors* in the algorithm). The toxicities listed in the algorithm are from the FDA package inserts and 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 primarily on studies from leukemia and transplant patients, and the listed toxicities may reflect the intravenous (IV) route of administration, which may differ from those of subcutaneous administration. Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars. See the full package inserts for specific product information.

Bone Pain

To date, the major consistently observed adverse event associated with G-CSF prophylaxis is mild to moderate bone pain in 10% to 30% of patients.^{7,11,90,113-116} Currently, data for the treatment of G-CSF–related bone pain is limited to case series, reviews, and small randomized trials. The available data 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.^{114,117} However, use of NSAIDs may not be appropriate for all patients on chemotherapy receiving G-CSF support due to comorbidities, side effects, drug-drug interactions, and drug-disease interactions.¹¹⁷ Additionally, some patients may experience bone pain that is refractory to NSAIDs.¹¹⁴ As an alternative, loratadine 10 mg daily or a similar anti-histamine can be used for 5 to 7 days after G-CSF administration to treat G-CSF–related bone pain.¹¹⁸⁻¹²¹ Some studies have suggested that using a reduced dose of pegfilgrastim may be effective in managing G-CSF–related bone pain without increasing the risk for FN.¹²²⁻¹²⁴ 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 were fatal.¹²⁵⁻¹³¹ These cases occurred in patients with underlying hematopoietic disorders, patients with solid tumors, and healthy donors of peripheral blood progenitor cells (PBPCs). The exact mechanism of G-CSF–induced splenic rupture is unknown, but is thought to involve intrasplenic accumulation of circulating granulocytes and myeloid precursors.⁶² Physicians should monitor patients closely for signs of splenic rupture, including abdominal pain (especially in the upper left quadrant), nausea, vomiting, and progressively worsening anemia. Prospective studies on health status, baseline spleen size, and complete blood count (CBC) may be required to identify risk factors for rupture in individual patients.⁶⁴

Bleomycin-Induced Pulmonary Toxicity

The risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSF. In a retrospective study of 141 patients with Hodgkin lymphoma receiving ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy, the rate of bleomycin-induced pulmonary toxicity was 26% in patients receiving G-CSF compared with 9% in patients who did not receive it ($P = .014$).¹³² The toxicity potential for patients following the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen is less clear, although bleomycin is given every 3 weeks in this regimen as opposed to every 2 weeks in ABVD. Due to the risk of pulmonary complications, the routine use of G-CSF is not recommended in conjunction with the most common chemotherapy regimens for classical Hodgkin lymphoma (ABVD and Stanford V). Two studies have shown that ABVD can be safely administered at full dose without G-CSF support.^{133,134} Due to the high incidence of toxicity and treatment delays, G-CSF support



is recommended for patients with Hodgkin lymphoma treated with the escalated BEACOPP regimen.

AML and MDS

Although there have been suggestions of a potentially increased risk for development of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) following MGF administration from epidemiologic studies, this has not been observed in individual randomized trials.^{125, 135-137} The meta-analysis by Lyman et al¹⁰⁰ reported a 0.41% increase in absolute risk (95% CI, 0.10%–0.72%; $P = .009$) and an estimated RR of 1.92 (95% CI, 1.19–3.07; $P = .007$) for the development of AML/MDS related to G-CSF use. While it was not possible from this meta-analysis to determine whether the risk for AML/MDS is secondary to G-CSF or related to higher total doses of chemotherapy, overall mortality was nevertheless decreased by the addition of G-CSF support. An updated meta-analysis and systematic literature review by Lyman et al largely 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.¹³⁸ Analyses using data from the SEER database have also shown a slightly elevated risk of developing AML/MDS in patients receiving G-CSF support.^{137, 139} However, these studies should be interpreted with caution since they cannot exclude the possibility that the increased risk was due to the use of G-CSF in cases that were more likely to progress into AML/MDS, regardless of the presence or absence of adjuvant therapy.

Other Toxicities

Some patients may develop allergic reactions to G-CSF involving the skin, respiratory system, or cardiovascular system. Other potential toxicities include acute respiratory distress syndrome, alveolar hemorrhage, and

hemoptysis.^{7, 11, 140} Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease receiving G-CSF, but not for patients with sickle cell trait.¹⁴¹⁻¹⁴³ Significant toxicity in patients with amyloidosis following G-CSF administration has also been described in two case reports.^{144, 145}

Adverse events have also been reported with GM-CSF use. In an early study, adverse reactions were seen in 65% of patients with advanced malignancy following administration of GM-CSFs, although they were not severe and were reversible. These reactions included mild myalgias, facial flushing, low-grade fever, headache, nausea, and dyspnea.¹⁴⁶ A side-effect profile of GM-CSF, completed several years later, reported a lower rate of 20% to 30% mild-to-moderate adverse events, and attributed this decline to improved dosing and delivery.¹⁴⁷ Although uncommon, severe side effects have also been reported with GM-CSF use. Less than 1% of patients develop blood clots, which may lead to pulmonary embolism or stroke in rare cases.¹⁴⁸⁻¹⁵⁰ There have also been reports of capillary leak syndrome,¹⁵¹⁻¹⁵³ a condition in which fluids move from the vascular system into the interstitial space resulting in hypotension and reduced blood flow to internal organs.¹⁴⁸ While this is more common with GM-CSF use, it has also been reported to occur with G-CSF use.^{154, 155}

Data regarding the safety of MGF administration following infusion of chimeric antigen receptor (CAR)-modified T cells are limited and institutional practices widely vary.¹⁵⁶⁻¹⁵⁸ The FDA label for tisagenlecleucel recommends avoiding use of MGFs, particularly GM-CSF, during the first 3 weeks after cell infusion or until cytokine release syndrome (CRS) has resolved.¹⁵⁹ Although data are not provided to support this recommendation, it is likely based on the potential for GM-CSF to promote antigen-presenting cell function that may exacerbate the severity or incidence of CRS.^{156, 160} Due to the high rates of neutropenic complications in patients undergoing CAR T-cell therapies and the potential for



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

promotion of CRS with the use of MGFs, more studies are needed to determine the safety of MGFs in this setting.

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. The 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 patients in the intermediate-risk group based on patient-specific risk factors (see *Patient Risk Factors for Developing FN* below). 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 in the assessment of FN risk, 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 development of FN is directly related to the dose intensity of the chemotherapy regimen. Chemotherapy regimens for which clinical trial data show an incidence of FN greater than 20% in chemotherapy-naïve

patients are considered by the panel to be high risk. It should be noted that the addition of monoclonal antibodies to chemotherapy regimens has the potential to increase the risk of FN. Of particular concern is rituximab, an anti-CD20 monoclonal antibody mainly used in the treatment of CD20+ hematologic malignancies, which is known to have an independent potential to cause severe neutropenia. Rituximab has been associated with prolonged, delayed-onset neutropenia both with and without chemotherapy.¹⁶¹

The algorithm lists common chemotherapy regimens associated with a high or intermediate risk of developing FN based on published data (see *Examples of Disease Settings and Chemotherapy Regimens with a High/Intermediate Risk for Febrile Neutropenia* in the algorithm). These lists are not comprehensive and are meant to serve as examples 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. It is emphasized that the chemotherapy regimen is only one component of risk assessment and needs to be combined with patient-specific risk factors and treatment to estimate the overall risk of FN.

Patient Risk Factors for Developing FN

Patient-specific risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk.¹⁶² 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. Many regimens for breast and lung cancers are associated with an intermediate risk of neutropenic complications, making it important to identify which patients would be considered high risk for FN development based on individual risk factors. Even a low-risk regimen may warrant the use of G-CSF in a patient with one or more clinical risk factors.



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

An important patient-specific risk factor for the development of FN is older age (>65 years; see [NCCN Guidelines for Older Adult Oncology](#)).¹⁶³⁻¹⁶⁸ Other identified risk factors that might prompt the use of prophylactic G-CSF include prior exposure to chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by the tumor, poor performance status, recent surgery and/or open wounds, renal or liver dysfunction, and HIV infection (see *Additional Evaluation of Patient Risk Factors for Prophylactic Use of MGFs* in the algorithm).¹⁶⁹ Chronic immunosuppression in the post-transplant setting (including organ transplant) may also warrant the use of G-CSF. Most of these have been confirmed as independent risk factors for the development of neutropenic complications in a risk model developed by Lyman et al that was validated in a study population of 3760 patients with cancer who were beginning chemotherapy.¹⁷⁰ This model and its associated risk factors have been retrospectively validated both internally and externally in an independent patient population.¹⁷¹ In the future, external validation of other proposed FN risk assessment models and novel patient-specific risk factors may enhance identification of patients at high risk of developing FN.^{108,172-175}

Patients at High Risk for FN

The NCCN Guidelines recommend prophylactic use of G-CSF if a patient's risk of developing FN is greater than 20% (category 1). The most recent updates of 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.^{176,177} This consistent recommendation is based on the results of several large randomized trials that have documented a significant reduction in FN incidence following primary G-CSF prophylaxis when the risk of FN without prophylaxis is greater than 20%.^{99,178} In one such example, a randomized, placebo-controlled, phase III trial in patients with breast cancer receiving TC (docetaxel and cyclophosphamide) chemotherapy found that the incidence of FN was significantly lower for

patients who received prophylactic G-CSF than those for who received placebo (1.2% vs. 68.8%, respectively; $P < .001$).¹⁷⁸ Patients in the G-CSF group also had lower rates of hospitalization and antibiotic use. Furthermore, prophylactic use of G-CSF 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.⁹⁹

The NCCN Guidelines recognize a variety of circumstances 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 be at high patient-specific risk, regardless of the treatment regimen or intent.

Patients at Intermediate Risk for FN

The NCCN Panel defines intermediate risk as a 10% to 20% probability of developing FN or a neutropenic event that would compromise treatment. For patients receiving intermediate-risk chemotherapy regimens, the panel recommends individualized consideration of prophylactic G-CSF use based on the presence of patient-specific risk factors. Patients with 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, the use of G-CSF is a difficult decision and requires careful discussion between the physician and patient. If the increased risk for FN is due to patient-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



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

less myelosuppressive chemotherapy, if of comparable benefit, should be explored.

Patients at Low Risk for FN

For patients receiving low-risk chemotherapy regimens, as defined by an FN risk of less than 10%, routine use of G-CSF prophylaxis is not recommended.^{101,179,180} However, use of prophylactic G-CSF may be appropriate if the patient 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, patient evaluation should be performed prior to each subsequent cycle to determine the FN risk categorization. If the patient experienced an episode of FN or a dose-limiting neutropenic event (a nadir count or a day-of-treatment count impacting the planned dose of chemotherapy) during the previous treatment cycle with the same dose and schedule planned for the current cycle, this patient is now in the high-risk group. Prophylactic G-CSF support should be considered for such patients who had not received prior G-CSF. In patients who 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 and a decision rendered regarding the indication for prophylactic G-CSF.

Dosing and Administration

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 being given concurrent chemotherapy and radiation.¹⁸¹ 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

The subcutaneous administration of filgrastim, tbo-filgrastim, or filgrastim biosimilars is a category 1 recommendation for the prevention of FN. Initial doses are administered the next day or up to 3 to 4 days after completion of myelosuppressive chemotherapy in a daily dose of 5 mcg/kg until post-nadir ANC recovery to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. Neutrophil counts should be monitored as indicated appropriate to the setting. The NCCN Panel recommends treatment of patients through post-nadir recovery since studies have shown shorter durations of G-CSF treatment to be less efficacious.¹⁸²

Pegfilgrastim and Pegfilgrastim Biosimilars

Pegfilgrastim and pegfilgrastim biosimilars are pegylated versions of filgrastim designed to have a longer half-life, which allows for a single administration of 6 mg to be sufficient. Based on clinical trial data, pegfilgrastim or pegfilgrastim biosimilars can be administered the day after myelosuppressive chemotherapy (category 1).¹⁸³ 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 for exacerbation of neutropenia resulting from stimulation of hematopoietic progenitor cells at the time of cytotoxic chemotherapy active in dividing cells, resulting in loss of the progenitors.^{184,185} A systematic literature review evaluating the relative merits of next-day versus same-day pegfilgrastim found that delivery of pegfilgrastim at least 24 hours after



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

myelosuppressive chemotherapy resulted in improved patient outcomes across a variety of tumor types.¹⁸³ Additionally, 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.¹⁸⁶ Another retrospective evaluation found that 50% of all FN hospitalization episodes among cancer patients occurred in those who either did not receive pegfilgrastim or received pegfilgrastim on the same day as chemotherapy.¹⁸² A large-scale retrospective evaluation of 53,814 patients receiving intermediate- or high-risk chemotherapy regimens also found the incidence of FN to be significantly higher in patients administered pegfilgrastim prophylaxis either the same day or 4 to 5 days after chemotherapy compared to those receiving pegfilgrastim on days 1 to 3 following chemotherapy.¹⁸⁷ In a direct comparison, Kaufman et al¹⁸⁸ administered either same-day or next-day pegfilgrastim in women with breast cancer receiving chemotherapy with TAC. FN was observed in 33% of patients treated in the same-day group compared with only 11% of patients treated in the next-day group.¹⁸⁸ A similar trend was seen in a prospective, randomized trial of patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like therapy for NHL, where same-day pegfilgrastim was associated with enhanced myelosuppression.¹⁸⁹

In contrast, some retrospective analyses have reported no statistically significant difference in FN rates among patients administered pegfilgrastim the next day versus the same day as chemotherapy.¹⁹⁰⁻¹⁹³ 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 ≥ 1 episode of FN in cycle 1 ($P = .814$).¹⁹³ Across all cycles, 9.3% in the same-day group and 8.9% in the next-day group experienced ≥ 1 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 cases of FN.¹⁹¹ Another 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.¹⁹² Although there are data for and against same-day pegfilgrastim administration, the FDA-approved dosing schedule of next-day administration is still recommended.

Panelists recognize that some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize travel burdens on long-distance patients. The FDA approval of a delivery device that can be applied the same day as chemotherapy and set to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application) is an alternative to same-day administration for patients who cannot return to the clinic for next-day administration of pegfilgrastim.¹⁹⁴ However, this on-body delivery device is currently only available for use with originator pegfilgrastim and not pegfilgrastim biosimilars. Rarely (1.7%–6.9%), there is a failure to inject that requires further medical attention.¹⁹⁴⁻¹⁹⁷

The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle lengths. In general, there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy. If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment. Based on phase III clinical trials,^{76,198} use of pegfilgrastim for chemotherapy regimens given every 3 weeks is a category 1 recommendation. Pegfilgrastim use is a category 2A recommendation for chemotherapy regimens given every 2 weeks, based on phase II studies.¹⁹⁹⁻²⁰⁴ There are insufficient data to support the use of pegfilgrastim for weekly regimens; therefore, pegfilgrastim should not be used. The panel has extended these recommendations to pegfilgrastim biosimilars.

**Therapeutic Use of MGFs**

Compared to prophylactic use, 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.^{97,205} 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. However, since pegfilgrastim and pegfilgrastim biosimilars are long-acting, those who have received these agents prophylactically should not be treated with additional G-CSF.²⁰⁶ There are no studies that address the therapeutic use of filgrastim for FN in patients who have already received prophylactic pegfilgrastim or a pegfilgrastim biosimilar. Pharmacokinetic data following treatment with pegfilgrastim demonstrate high levels during neutropenia and suggest that additional G-CSF use may not be beneficial. 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.

For patients presenting with FN who have not received prophylactic G-CSF, the NCCN Panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome. Features associated with poor outcome include age greater than 65 years; sepsis syndrome; ANC less than 100 neutrophils/mcL; anticipated prolonged (>10 days) neutropenia; pneumonia or other clinically documented infection; invasive fungal infections; hospitalization at the time of fever; and prior episode(s) of FN. If risk factors are present, use of therapeutic MGFs should be considered. Filgrastim, tbo-filgrastim, filgrastim biosimilars, or sargramostim may be administered in the therapeutic setting. Pegfilgrastim and pegfilgrastim biosimilars have only been studied

for prophylactic use and are not recommended for therapeutic use at this time.

Filgrastim, pegfilgrastim, and sargramostim are also FDA-approved for the treatment of patients with radiation-induced myelosuppression following a radiologic/nuclear incident (H-ARS).^{7,11,17,148,207} The panel also recommends use of tbo-filgrastim 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, initiation of MGFs should be strongly considered for patients who received greater than or equal to 2 Gy whole body exposure or greater than or equal to 2 Gy significant partial body exposure and have an ANC less than or equal to 500 cells/mm³, will likely have prolonged periods of significant neutropenia, or have trauma and/or burns, which worsen the clinical outcome compared to radiation exposure alone.²⁰⁸ Most of the data in support of MGF used 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 the treatment of FN in select high-risk patients 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/m². 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/m².²⁰⁸ 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, as reflected by the requirement of higher doses of G-CSF, appear to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following these patients carefully. Currently, the only alternative therapy for severe chronic neutropenia is HCT. For further reading on severe chronic neutropenia, refer to the website developed by The Severe Chronic Neutropenia International Registry: <http://depts.washington.edu/registry/index.html>.

Management of 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.²⁵⁻²⁷ Platelet transfusion offers only temporary improvement in platelet count and is often unreliable and impractical to continue for extended periods.²⁶ 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 the production of platelets.²⁵ Romiplostim is FDA-approved to treat immune thrombocytopenia. Although romiplostim is widely used to treat CIT, there is currently no FDA-approved treatment for CIT.

Patients with suspected CIT should be evaluated and treated accordingly 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-induced myelosuppression, hematologic malignancy, consumption of platelets secondary to blood loss, and thrombotic microangiopathies, among others. 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 AABB (formerly the American Association of Blood Banks) 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 dose schedule and intensity of chemotherapy when such benefit is thought to outweigh potential risks. In patients for whom a TPO-RA is being considered for management of CIT, participation in clinical trials is encouraged whenever possible. Romiplostim dosing strategies include weekly dosing



beginning at 2 to 4 mcg/kg, increased no more than 1 to 2 mcg/kg per week to target platelet count 100,000 to 150,000/mcL.^{25,26} 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.^{26,220,221} Romiplostim use in non-myeloid hematologic malignancies has not been evaluated. In a multicenter retrospective analysis of 173 patients, 71% of patients with solid tumors achieved a response to romiplostim.²⁶ A case series of 20 patients with solid tumors and CIT reported that romiplostim treatment improved platelet counts in all patients allowing for resumption of chemotherapy.²²¹ In a recent phase II randomized trial comparing romiplostim to untreated observation in patients with solid tumors and CIT, 93% of romiplostim-treated patients experienced correction of their platelet count within 3 weeks compared with 12.5% of control patients ($P < .001$), showing that romiplostim is effective in correcting CIT.²⁵ However, data suggest that use of TPO-RAs for CIT may increase the risk of venous thromboembolism (VTE) in patients with cancer.^{25,26,220,221} 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.^{222,223} Patients with thrombocytopenia post-HCT should be evaluated for the other potential causes of thrombocytopenia mentioned above as well as primary or secondary graft failure, graft-versus-host disease, relapse of hematologic malignancy, and transplant-associated thrombotic microangiopathy (TA-TMA). For 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.

Recent data have suggested activity for the TPO-RAs lusutrombopag and eltrombopag for thrombocytopenia in patients with cancer or thrombocytopenia post-HCT. Lusutrombopag is currently FDA approved for management of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a medical or dental procedure and eltrombopag is approved for patients with chronic immune thrombocytopenia or severe aplastic anemia. 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.²²⁴ In a phase II randomized trial of 60 patients with post-HCT thrombocytopenia, a significantly higher proportion of patients in the eltrombopag arm achieved a platelet count of $\geq 50,000/\mu\text{L}$ compared with the placebo arm (21% vs. 0%; $P = .046$). However, overall survival (OS), progression-free survival, relapse rate, and non-relapse mortality were similar in the two arms. Although these reports are promising, outside of a clinical trial setting, insufficient data are available to support use of TPO-RA other than romiplostim for treatment of CIT.

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.²²⁵ 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



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

factors.^{226,227} The malignancy itself can lead to or exacerbate anemia in a number of ways.²²⁸ 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.^{20,229-231}

Many chemotherapy agents produce myelosuppression, which contributes to anemia.²³¹ Chemotherapeutic agents induce anemia by directly impairing hematopoiesis in the bone marrow, including disruption of RBC precursor production.²²⁸ Additionally, the nephrotoxic effects of some cytotoxic agents (eg, platinum-containing agents) can result in decreased production of erythropoietin by the kidneys.²²⁸ RT to the skeleton has also been associated with hematologic toxicity. In a retrospective analysis of 210 patients undergoing craniospinal RT for treatment of primary tumors of the central nervous system, approximately one-third of patients developed grade 3/4 hematologic toxicities including anemia.²³² Newer modalities such as immunotherapies may also produce anemia, although data are limited.²³³⁻²³⁶ Clinicians should become familiar with the adverse effects of immunotherapy drugs, including hematologic toxicities, and be observant for other less-documented clinical conditions as these therapies become more prevalent in cancer care.

The myelosuppressive effects of particular cytotoxic agents are likely to accumulate over the course of repeated cycles of therapy, resulting in a steady increase in the rate and severity of anemia with additional chemotherapy cycles. In the European Cancer Anaemia Survey (ECAS),²³⁰ the rate of anemia (Hb level <12 g/dL) was found to increase

from 19.5% in cycle 1 to 46.7% by cycle 5.²³⁰ An increase in the fraction of grade 2 to 3 anemia was also associated with a greater number of chemotherapy cycles. Other factors to consider when evaluating the risk for CIA include the nadir Hb level, the time to the nadir Hb level (roughly estimated at 2 weeks, but time can vary), and whether an Hb measurement is considered to be pre- or post-nadir.²²⁸

Initial Evaluation of Anemia

Given the wide variation in Hb levels among healthy subjects, a universal “normal” value is difficult to define. According to the NCCN Panel, an Hb level less than or equal to 11 g/dL should prompt an evaluation of anemia in patients with cancer. A drop of 2 g/dL or more 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.²³⁷ 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 al²²⁵). The overall goals of evaluation are to characterize the anemia and identify any potentially correctable underlying comorbidities prior to initiating treatment.

Initial characterization of anemia involves a CBC with indices to determine if other cytopenias are present. A visual review of the peripheral blood smear morphology is critical to confirm the size, shape, and Hb content of RBCs. A detailed history and physical 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 in female patients. 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.²³⁸ The above clinical manifestations are neither sensitive nor specific to the type of anemia. Clinicians should watch for signs of underlying etiologies such as jaundice, splenic enlargement, neurologic symptoms, blood in the stool, petechiae, and heart murmur, among others.

Approaches to Evaluation

There are two common approaches to evaluating anemia: morphologic and kinetic. A complete evaluation should 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 medications²³⁹ and alcoholism, both of which are forms of non-megaloblastic anemia. MDS also causes mild macrocytosis. Macrocytosis seen in megaloblastic anemia is most frequently caused by vitamin deficiency resulting from inadequate intake (folic acid or B₁₂) or inadequate absorption of B₁₂ from lack of intrinsic factor or antibodies to parietal cells. Macrocytosis accompanies increased reticulocyte counts following brisk hemorrhage or hemolysis.
- Normocytic (80–100 fL)—may be due to hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation, or renal insufficiency.

The 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.

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

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

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

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 B₁₂ or red cell folate levels (commonly tested together with iron studies). Ferritin values are also useful in evaluating iron stores. Fasting values are preferred for serum iron and TIBC studies.



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

- Hemorrhage—stool guaiac positive, endoscopy findings.
- Hemolysis—direct antiglobulin test positive, disseminated intravascular coagulation panel positive, low haptoglobin levels, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH).
- Renal dysfunction—glomerular filtration rate <60 mL/min/1.73 m² for ≥3 consecutive months.
- Inherited anemia—personal and/or family history.
- Sideroblastic anemia—sideroblasts present in bone marrow biopsy.
- Hormone dysfunction—hypogonadism, adrenal dysfunction, hyper/hypothyroidism.
- Chronic inflammation—increased C-reactive protein level and/or erythrocyte sedimentation rate.²⁴⁰

Any cause of anemia that is found to be 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 anemic patient is necessary to determine the initial intervention plan. The decision regarding the best treatment option is dependent on many factors. While PRBC transfusion is best for symptomatic patients requiring an immediate boost in Hb levels, consideration of ESA therapy with or without iron supplementation may be warranted for the long-term management of anemia in high-risk patients or in asymptomatic patients with comorbidities.

Red Blood Cell Transfusion

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

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

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

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



preservatives. Further enhancements include leukoreduction, γ -irradiation, freezing, and washing. Patients who are immunocompromised may need PRBCs that are cytomegalovirus (CMV) negative. Leukoreduction is often sufficient to reduce the risk of CMV transmission. For example, patients who are candidates for or undergoing autologous or allogeneic HCT require blood products that have undergone leukocyte reduction and γ -irradiation to reduce the risks of transfusion-associated graft-versus-host disease (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.²⁴¹

Benefits and Risks of Red Blood Cell Transfusion

Benefits of Red Blood Cell Transfusion

The major benefit of transfusion with PRBCs, offered by no other anemia treatment, is a rapid increase in Hb and Hct levels and thus, a rapid improvement in anemia-related symptoms. Hence, PRBC transfusion is the best option for patients who require immediate correction of anemia. Transfusion of 1 unit (~300 cc) of PRBCs has been estimated to result in an average increase in Hb level by 1 g/dL or in Hct level by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.^{241,242} 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.^{243,244} 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 2004.²⁴⁴ Since the implementation of screening, fewer than 10 deaths from bacterial sepsis per year have been reported in PRBC transfusion patients. Additionally, pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse event.^{245,246}

Red Blood Cell Transfusion Goals and Basic Principles

The overall goal of PRBC transfusion is to treat or prevent deficiencies in the oxygen-carrying capacity of the blood to improve oxygen delivery to bodily tissues. In 2016, the AABB published clinical practice guidelines based on a systematic review of randomized controlled trials evaluating Hb thresholds for RBC transfusion.²⁴⁷ AABB recommendations include: 1) using an Hb level of 7 g/dL as a threshold for hospitalized adult patients who are hemodynamically stable; 2) using an Hb level of 8 g/dL as a threshold for patients undergoing orthopedic surgery, cardiac surgery, or those with pre-existing cardiovascular disease; and 3) using RBC units selected at any point within their licensed dating period rather than limiting patients to transfusion of only fresh RBC units. However, there was a lack of evidence to provide specific recommendations for the cancer population. NCCN Panelists agree that no single target Hb level is appropriate for all cases and that the balance between transfusion risks and benefits should be evaluated on an individual basis. Clinicians are urged to exercise their clinical judgment based on patient symptoms, cancer course and treatment, comorbidities, and patient preference.

Prior to transfusion, PRBCs must be crossmatched to confirm compatibility with ABO and other antibodies in the recipient. There is no evidence to support routine premedication with acetaminophen or an antihistamine to prevent allergic and febrile non-hemolytic transfusion reactions.^{248,249}



However, if repeated transfusions are required, leukocyte-reduced blood and the use of premedication may minimize adverse transfusion reactions. In most instances, PRBCs should be transfused by the unit, and reassessment should be conducted after each transfusion. When considering PRBC transfusion, refer to the 2016 AABB clinical practice guidelines.²⁵⁰

Patients with CIA Who Refuse Blood Transfusions

Patients with CIA who refuse blood transfusions are occasionally seen in clinical practice. Religious beliefs or personal preferences may prohibit such patients from using blood products. For such patients, clinicians should consider the risk of anemia when making treatment decisions. Although there are limited available data on the best management of CIA in patients who refuse blood transfusions, several strategies can be used to reduce anemia in this patient population, including minimizing blood loss,²⁵¹⁻²⁵⁵ use of ESAs,^{254,256,257} or use of blood substitute products.^{251,254,256-259} Strategies to reduce blood loss include batching routine laboratory testing, using pediatric blood collection tubes, minimizing phlebotomy, and returning discard in a closed system.²⁵¹⁻²⁵⁵ Additionally, consider daily folic acid and vitamin B₁₂ supplementation prior to initiation of myelosuppressive chemotherapy. Nutritional sufficiency for iron, folate, and vitamin B₁₂ should be evaluated and deficiencies corrected. Iron deficiency should be corrected using IV iron. Baseline coagulation abnormalities should also be fully evaluated and corrected prior to myelosuppressive treatment.

The majority of data regarding the use of ESAs in patients who refuse blood transfusions are from published case reports and small cohort series involving patients who are Jehovah's Witnesses. These types of reports carry inherent bias and vary significantly in reporting outcomes, regimens, and dosing.²⁵⁶ A 2008 analysis of 14 case reports of Jehovah's Witness patients receiving ESA therapy in a variety of clinical situations concluded

that while administration of ESAs enhanced Hb levels in each situation, time to the start of treatment, dosage, route of administration, and treatment duration varied widely among included studies.²⁶⁰ Additionally, there was a lack of data regarding Jehovah's Witness patients with CIA. More recent case reports on Jehovah's Witness patients, including three involving patients with cancer, have reported similar results on the effectiveness of ESAs in increasing Hb levels.²⁶¹⁻²⁶⁷ In one case report, a 57-year-old male Jehovah's Witness diagnosed with CIA secondary to aggressive NHL was administered darbepoetin alfa once per week. This therapy increased his Hb level from 7.5 to 11.5 g/dL within 1 month and enabled completion of intensive chemotherapy.²⁶¹ Although there is a lack of prospective data, ESAs should be considered given that there is no option for transfusion in such patients.^{254,256} However, ESAs are not recommended for patients with cancer who are not receiving chemotherapy or patients receiving non-myelosuppressive chemotherapy. If ESAs are prescribed off-label for these indications, patients should be made aware of the potential increased risks of thrombosis and tumor progression and should know that under these circumstances the ESAs are being used off-label. It should be noted that the effects of ESA therapy on Hb level may not be evident for several days after administration. Therefore, in extreme cases of severe, life-threatening anemia, pure oxygen (400 mm Hg, S_AO₂ = 1.0) by mechanical ventilation can be used to increase blood oxygenation.²⁶⁸

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.^{251,254,256-259,269} 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.²⁵⁶ Despite these benefits, few products have advanced to phase III trials and no products



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

have produced a significant decrease in the need for transfusions (in patients who accept transfusion support). The use of HBOCs has been associated with serious adverse reactions.²⁵⁹ 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.²⁷⁰ However, with compassionate use, HBOCs have successfully treated Jehovah's Witnesses with severe anemia in emergent settings.^{258,271-275} Therefore, 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. Since a case series evaluation has suggested that delay in receipt of HBOCs is independently associated with mortality in patients who refuse blood transfusions, clinicians should consider starting the regulatory process for procurement of HBOCs early on in the course of treatment.²⁷⁶

Erythropoietic Therapy

ESAs have been shown to stimulate erythropoiesis in patients with low RBC levels, although not all patients have disease that responds to ESA therapy. In a study of 2192 patients with cancer receiving ESA therapy, an Hb increase of greater than or equal to 1 g/dL was attained in 65% of patients.²⁷⁷ Unlike transfusion, which immediately boosts the Hb level, ESAs can take weeks to elicit an Hb response, but they are effective at maintaining a target Hb level with repeated administration. Iron studies (serum iron, TIBC, and serum ferritin) should accompany ESA therapy to monitor the development of iron deficiency (See *Iron Monitoring and Supplementation* below for more information).

Benefits of ESA Therapy

A gradual improvement in anemia-related symptoms and avoidance of transfusion are the main goals of ESA therapy. In a randomized, placebo-controlled study, epoetin alfa was shown to increase Hb levels (2.2 vs. 0.5 g/dL; $P < .001$) and reduce transfusion requirements (24.7% vs. 39.5%; $P = .0057$) in patients with anemia receiving chemotherapy.²⁷⁸ In a randomized phase III study, patients with lung cancer with Hb less than or equal to 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.²⁷⁹ The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review that enrolled a total of 20,102 patients undergoing treatment for cancer with concomitant ESA therapy.²⁸⁰ A decreased RR for transfusion was observed in patients receiving ESAs (RR, 0.65; 95% CI, 0.62–0.68).²⁸⁰ Of the patients treated with ESAs, 25 out of 100 subsequently received a transfusion versus 39 out of 100 patients in the untreated group, equating to a one-unit reduction in transfusion in ESA-treated patients. The first patient-level meta-analysis evaluating the efficacy of darbepoetin alfa treatment when initiated at Hb ≤ 10 g/dL in patients with CIA found that more patients who received darbepoetin alfa than placebo achieved an Hb increase of greater than or equal to 1 g/dL (fixed-effects HR, 2.07; 95% CI, 1.62–2.63) or greater than or equal to 2 g/dL (HR, 2.91; 95% CI, 2.09–4.06).²⁸¹ Transfusions were also less common in these patients (HR, 0.58; 95% CI, 0.44–0.77).

Risks of ESA Therapy

ESAs have associated toxicities, including increased thrombotic events, possible decreased survival, and shortened time to tumor progression. When considering ESAs, discuss the risks of ESA therapy with patients including the potential for tumor growth, death, blood clots, and hypertension.



Possible Increased Mortality and Tumor Progression

Since their approval in 2007, the FDA has made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa,^{21,22} including the addition of black-box warnings. 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).²⁸²⁻²⁸⁹ Of the eight studies, four investigated ESAs in patients who underwent 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 greater than 12 g/dL. Additional meta-analyses of randomized controlled trials have confirmed worsened health outcomes associated with the use of ESAs when targeting Hb levels greater than 12 g/dL.^{280,290-293} Data from the Cochrane Database also reported increased mortality associated with ESA use in patients when targeting Hb levels greater than 12 g/dL.²⁸⁰ 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 less than 12 g/dL. Data from a systematic review by the Agency for Healthcare Research and Quality (AHRQ) showed that delaying ESA treatment until Hb is less than 10 g/dL resulted in fewer thromboembolic events and a reduced mortality.²⁹³

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.^{294,295} Pharmacovigilance trials have also reported no adverse effects on survival in patients with CIA receiving ESAs.^{296,297} 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.²⁹⁸ In this study, no impact on event-free survival (EFS) (darbepoetin alfa, 89.3% vs. no darbepoetin alfa, 87.5%; $P_{\log\text{-rank}} = 0.55$) or OS (darbepoetin alfa, 95.5% vs. no darbepoetin alfa, 95.4%; $P_{\log\text{-rank}} = 0.77$) was observed with the use of ESAs. In the AGO-ETC trial, which included 1284 high-risk breast cancer patients, epoetin alfa resulted in improved Hb levels and decreased transfusions without an impact on relapse-free survival or OS.²⁹⁹ Additionally, data from randomized studies showed no increase in mortality in patients receiving chemotherapy for small cell lung cancer when ESAs were given according to the prescribing label.³⁰⁰⁻³⁰² A recent systematic review also showed no major change in OS with ESA therapy in patients with cancer.³⁰³ While these data suggest that use of ESAs may not be associated with decreased survival or increased disease progression as previously thought, additional prospective trials designed and powered to measure survival of patients with cancer are needed to provide clinicians with data to guide optimal use of ESAs.

Thromboembolism

Increased thromboembolic events, including VTE, have been associated with ESA therapy in patients with cancer.^{280,290,292-295,303} The cause of VTE in patients with cancer is complex with a heightened baseline risk related to both the malignancy itself and to the chemotherapy regimen used (see [NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease](#)).³⁰⁴⁻³⁰⁷ Risk factors for VTE in patients with cancer include prior history of VTE, inherited or acquired mutations, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, prolonged immobility, steroid use, and comorbidities such as hypertension.³⁰⁸ Patients with risk factors may be at a higher risk for thrombosis with the use of ESAs. Therefore, risk factors should be evaluated in each patient before administration of ESA therapy. The NCCN Panel cautions physicians to be alert to the signs and symptoms of thromboembolism in patients with cancer receiving ESAs.



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

In an analysis of phase III trials comparing ESAs with placebo for the treatment of CIA, the absolute risk of VTE was 7.5% in patients treated with ESAs compared with 4.9% in control patients.²⁹⁰ 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).³⁰⁹ ESA use was also associated with a significantly increased risk of stroke (OR, 1.83; 95% CI, 1.26–2.65) in a retrospective case-controlled study of CKD patients with cancer.³¹⁰ It is important to note that the thrombotic potential of ESAs is independent of Hb levels.³¹¹

Hypertension

An increased risk for hypertension with ESA usage in patients with cancer was reported by a Cochrane review (RR, 1.30; 95% CI, 1.08–1.56).²⁸⁰ A recent systematic review also reported increased hypertension risk in patients with cancer on ESAs.³⁰³ Blood pressure should be controlled in all patients prior to initiating ESA therapy and must be monitored regularly throughout treatment. Hb levels should be monitored before and during the use of ESAs to decrease the risk of hypertension.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count and loss of bone marrow erythroblasts caused by the development of neutralizing antibodies against erythropoietin. A marked rise in incidence (197 cases) of PRCA was observed between 1998 and 2004, although more than 90% of cases occurred with an epoetin alfa product used outside of the United States.^{312,313} Causation was attributed to formulations without human serum albumin, subcutaneous administration, and use of uncoated rubber stoppers.³¹⁴ Interventions, designed accordingly to address these issues, reduced the incidence of PRCA by 83%. In 2005, the FDA's interpretation of anemia

associated with neutralizing antibodies evolved to include both PRCA and severe anemia, resulting in a class label change for all ESAs.^{21,22} Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa in patients with chronic renal failure.³¹⁴ Therefore, patients who develop a loss of response to ESAs should be evaluated for possible PRCA, and if present, all ESA drugs should be discontinued.³¹²

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.³¹⁵ The FDA made this determination based on an evaluation of the results of the REMS Assessments and additional FDA analyses. For patients with cancer, the black box warning on the revised FDA label states that ESAs should only be used to treat CIA and should be discontinued once the chemotherapy course is complete.²¹ 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.³⁰⁰⁻³⁰² 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



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

circumstances, if no other cause of anemia has been identified, physicians should first consider PRBC transfusion or clinical trial enrollment, if available, for anemia management. Upon the decision to use an ESA, physicians are advised to use the lowest dose necessary to eliminate symptoms and avoid transfusion.

CKD is an independent indication for ESA therapy. Controlled clinical trials have associated increased risks of mortality and adverse cardiovascular outcomes with ESA use in CKD patients when targeted to Hb levels greater than 11 g/dL.^{309-311,316-318} 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 that requires personalized use of ESAs based on very careful evaluation of risks and benefits (reviewed by Bennett et al³¹⁹). In a study comparing darbepoetin alfa to placebo, a significant increase in cancer-related death was seen in patients with CKD with pre-existing cancer at baseline treated with ESA therapy ($P = .002$).³⁰⁹ 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.³¹⁰ Patients with CKD not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor carefully dosed ESAs over transfusion to treat severe anemia. 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

Epoetin alfa, epoetin alfa-epbx, and darbepoetin alfa are recommended equivalently by the NCCN Panel. Head-to-head comparisons of epoetin alfa versus darbepoetin alfa are inconclusive with regard to the superiority

of one agent over the other.^{293,320,321} Recommended dosing schedules for patients receiving chemotherapy are summarized in the algorithm (see *Erythropoietic Therapy – Dosing, Titration, and Adverse Effects*). The panel recommends two initial dosing schedules for epoetin alfa and epoetin alfa-epbx: 150 units/kg 3 times weekly^{278,322} or 40,000 units once weekly^{285,288,289,323} 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 weeks³²⁴ and a dose of 120,000 units administered once every 3 weeks.³²⁵

Although darbepoetin alfa doses were initially administered at 2.25 mcg/kg every week,^{279,283,326} there has been interest in implementing either fixed doses or higher doses at decreased frequency. A randomized trial comparing weekly dosing at 2.25 mcg/kg versus fixed dosing at 500 mcg every 3 weeks in 705 anemic patients with 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 patients receiving darbepoetin alfa every 3 weeks (84% vs. 77%).³²⁶ Dosing once every 3 weeks was further refined in two studies, which reduced the dose to 300 mcg. Initially, a multicenter study of 1493 patients showed that 79% of patients receiving this dose achieved a target Hb level greater than or equal to 11 g/dL.³²⁷ A head-to-head comparison with 500 mcg in a phase II randomized study further confirmed the efficacy of 300 mcg. In this study, no difference in the proportion of patients who achieved target Hb levels (≥ 11 g/dL) was seen between those receiving 300 mcg versus 500 mcg darbepoetin alfa (75% vs. 78%, respectively).³²⁸ Alternative dosing schedules for darbepoetin alfa include a fixed weekly dose of 100 mcg²⁷⁹ and a fixed dose of 200 mcg every 2 weeks.³²⁹ The NCCN Panel recommends these alternative regimens to support the delivery of the lowest ESA dose possible while maintaining maximal efficacy.

***Response Assessment and Dose Titration***

Response to ESA therapy should be assessed to determine whether the initial dose should be reduced, escalated, or withheld. Decisions related to ESA dose adjustment are based on the goal of maintaining the lowest Hb level sufficient to avoid transfusion. ESAs require at least 2 weeks of treatment before there is an increase in the number of RBCs. Hb level should be measured weekly until stabilized. Dose reduction (generally 25% for epoetin alfa or epoetin alfa-epbx and 40% for darbepoetin alfa) should be implemented once Hb reaches a level sufficient to avoid transfusion or if the Hb level increases by greater than or equal to 1 g/dL during a 2-week period.

Conversely, the 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 recent Cochrane Database review concluded that the addition of iron to ESA therapy offers superior hematopoietic response, reduces the risk of transfusions, improves Hb levels, and appears to be well tolerated.³³⁰ A meta-analysis of randomized controlled trials also showed that the addition of parenteral iron reduces the risk of transfusions by 23% and increases the chance of hematopoietic response by 29% when compared with ESAs alone.³³¹ ESA therapy should be discontinued and PRBC transfusion should be considered in patients showing no response despite iron supplementation after 8 weeks of therapy. ESAs should also be discontinued when chemotherapy is completed or withdrawn.

Iron Monitoring and Supplementation***Iron Deficiency Evaluation and Definitions of Iron Status***

Iron deficiency is reported in 32% to 60% of patients with cancer, most of whom are also anemic.³³² Iron studies, including serum iron, TIBC, and serum ferritin, should be performed prior to ESA treatment to rule out absolute iron deficiency, which may respond to oral or IV iron monotherapy. Serum iron and TIBC levels may be falsely elevated by diet (reviewed in Collings et al³³³); therefore, fasting is recommended to provide more accurate measurements. Transferrin saturation (TSAT) should be calculated from these values using the following formula:

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

Treatment for iron deficiency is guided by iron status, defined in these guidelines as absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. In the absence of a universal numerical definition of iron deficiency in relevant studies, the NCCN Panel recognizes that ferritin and TSAT values defining absolute and functional iron deficiencies represent moving targets.²²⁵ 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 less than 20% and a ferritin level less than 30 ng/mL. If the TSAT and ferritin parameters are discordant, a low ferritin value should take precedence in determining whether iron supplementation will be beneficial. The reference interval for serum ferritin depends on the specific laboratory used, but in general, the lower the level, the more probable that true iron deficiency is present. However, in the cancer setting, clinicians



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

should be aware of a chronic inflammatory state, which may falsely elevate serum ferritin levels.

Although IV iron is preferred, either IV or oral iron products alone (without an ESA) are recommended for patients with cancer who develop absolute iron deficiency. Hb levels should increase after 4 weeks of treatment.

Periodic evaluation of ferritin and TSAT levels is required as some patients, especially those with continued internal bleeding, may suffer a relapse. If the patient initially receives oral iron and the anticipated response is not seen after 4 weeks, a trial of IV iron should be considered. If Hb is not improved after 4 weeks following IV iron supplementation, the patient should be evaluated for functional iron deficiency. Although data are conflicting in the literature, concerns exist regarding the possibility of IV iron promoting inflammation and bacterial growth.³³⁴ Hence, IV iron supplementation is not recommended for patients with an active infection.

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

Functional Iron Deficiency

Functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production is deficient.

This may occur when infection or inflammation blocks iron transport to the bone marrow, as seen in anemia of chronic inflammation. Functional iron deficiency is defined in these guidelines as a ferritin level between 30 and 500 ng/mL and a TSAT level less than 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). However, there are insufficient data to routinely recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency. Functional iron deficiency often arises following continued ESA use, resulting in a blunted erythropoietic response to

anemia. Hence, iron supplementation will eventually be required in most patients to maintain optimal erythropoiesis.^{335,336}

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

Possible Functional Iron Deficiency

Possible functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production may be deficient. These patients are defined by a TSAT level less than 50% and a ferritin level of 500 to 800 ng/mL. Although clinical trials suggest that these patients may have functional iron deficiency, there are insufficient data to support the routine use of IV iron in this setting. The panel recommends no iron supplementation or the consideration of IV iron supplementation for select patients. Administration of IV iron to these patients should be individualized with the goal of avoiding 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 greater than 800 ng/mL or a TSAT greater than or equal to 50% are not iron deficient. These patients do not require iron supplementation or ESA therapy.

Intravenous Versus Oral Iron

Iron can be administered orally or intravenously. Although oral iron is appropriate for most iron-deficient anemic patients, many patients with CIA either do not respond to oral iron, may be intolerant of oral iron, or may require higher iron doses than achievable with oral iron, making IV iron therapy a valuable option.³³⁷ Evidence from several published studies



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

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.³³⁸⁻³⁴³ In 2011, a trial published by Steensma et al challenged these positive results.³⁴⁴ 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 observed in this study may have been attributable to problems with the study design, including a suboptimal IV iron dosing regimen and a high proportion of participant dropouts.³⁴⁵ 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.³⁴⁶ It should be noted that patients with a baseline TSAT level less than 20% have a higher response rate to IV iron supplementation when given in addition to an ESA. As the TSAT level increases from 20% to 50%, the response rate to IV iron is diminished and the time to response is prolonged. Hence, for patients with TSAT levels between 20% and 50%, the decision to offer IV iron should be reserved for those in whom the benefits are likely to outweigh the risks. Future studies on the parameters that make patients more or less likely to benefit from IV iron, as well as studies of alternative dose schedules of IV iron, are needed.

None of the studies on iron supplementation in conjunction with ESAs provided instruction on how or when to re-dose iron after the initial cumulative dose has been given. Generally, repeat iron studies are not recommended within 3 to 4 weeks of administration. Clinicians may consider repeating iron studies when the MCV declines or hypochromic RBCs are seen on the peripheral blood smear. Additionally, repeat iron studies can be considered for patients with anemia that does not respond to iron supplementation 4 to 6 weeks after administration of the total

intended dose.^{340,344} If evidence exists of iron overload, do not administer IV iron. Subsequent doses of iron should be withheld if the serum ferritin exceeds 800 ng/mL or if the TSAT exceeds 50%.³³⁹⁻³⁴¹

Since the majority of studies show that IV iron is superior to oral iron, the panel recommends that IV iron supplementation be used in most clinical circumstances. Low-molecular-weight iron dextran, ferric gluconate, iron sucrose, ferric carboxymaltose, and ferumoxytol 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.³⁴⁷⁻³⁴⁹ Dosage details for administering IV iron therapy are listed in the algorithm (see *Recommendations for Administering Parenteral Iron Products* 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).³³⁸ Increases in Hb concentration were greater with IV iron dextran (groups 3 and 4) compared to oral iron or no iron ($P < .02$). Importantly, there was no difference between the oral and no iron groups ($P = .21$). Additionally, there was no statistically significant difference between groups 3 and 4 ($P = .53$), suggesting that lower, intermittent doses of IV iron dextran are equally as efficacious as TDI. Most adverse events associated with iron dextran, such as headaches, dizziness, nausea, vomiting, and diarrhea, occurred with high-molecular-weight iron dextran.³⁵⁰ Therefore, the recommended iron dextran product is low-molecular-weight iron dextran.³⁵¹ Test doses are required for iron dextran (25 mg slow IV push over 1–2 minutes; if tolerated, follow with 75 mg IV bolus for a total dose of 100 mg).³³⁸ As reactions to the IV iron dextran test dose may be severe, premedication of the patient should occur prior to administration of the test dose.



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

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.³⁴¹ 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.³⁴² 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 CIA with non-myeloid malignancies undergoing chemotherapy, patients were treated with darbepoetin alfa with or without IV ferric gluconate every 3 weeks for 16 weeks.³³⁹ Erythropoietic responses were improved in the IV ferric gluconate arm. Most significantly, this was the first study to associate IV iron with fewer RBC transfusions in patients with cancer (9% vs. 20%; $P = .005$).

Iron Sucrose

A randomized controlled trial involving 64 patients with gynecologic cancers compared the efficacy of IV iron sucrose to oral ferrous fumarate for the primary prevention of anemia (ie, patients did not present with anemia).³⁵² In this study, patients were given a single dose of 200 mg iron sucrose following each course of chemotherapy infusion for 6 cycles. The

number of patients requiring a blood transfusion was double in the oral iron group compared to the IV iron sucrose group (56.3% vs. 28.1%; $P = .02$). Furthermore, patients receiving IV iron sucrose who received transfusion required 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.³⁴⁰ 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 iron group.

Ferric Carboxymaltose

An observational study by Steinmetz et al³⁵³ evaluated the use of ferric carboxymaltose with and without an ESA in patients with cancer. Of the 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 median Hb levels to greater than 11 g/dL within 5 weeks of treatment.³⁵³ 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) when measured over a 3-month period.³⁵⁴ A retrospective analysis of 303 anemic patients with gastrointestinal cancers 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 (interquartile range [IQR]: -0.1 to 1.6) g/dL.³⁵⁵ In the randomized clinical IVICA trial, which included 116 anemic colorectal cancer patients, preoperative administration of ferric carboxymaltose resulted in higher Hb levels after surgery compared to oral ferrous sulfate (11.9 vs. 11.0 g/dL;



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

$P = .002$).³⁵⁶ 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.³⁵⁷ Preoperative treatment with ferric carboxymaltose in patients with colon cancer and anemia was also 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 patients not receiving IV iron.³⁵⁸

Ferric carboxymaltose has been associated with severe phosphate deficiency that is often asymptomatic.³⁵⁹⁻³⁶³ Lack of awareness of this complication causes delayed time to diagnosis and results in significant morbidity.³⁵⁹ Therefore, patients receiving ferric carboxymaltose should be closely monitored for hypophosphatemia.

Ferumoxytol

Ferumoxytol is a colloidal iron oxide that is indicated for the treatment of iron-deficiency anemia in patients with CKD or an intolerance or poor response to oral iron.³⁶⁴⁻³⁶⁶ However, ferumoxytol has not been prospectively evaluated in patients with CIA.³⁶⁷ In a phase III trial involving patients with anemia due to various causes, 81.1% of patients treated with ferumoxytol achieved an Hb increase greater than or equal to 2.0 g/dL at week 5 compared to only 5.5% of patients given placebo ($P < .0001$).³⁶⁶ However, only a small percentage of patients in this study had cancer ($n = 39$).³⁶⁶ Although a positive trend in favor of ferumoxytol was demonstrated in the cancer subgroup compared with placebo (ferumoxytol, 51.7% vs. placebo, 30.0%; $P < .2478$), the difference was not statistically significant.³⁶⁶ In a randomized phase III study of patients with iron-deficiency anemia who had not responded to oral iron, ferumoxytol was noninferior to iron sucrose as measured by the proportion of patients who had greater than or equal to 2 g/dL increase in Hb from baseline to week 5

(84% with ferumoxytol vs. 81.4% with iron sucrose).³⁶⁵ However, noninferiority was not reached in the cancer subgroup ($n = 31$), potentially due to the small sample size. A recent post-hoc analysis of pooled data from these two trials found that both ferumoxytol and iron sucrose produced significant increases in Hb from baseline compared to placebo (1.8 g/dL, $P < .0001$ and 1.9 g/dL, $P = .002$, respectively) in a subgroup of 98 patients with cancer.³⁶⁷

It should be noted that ferumoxytol may cause interference with MRI, causing potential false interpretation of organ iron overload.³⁶⁸ 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. However, ferric derisomaltose has not been prospectively evaluated in patients with CIA. Ferric derisomaltose was shown to be non-inferior to iron sucrose in increasing Hb levels based on two randomized phase III trials in patients with iron-deficiency anemia.^{369,370} The FERWON-IDA trial demonstrated that a single dose of IV ferric derisomaltose at 1000 mg resulted in a significantly more rapid hematologic response in the first two weeks, more rapid reduction in fatigue, and a similar safety profile compared to repeated doses of iron sucrose.³⁶⁹ The FERWON-NEPHRO trial of iron-deficiency anemia patients with CKD demonstrated that ferric derisomaltose induced a non-inferior 8-week hematologic response, lower rates of hypersensitivity reactions, and a significantly lower incidence of cardiovascular adverse events compared to iron sucrose.³⁷⁰ Additionally, the PHOSPHARE trials demonstrated that the incidence of hypophosphatemia was significantly lower following ferric derisomaltose treatment compared to ferric carboxymaltose.³⁷¹ The phase III



NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

PROFOUND trial analyzed the safety and efficacy of ferric derisomaltose for the treatment of iron-deficiency anemia in 350 patients with cancer.³⁷² Results showed that ferric derisomaltose was non-inferior to oral iron sulfate for change in Hb concentration from baseline to week 4. A faster onset of Hb response was observed with ferric derisomaltose and a higher proportion of patients treated with oral iron experienced adverse drug reactions. Hypophosphatemia was reported at similar low frequencies among 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 398000/μL. She does not have CKD. Serum folate, vitamin B₁₂ levels, indirect bilirubin, and serum LDH are within normal limits. Bleeding has ceased, but given her baseline anemia and red cell indices, iron studies have 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 less than 30 ng/mL and a TSAT level less than 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.³³⁸

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

With low ferritin and normal TSAT levels, we can postulate that iron stores are becoming depleted. Iron is being mobilized, but signs of iron-restricted erythropoiesis are beginning to emerge. If the ferritin and TSAT levels are discordant, the low ferritin level should take precedence to determine if IV iron therapy would be beneficial. 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 greater than 100 ng/mL could be treated with IV iron. However, an ESA should be considered first because as the ferritin level moves across the spectrum from absolute iron deficiency to iron overload, the response to either an ESA or IV iron will diminish.



NCCN Guidelines Version 2.2023 Hematopoietic Growth Factors

Concomitant IV iron can be considered as it may increase the percentage of patients who respond to the ESA as well as reduce the time to response.

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

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

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

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

1 (mild)	10 – <lower limit of normal
2 (moderate)	8 – <10
3 (severe)	<8
4 (life-threatening)	Life-threatening consequences; urgent intervention indicated
5 (death)	Death

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

Table 2. Correction Factor for RPI Calculation

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

Tables

Table 1. National Cancer Institute Anemia Scale

Grade	Scale (hemoglobin level in g/dL)
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NCCN Guidelines Version 2.2023

Hematopoietic Growth Factors

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NCCN Guidelines Version 2.2023

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