National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer- and Chemotherapy-Induced Anemia

Version 2.2018 — November 21, 2017

NCCN.org

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NCCN Guidelines Version 2.2018 Panel Members
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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2018 Updates Cancer- and Chemotherapy-Induced Anemia

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Updates in Version 2.2018 of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from Version 1.2018 include:

MS-1

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

Updates in Version 1.2018 of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from Version 2.2017 include:

General

- **All details about the REMS program have been removed. Former page ANEM-C has been deleted.**

ANEM-1

- **The following has been added to the list of possible causes of anemia to consider: "Hormone dysfunction (ie, hypogonadism, adrenal dysfunction, hyper/hypothyroidism)."**
- **The last line of footnote "d" has been revised: "Fasting is preferred when testing for serum iron *and* total iron-binding capacity~~, and serum ferritin~~."**

ANEM-3

- **Revision to line above the table: "~~Listed below are~~ *Discuss the following* risks and goals *with patients when considering ~~of each~~* anemia treatment *options:*"**
- **Bullets added below the table:**
  - **Discuss the risks of ESAs with patients including the potential for tumor growth, death, blood clots, and serious heart problems.**
  - **Refer patients to the following medication guides for more information on the benefits and risk of ESAs: Epoetin Alfa Medication Guide and Darbepoetin Alfa Medication Guide**

ANEM-4

- **For patients undergoing palliative treatment, added clinical trial as an option for patients to consider based on preference.**
- **The following option has been revised where recommended for special categories in considering ESA use: "Consider ESAs by FDA ~~indications/~~dosing/dosing adjustments~~, under REMS guidelines, with informed consent of patient~~."**
- **Footnote removed: "Health care providers prescribing ESAs need to enroll in the ESA APPRISE Oncology Program. See REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis-Stimulating Agents (ESAs) (ANEM-C)."**

ANEM-A

- **Last bullet and sub-bullet removed: "Anemia in setting of acute coronary syndromes or acute myocardial infarction: Transfusion goal is unclear and is being evaluated. Consider clinical context and published guidelines."**

ANEM-B (4 of 5)

- **Under ESA-Neutralizing Antibodies, the last line has been revised: "Patients should not be *immediately* switched to other ESA products as antibodies may cross-react."**

ANEM-C (2 of 3)

- **For dosage administration of total dose infusion of low-molecular-weight iron dextran, added: "Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h." Addition was made based on the following reference: Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: A multicenter, open-label, randomized trial. Journal of Clinical Oncology 2004;22:1301-1307.**

ANEM-D

- **Bullet revised: "Consider use of ESAs for select patients by FDA ~~indications/~~dosing/dosing adjustments~~, under REMS guidelines, with informed consent of patient~~."**
- **Bullet removed: "In addition, prior approval from third-party payers should be sought to prevent increasing the financial burden of the patient."**

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HEMOGLOBIN CONCENTRATION TO PROMPT AN EVALUATION OF ANEMIA

EVALUATION OF ANEMIA[a,b]

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

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

→

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

- **First check**
  - **Reticulocyte count[c] and mean corpuscular volume (MCV)**
- **Then consider**
  - **Hemorrhage (stool guaiac, endoscopy)**
  - **Hemolysis (direct antiglobulin test [DAT], disseminated intravascular coagulation [DIC] panel, haptoglobin, indirect bilirubin, lactate dehydrogenase)**
  - **Nutritional (iron, total iron-binding capacity, ferritin, B_{12}, folate)[d]**
  - **Inherited (prior history, family history)**
  - **Renal dysfunction (Glomerular filtration rate [GFR] <60 mL/min/1.73 m^2)**
  - **Radiation-induced myelosuppression**
  - **Hormone dysfunction (ie, hypogonadism, adrenal dysfunction, hyper/hypothyroidism)**
- **See Evaluation of Iron Deficiency (ANEM-5)**

Treat as indicated

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

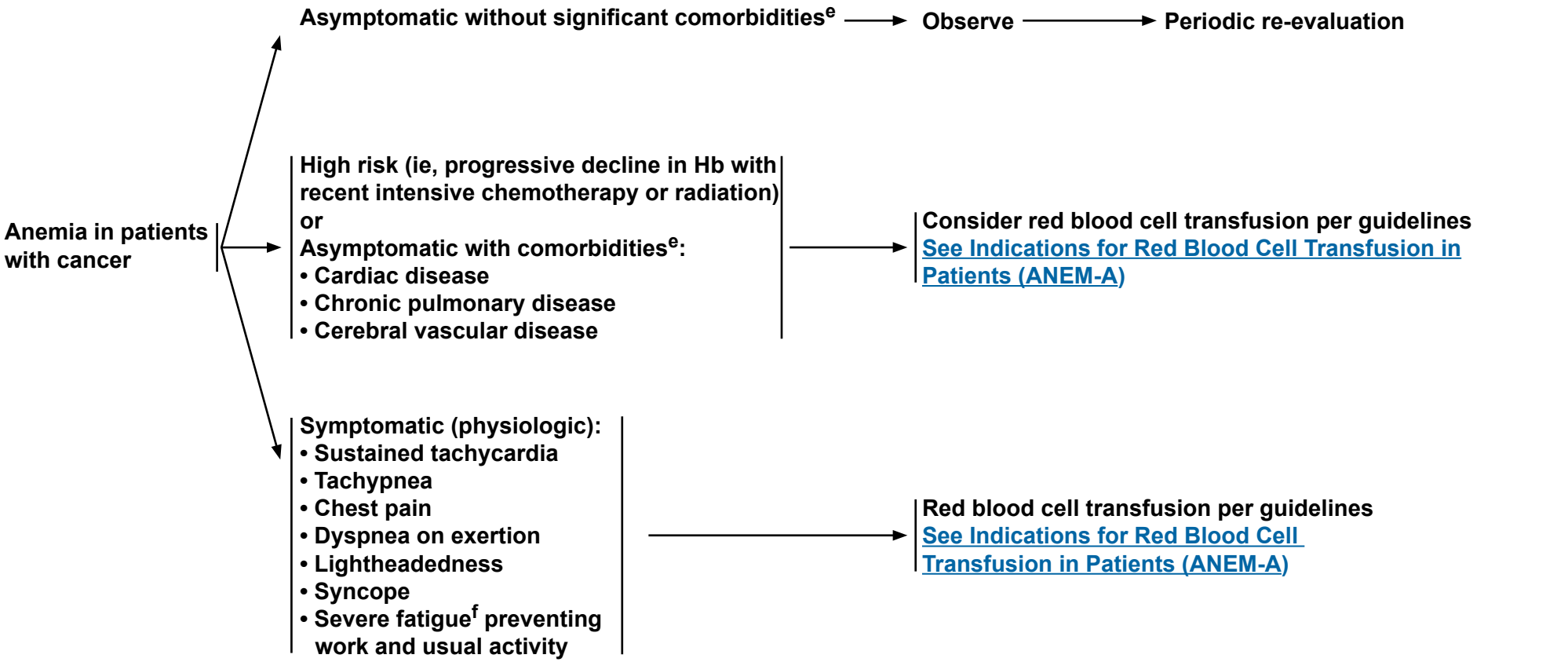
Myelodysplastic syndromes → **See NCCN Guidelines for Myelodysplastic Syndromes**

Myeloid malignancies or Acute lymphoblastic leukemia → **Treat underlying disease per NCCN Guideline**
See NCCN Guidelines Table of Contents

[a]The NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia were formulated in reference to adult patients.
[b]This is a basic evaluation for possible causes of anemia.
[c]Correct reticulocyte count for degree of anemia. See Discussion.
[d]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. Fasting is preferred when testing for serum iron and total iron-binding capacity.

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.

RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING



See Comparison of Risks and Goals of ESA Use Versus Red Blood Cell Transfusion (ANEM-3)

See Special Categories in Considering ESA Use (ANEM-4)

[e]Degree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating red blood cell transfusion.
[f]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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COMPARISON OF RISKS AND GOALS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION[g]

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

	ESA in the Cancer Setting	Red Blood Cell Transfusion
Risks	• Increased thrombotic events • Possible decreased survival • Time to tumor progression shortened	• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury) • Transfusion-associated circulatory overload (TACO) • Virus transmission (eg, hepatitis, HIV) • Bacterial contamination • Iron overload • Increased thrombotic events • Possible decreased survival • Alloimmunization • Increased risk of poor response to future platelet transfusions due to HLA immunization
Goals	• Transfusion avoidance • Gradual improvement in anemia-related symptoms	• Rapid increase of Hb and hematocrit levels • Rapid improvement in anemia-related symptoms

See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-B)

When considering ESAs:

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

[g]See Discussion for detailed information regarding the risks and benefits of ESA use and red blood cell transfusion.

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SPECIAL CATEGORIES IN CONSIDERING ESA USE

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

Patient undergoing palliative treatment[h] →

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

Consider based on patient preferences:
- **ESAs by FDA dosing/dosing adjustments[j,k]** →
  or
- **Red blood cell transfusion per guidelines (See ANEM-A)**
  or
- **Clinical trial**

→ **See Evaluation of Iron Deficiency (ANEM-5)**

Select patients who refuse blood transfusions → **Consider ESAs by FDA dosing/dosing adjustments[j,k]**
See Management of Patients Who Refuse Blood Transfusions (ANEM-D) →

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

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

[h] See Comparison of Risks and Goals of ESA Use Versus Red Blood Cell Transfusion (ANEM-3).

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

[j] See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-B).

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

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

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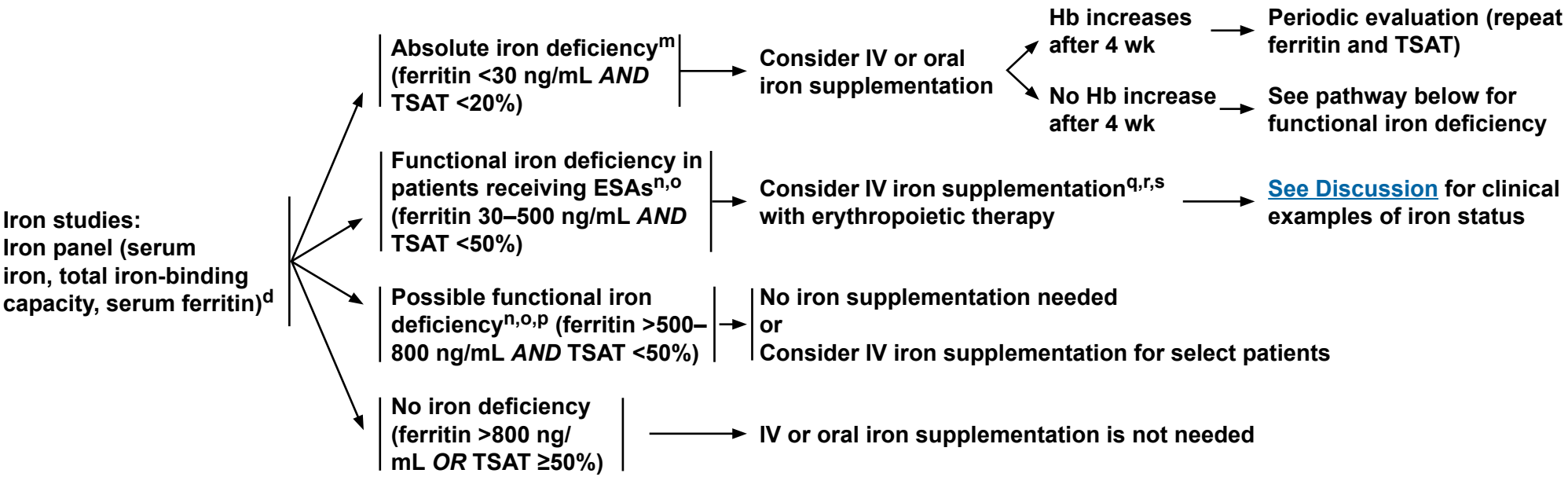

See Parenteral Iron Preparations (ANEM-C)

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

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

[n]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.

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

[p]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.

[q]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-C).

[r]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.

[s]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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INDICATIONS FOR RED BLOOD CELL TRANSFUSION IN PATIENTS[a,b,c]

Goal: Prevent or treat deficit of oxygen-carrying capacity in blood

Asymptomatic Anemia

- **Hemodynamically stable chronic anemia:**
  - **Transfusion goal to achieve Hb >7 g/dL.**

Symptomatic Anemia

- **Acute hemorrhage with evidence of hemodynamic instability or inadequate oxygen delivery:**
  - **Transfuse to correct hemodynamic instability and maintain adequate oxygen delivery.**

- **Symptomatic (including tachycardia, tachypnea, postural hypotension) anemia:**
  - **Transfusion goal to maintain Hb as needed for prevention of symptoms.**

[a]The AABB has also made recommendations regarding appropriate levels for red blood cell transfusion. See Discussion for details. (Carson JL, Grossman BJ, Kleinman S, et al; for the Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2012;157:49-58; Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines from the AABB: Red blood cell transfusion thresholds and storage. JAMA 2016, in press.)

[b]If there is a regimen (either research or standard protocol) for which a higher hemoglobin is required for full-dose treatment, it would be acceptable to be more aggressive with the hemoglobin target.

[c]See Management of Patients Who Refuse Blood Transfusions (ANEM-D).

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (1 of 5)[1-4]

INITIAL DOSING	TITRATION FOR NO RESPONSE	TITRATION FOR RESPONSE
PACKAGE INSERT DOSING SCHEDULE		
Epoetin alfa 150 units/kg 3 times per wk by subcutaneous injection	→ Increase dose of epoetin alfa to 300 units/kg 3 times per wk by subcutaneous injection	• The dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid red blood cell transfusion. • If Hb reaches a level needed to avoid transfusion or increases >1 g/dL in any 2-wk period, reduce dose by 25% for epoetin alfa and by 40% for darbepoetin alfa.
or		
Epoetin alfa 40,000 units every wk by subcutaneous injection	→ Increase dose of epoetin alfa to 60,000 units every wk by subcutaneous injection	
or		
Darbepoetin alfa 2.25 mcg/kg every wk by subcutaneous injection	→ Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection	
or		
Darbepoetin alfa 500 mcg* every 3 wks by subcutaneous injection		
ALTERNATIVE REGIMENS		
Darbepoetin alfa 100 mcg fixed dose every wk by subcutaneous injection	→ Increase darbepoetin alfa to up to 150–200 mcg fixed dose every wk by subcutaneous injection[5]	
or		
Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection[7]	→ Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection[6]	
or		
Darbepoetin alfa 300 mcg* fixed dose every 3 wks by subcutaneous injection	→ Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection[7]	
or		
Epoetin alfa 80,000 units every 2 wks by subcutaneous injection[8]		
or		
Epoetin alfa 120,000 units every 3 wks by subcutaneous injection[9]		

See Footnotes and References (ANEM-B 2 of 5)

See Erythropoietic Therapy - Adverse Effects (ANEM-B 3 of 5)

*Data indicate that darbepoetin alfa 300 mcg is equivalent in terms of efficacy to darbepoetin alfa 500 mcg for initial dosing.[10]

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 of 5)

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

Footnotes

[1]The head-to-head comparisons of regimens are inconclusive with regard to superiority of one drug over another. Schwartzberg LS, Yee LK, Senecal, FM, et al. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. Oncologist 2004;9:696-707. Waltzman R, Croot C, Justice G, et al. Randomized comparison of epoetin alfa (40 000 U weekly) and darbepoetin alfa (200 mcg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist 2005;10:642-650. Grant MD, Piper M, Bohlius J, et al. AHRQ Comparative Effectiveness Reviews. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

[2]Less-frequent dosing regimens could be considered as an alternative to dose reduction.

[3]The dosages and regimens included in this table have been evaluated in patients with cancer receiving chemotherapy.

[4]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-C).

References

[5]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.

[6]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.

[7]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.

[8]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.

[9]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.

[10]Auerbach M, Silberstein PT, Webb RT, et al. Darbepoetin alfa 300 or 500 mcg 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-B 1 of 5)

See Erythropoietic Therapy- Adverse Effects (ANEM-B 3 of 5)

Note: All recommendations are category 2A unless otherwise indicated.
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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: http://www.fda.gov/cder/drug/infopage/RHE/default.htm. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.
- While three meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,[9,10-12] two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.[13,14]
- Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.[15-17]
- The risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL.
- Additional prospective clinical trials designed and powered to measure survival of patients with cancer are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus red blood cell transfusion. (See Comparison of Risks and Goals of ESA Use Versus Red Blood Cell Transfusion - ANEM-3).
- Recent studies suggest that use of ESAs may be deleterious when used in patients with metastatic breast cancer. See Discussion.

Thrombosis

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

Erythropoietic Therapy - Adverse Effects continued (ANEM-B 4 of 5)

See References (ANEM-B 5 of 5)

Note: All recommendations are category 2A unless otherwise indicated.
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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 of 5)

Hypertension/Seizures

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

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

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

See References (ANEM-B 5 of 5)

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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)

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Note: All recommendations are category 2A unless otherwise indicated.
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PARENTERAL IRON PREPARATIONS[1-7] (1 of 3)

- **Parenteral iron preparations studied in patients with cancer:[b]**
  - **Low-molecular-weight iron dextran**
  - **Ferric gluconate**
  - **Iron sucrose**
  - **Ferric carboxymaltose[a]**
- **Five[2-6] of six[8] studies have shown that parenteral iron products show improved Hb response rates in treating absolute or functional iron deficiency in patients with cancer who are receiving ESAs.**
  - **None of the six studies provided instruction on how or when to redose 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 if/when the MCV is <80 fL, or if/when evidence of hypochromic red blood cells is seen in the peripheral blood.**
  - **If treatment with iron fails after 4 to 6 weeks and after the total intended dose has been administered, repeat iron studies may be considered.[5,8] Patients should be monitored for evidence of iron overload, including signs and symptoms of cardiomyopathy, endocrinopathy, and hepatotoxicity. If evidence exists of iron overload, do not administer IV iron. Subsequent doses of iron should be withheld if the serum ferritin exceeds 1000 ng/mL[5,6] or TSAT exceeds 50%.[2]**
- **Test doses are required for low-molecular-weight iron dextran, but not for ferric gluconate, iron sucrose, or ferric carboxymaltose. Test doses are strongly recommended for ferric gluconate and iron sucrose if patients have exhibited sensitivities to low-molecular-weight iron dextran or other IV iron preparations, or if they have multiple drug allergies.**
- **High-molecular-weight iron dextran is not recommended.[9,10]**
- **Patients with an active infection should not receive IV iron therapy.**

See Recommendations for Administering Parenteral Iron Products (ANEM-C 2 of 3)

See References (ANEM-C 3 of 3)

[a]Ferric carboxymaltose has not been prospectively evaluated and therefore should only be considered when other parenteral iron preparations fail.[7] Ferric carboxymaltose is indicated for adult patients when oral iron is not tolerated or there is a limited response. It is also indicated for patients with non-dialysis–dependent chronic kidney disease.[11,12]

[b]Ferumoxytol is indicated for the treatment of iron deficiency in adult patients with chronic kidney disease. There are no data to show the efficacy of ferumoxytol in patients with cancer. Ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.[13]

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PARENTERAL IRON PREPARATIONS[1-6] (2 of 3)[a]

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran[15,c]	Ferric Gluconate[16,c]	Iron Sucrose[17,c]
Test dose[d]	Test dose required: 25 mg slow IV push	Test dose at MD discretion based on risk factors for reaction.	Test dose at MD discretion based on risk factors for reaction.
Dosage[14,e]	100 mg IV over 5 min[3] • Repeated dosing given once weekly for 10 doses to achieve total dose of 1 g or • Total dose infusion given over several hours[18,f] ▸ Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h[19]	125 mg IV over 60 min[2,4,5,8] • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommended based on published trial results[8] • Total treatment course = 1000 mg	200 mg IV over 60 min[6] • Repeated dosing given every 2–3 wks or 200 mg IV over 2–5 min • Repeated dosing given every 1–4 wks • Individual doses above 300 mg are not recommended[20] • Total treatment course = 1000 mg
Routes	IV infusion IM (not recommended)	IV injection/infusion	IV injection/infusion

[a]Ferric carboxymaltose has not been prospectively evaluated and therefore should only be considered when other parenteral iron preparations fail.[7] Ferric carboxymaltose is indicated for adult patients when oral iron is not tolerated or there is a limited response. It is also indicated for patients with non-dialysis–dependent chronic kidney disease.[11]

[c]Examples of adverse events associated with FDA-approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness. Adverse effects associated with low-molecular-weight iron dextran may be delayed 24–48 hours.

[d]Premedications should be given prior to the IV iron test dose as reactions to the test dose may be severe.

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

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

See References (ANEM-C 3 of 3)

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PARENTERAL IRON PREPARATIONS[1-6] (3 of 3)

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

- **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) has been used to increase blood oxygenation.**
- **To reduce blood loss, minimize phlebotomy, use pediatric tubes, and batch test.**
- **Prior to initiation of myelosuppressive chemotherapy:**
  - **Consider anemia risk when making treatment decisions**
  - **Consider daily folic acid and B_{12} supplementation**
  - **Evaluate and correct baseline coagulation abnormalities**
  - **In patients with high clinical suspicion of folate and vitamin B_{12} deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using intravenous (IV) iron.**
- **Consider use of ESAs for select patients by FDA dosing/dosing adjustments.**
  - **ESAs are NOT recommended for:**
    - ◊ **Patients with cancer not receiving chemotherapy**
    - ◊ **Patients receiving non-myelosuppressive therapy**
    - ◊ **Patients receiving myelosuppressive chemotherapy with curative intent**
  - **Therefore, if ESAs are prescribed off-label for the indications listed immediately above, patients should be made aware of the potential increased risks of thrombosis and tumor progression, and should know that under these circumstances the ESAs are being used off-label.**

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise indicated.

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Overview

Cancer- and chemotherapy-induced anemia (CIA) is prevalent, occurring in 30% to 90% of patients with cancer.[1] Correction of anemia can be achieved by either treating the underlying etiology or by providing supportive care that may entail transfusion with packed red blood cells (PRBCs) or administration of erythropoiesis-stimulating agents (ESAs), with or without iron supplementation. The first ESA approved by the U.S. Food and Drug Administration (FDA) for the treatment of anemia in patients receiving myelosuppressive chemotherapy was epoetin alfa, a recombinant human erythropoietin (rhEpo). A second-generation rhEpo, darbepoetin alfa, has also been FDA-approved for this indication.

The pathophysiologic origins of anemia can be grouped into three categories: 1) decreased production of functional red blood cells (RBCs); 2) increased destruction of RBCs; and 3) blood loss. Hence, anemia is characterized by a decrease in hemoglobin (Hb) concentration, RBC count, or hematocrit (Hct) to subnormal levels. The degree of anemia can be graded according to the anemia scale provided by the National Cancer Institute (Table 1).

Table 1. National Cancer Institute Anemia Scale

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

Source: Adapted from the Common Terminology Criteria for Adverse Events. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

The purpose of these NCCN Guidelines is two-fold: 1) to operationalize the evaluation and treatment of anemia in adult patients with cancer, with an emphasis on patients with anemia who are receiving concomitant chemotherapy; and 2) to enable the patient and clinician to assess anemia treatment options in the context of an individual patient's condition.

The NCCN Guidelines start with an evaluation of anemia to delineate the etiology. This is followed by a risk assessment to determine the initial intervention plan. Individual patient risk factors and comorbidities may affect the prescribed course of treatment. Further information is provided for treatment options including RBC transfusion, erythropoietic therapy, and iron monitoring and supplementation. These guidelines are mainly focused on patients with solid tumors and lymphoid malignancies. For anemia associated with myelodysplastic syndromes (MDS), myeloid malignancies, and acute lymphoblastic leukemia, clinicians are referred to relevant guidelines listed in the NCCN Guidelines for Treatment of Cancer by Site.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Cancer and Chemotherapy-Induced Anemia, an electronic search of the PubMed database was performed to obtain key literature published between 03/14/2016 and 03/10/2017**,** using the following search terms: cancer anemia or cancer-related anemia or cancer-induced anemia or chemotherapy-induced anemia or chemotherapy anemia or chemotherapy-related anemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[2]

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

The PubMed search resulted in 75 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Etiology

Causes of anemia in patients with cancer are often multifactorial, adding to the complexity of evaluation.[3] Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, nutritional deficiencies, hereditary disease, renal insufficiency, hormone dysfunction, or a combination of these factors.[4,5] The malignancy itself can lead to or exacerbate anemia in a number of ways.[6] 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 even shorten RBC survival. Chronic blood loss at tumor sites from blood vessels or organ damage can further 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 capability. For this myriad of reasons, anemia is prevalent among patients with cancer at initial presentation. For example, 32% of non-Hodgkin's lymphoma patients and 49% of patients with gynecologic cancers are anemic at diagnosis.[7,8] In addition, the myelosuppressive effect of many chemotherapy agents is a significant contributing factor to anemia for patients undergoing cytotoxic treatment.[9,10] Radiation therapy (RT) to the skeleton is also associated with hematologic toxicity. In a retrospective analysis, approximately one-third of the 210 patients undergoing craniospinal RT for treatment of primary tumors of the central nervous system developed grade 3 and 4 hematologic side effects.[11]

Newer modalities, such as immunotherapies, may also have an associated risk of anemia, though data are limited.[12,13] A recent study recognized hemolytic anemia as a potential complication of treatment with nivolumab, an anti-PD-1 antibody.[14] Although a definitive link between the use of nivolumab and the development of autoimmune hemolytic anemia has not been clearly established, several reported cases of autoimmune hemolytic anemia after use of nivolumab have been recently documented in the literature, including a case of fatal autoimmune hemolytic anemia refractory to steroids in a patient treated with nivolumab for metastatic lung cancer.[15-17] In another case report, a 52-year-old woman with malignant melanoma undergoing sequential treatment with ipilimumab (an anti-CTLA-4 antibody) and pembrolizumab (another anti-PD-1 antibody) presented with acute autoimmune hemolytic anemia with pure red-cell aplasia, a potentially life-threatening complication.[18] Therefore, clinicians should become familiar with the adverse effects of immunotherapy drugs, including hemolytic anemia, and be observant for other less documented clinical conditions as these therapies become more prevalent in cancer care.

Anemia Associated with Myelosuppressive Chemotherapy

Chemotherapeutic agents induce anemia by directly impairing hematopoiesis in the bone marrow, including disruption of RBC precursor synthesis.[6] Additionally, nephrotoxic effects of particular cytotoxic agents (eg, platinum-containing agents) can lead to anemia through decreased production of erythropoietin by the kidneys.[6]

Studies have identified patients with lung cancer and gynecologic malignancies as having particularly high incidences of chemotherapy-induced anemia (CIA).[8,9] Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well-known to induce anemia due to combined bone marrow and kidney toxicities.[9] It is important to review the toxicity profile of each agent as newer regimens may or may not cause anemia. This is evidenced by the comparison of single-agent cabazitaxel, docetaxel, and enzalutamide, which have been shown to cause grade 3 to 4 anemia in 11%, 9%, and 0% of patients, respectively.[19-21]

The myelosuppressive effects of particular cytotoxic agents are likely to accumulate over the course of repeated cycles of therapy, resulting in a steady increase in the rate and severity of anemia with additional chemotherapy cycles. For example, in the European Cancer Anaemia Survey (ECAS)[8], 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.[8] 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.[6]

Screening Evaluation

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 of 11 g/dL or less should prompt an evaluation of anemia in a patient with cancer. For patients with a high baseline level, a drop of 2 g/dL or more is also cause for concern and assessment. As discussed above, a patient with cancer may suffer from anemia as the result of a combination of causes, some of which may not be directly related to the cancer (reviewed by Gilreath et al[3]). The overall goals of evaluation are to characterize the anemia and identify any potentially correctable underlying comorbidities prior to initiating treatment.

Initial Assessment

Initial broad characterization of anemia involves a complete blood count (CBC) with indices to determine if other cytopenias are present. A visual review of the peripheral blood smear morphology is critical to confirm the size, shape, and Hb content of RBCs. A detailed history and physical exam must be taken. The history should include the onset and duration of symptoms, comorbidities, family history, and whether there has been any exposure to antineoplastic drugs or radiation. Common complaints are syncope, exercise dyspnea, headache, vertigo, chest pain, fatigue that is disruptive to work and daily activities, and abnormal menstruation in female patients. Pallor may be apparent. A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that cancer-related fatigue is less likely to be ameliorated by rest (see NCCN Guidelines for Cancer-Related Fatigue).[22] The above clinical manifestations are neither sensitive nor specific to the type of anemia. Clinicians should watch out for signs of underlying etiologies such as jaundice, splenic enlargement, neurologic

symptoms, blood in the stool, petechiae, and heart murmur, among others.

Approaches to Evaluation

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

- Microcytic (<80 fL)—most commonly caused by iron deficiency; other etiologies include thalassemia, anemia of chronic disease, and sideroblastic anemia.
- Macrocytic (>100 fL)—most commonly caused by medications[23] 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 inadequate absorption from lack of intrinsic factor. Macrocytosis accompanies increased reticulocyte counts following brisk hemorrhage or hemolysis.
- Normocytic (80–100 fL)—may be due to hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation, or renal insufficiency. The key follow-up test is the reticulocyte (immature RBC) count (see below).

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

- RI = Reticulocyte count (%) x [(observed Hct)/(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 x (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, B_{12}/folate deficiency, aplastic anemia, or bone marrow dysfunction due to cancer or cancer-related therapy (eg, radiation, myelosuppressive chemotherapy).
- High RI/RPI ratio (>1) indicates normal RBC production, suggesting blood loss or hemolysis in the anemic patient.

Table 2: Correction Factor for RPI Calculation

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

A comprehensive review to the follow-up and treatment of each subtype of anemia related to causes independent of myelosuppressive cancer therapy is beyond the scope of this guideline. However, a summary of some additional signs and symptoms of common underlying ailments and/or informative diagnostic tests are as follows:

- Nutritional deficiency—low iron and elevated total iron-binding capacity (TIBC) and/or low vitamin B_{12} or red cell folate levels (commonly tested together with iron studies). Ferritin values are also useful in evaluating iron stores. Fasting values are preferred for serum iron and TIBC studies.
- Hemorrhage—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 m^2 for three or more consecutive months.
- Inherited anemia—personal and family history.
- Sideroblastic anemia—sideroblasts present in bone marrow biopsy.

Clinicians are advised to consult the *Iron Monitoring and Supplementation* section for details on management of iron deficiency. Any other cause of anemia that may be rectified independent of cancer therapy should be treated as indicated. When no such etiology is identified, the effects of cancer-related inflammation and/or myelosuppressive chemotherapy (if applicable) should be considered the cause of anemia.

Follow-up Risk Assessment

If the likely cause of anemia is cancer-related inflammation and/or myelosuppressive chemotherapy (for solid tumors or lymphoid malignancies), a risk assessment of the anemia is necessary to determine the initial intervention plan. The decision regarding the best treatment is dependent on many factors. While PRBC transfusion is the only option if the patient requires an immediate boost in Hb levels, consideration of ESA therapy and iron supplementation may be warranted for the long-term management of anemia as determined by risk assessment.

Red Blood Cell Transfusion

The decision to offer PRBC transfusion should not be made on the basis of whether the Hb level of the patient has reached a certain threshold or “trigger.” Instead, the NCCN panel outlines three general categories: 1) asymptomatic without significant comorbidities, for which observation and periodic re-evaluation are appropriate; 2) high risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation) or asymptomatic with comorbidities (eg, cardiac disease, chronic pulmonary disease, cerebral vascular disease), for which transfusion can be considered; and 3) symptomatic, for which patients should receive transfusion.

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 leuko-reductions, γ-irradiation, freezing, and washing. Patients who are immunocompromised may need PRBCs that are cytomegalovirus negative. One unit of PRBCs (300 cc) can have an Hct ranging from 50% to 80%, and typically contains 42.5 to 80 g of Hb (with 147–278 mg of iron) or 128 to 240 mL of pure RBCs.[24]

Benefits of Transfusion

The major benefit of transfusion with PRBCs, offered by no other anemia treatment, is a rapid increase in Hb and Hct levels. Hence, PRBC transfusion is the only option for patients who require immediate correction of anemia. Transfusion of 1 unit (300 cc) of PRBCs has been estimated to result in an average increase in Hb level by 1 g/dL or in Hct level by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.[24,25] It should be noted that patients receiving concomitant fluid resuscitation may not experience an Hb increase of 1 g/dL per unit of blood transfused.

Results from a number of studies evaluating the impact of transfusion on mortality in patients with cancer have been conflicting, with some studies showing a survival benefit for patients receiving transfusion. For example, in a study of 56 consecutive patients with unresectable esophageal cancer receiving chemoradiation therapy, blood transfusion was associated with an increase in overall survival (OS) (hazard ratio [HR], 0.26; 95% CI, 0.09–0.75, P = .01).[26] A retrospective study of data collected from 605 patients with carcinoma of the cervix evaluated Hb levels prior to therapy and through completion of therapy. Patients with high Hb levels prior to therapy had a significant increase in disease-free survival and OS. Patients who were transfused to increase Hb levels had a survival rate that was similar to patients who had the same initial Hb value but did not receive transfusion. Therefore, blood transfusion may reduce the negative prognostic implication of low Hb.[27]

Risks of Transfusion

Risks associated with PRBC transfusion include transfusion-related reactions, transfusion-associated circulatory overload, virus transmission, bacterial contamination, iron overload (reviewed by Spivak, Gascon, and Ludwig[28]), and alloimmunization of RBCs or platelets. Since 1984, the introduction of numerous safety interventions to screen the U.S. blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections.[29,30] Bacterial infection is the most common form, and occurred as frequently as 1 in 3000 random-donor samples before the mandate of bacterial screening in 2004.[30] Since the implementation of screening, fewer than 10 deaths from bacterial sepsis per year have been reported. Pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse event.[31,32]

Khorana et al[33] analyzed data from discharge summaries of patients with cancer admitted to 60 U.S. medical centers between 1995 and 2003 and found increased risks ($P < .001$) of venous thromboembolism (VTE) (overall risk [OR], 1.60; 95% CI, 1.53–1.67), arterial thromboembolism (OR, 1.53; 95% CI, 1.46–1.61), and in-hospital mortality (OR, 1.34; 95% CI, 1.29–1.38) associated with PRBC transfusions.[33] However, the increased thrombotic events and decreased survival may reflect a bias of more severe anemia and/or more advanced cancer in patients who required transfusions. A cause-effect relationship could not be established due to the retrospective nature of the study. Therefore, greater investigation into the relationship between blood transfusions and the incidence of VTE and mortality is warranted.

RBC alloimmunization can be a significant complication for patients who are chronically transfused. It has been reported that 15% of transfusion-dependent patients with MDS or chronic myelomonocytic leukemia have alloimmunization.[34,35] Platelet alloimmunization may also occur. Antibodies against HLA antigens can cause platelet transfusion refractoriness, which can translate into increased patient bleeding, prolonged hospitalization, and decreased survival.[36,37]

Iron Overload

The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anemia (eg, patients with MDS).[38] However, iron overload is unlikely to occur in patients receiving transfusions that are limited to the time period corresponding to chemotherapy treatment (usually <1 year). As previously mentioned, each transfusion of PRBCs contains 147 to 278 mg of unexcretable excess iron.[24] When iron stores become saturated, iron remains as non-transferrin–bound iron.[39] Typically after 10 to 15 transfusions of PRBCs, excess iron will have deposited in the liver, heart, skin, and endocrine organs. Patients experiencing iron overload may present with fatigue, dark skin, arthralgia, hepatomegaly, cardiomyopathy, or endocrine disorders. Benefits of PRBC transfusion need to be weighed against the risks of cumulative cardiac and hepatic toxicities.[40,41]

Serum ferritin levels and any associated end-organ dysfunction need to be monitored in patients requiring chronic PRBC transfusions. While a survival benefit to chelation therapy has not been shown in patients requiring transfusion support for cancer-induced anemia or MDS, the general target value is a ferritin level of less than 800 mcg/L. Imaging modalities such as FerriScan and T2 star-weighted cardiac MRI provide useful organ-specific iron overload assessment.[42,43]

Transfusion Goals and Basic Principles

There is wide variation in reported PRBC transfusion practice,[29,44] but institutional and clinical practice guidelines are often “restrictive” regarding limiting exposure to allogeneic blood. A recent systematic review comparing the efficacy and safety of restrictive versus liberal transfusion strategies in patients with cancer found no difference in mortality or adverse events between the strategies.[45] Furthermore, restrictive transfusion strategies were associated with a 36% reduced risk of receiving a perioperative transfusion Therefore, restrictive transfusion strategies appear to decrease blood utilization without increasing morbidity or mortality in cancer patients.

The overall goal of transfusion is to treat or prevent deficiencies in the oxygen-carrying capacity of the blood, in order to improve oxygen delivery to bodily tissues. Transfusion is rarely indicated when the Hb level is above 10 g/dL.[46] The AABB (formerly the American Association of Blood Banks) published guidelines based on a systematic review of randomized trials evaluating transfusion thresholds and using GRADE

guidelines methodology.[44] AABB recommendations include: 1) using an Hb level of 7 g/dL as a threshold for hospitalized patients who are hemodynamically stable; 2) considering transfusions for hospitalized patients with pre-existing cardiovascular disease who have symptoms and an Hb level of 8 g/dL or less; and 3) making transfusion decisions for all patients based on symptoms as well as Hb levels. 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 nonhemolytic transfusion reactions.[47,48] 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.

Patients with Cancer Who Refuse Blood Transfusions

Patients with cancer-induced anemia or CIA who refuse blood transfusions are occasionally seen in clinical practice. Their religious beliefs or personal preferences prohibit them from using blood products in their treatment, so clinicians who agree to treat these patients must base treatment on limited available data. However, several strategies may be employed to reduce anemia. For example, intensive myelosuppressive chemotherapy would induce symptomatic anemia in most patients with cancer, but investigators have outlined strategies to permit such treatment to be given without transfusion.[49-51] Strategies include minimizing blood loss by restricting and/or batching routine laboratory testing, using pediatric blood collection tubes, using anti-fibrinolytic drugs for oral bleeding, aggressively treating mucositis, suppressing menses, and minimizing gastrointestinal bleeding by using proton pump inhibitors and stool softeners. Additionally, baseline coagulation abnormalities should be fully evaluated and corrected prior to myelosuppressive treatment.

Nutritional deficiencies have a low prevalence in both the general population[52,53] and in patients with cancer.[3,54] However, in patients with high clinical suspicion of folate and vitamin B_{12} deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using intravenous (IV) iron. ESAs may be considered for select patients; however, patients should be made aware of the potential increased risks of thrombosis and tumor progression. ESAs are not recommended for the following: 1) patients with cancer who are not receiving chemotherapy; 2) patients receiving non-myelosuppressive therapy; or 3) patients receiving myelosuppressive chemotherapy with curative intent. Lastly, in extreme cases with severe, life-threatening anemia, pure oxygen (400 mm Hg, S_AO_2 = 1.0) has been used to increase blood oxygenation.[50]

Erythropoietic Therapy

RBC production is normally controlled by erythropoietin, a cytokine produced in the kidneys. ESAs have been shown to stimulate erythropoiesis in patients with low RBC levels, though not all patients have disease that responds to ESA therapy. In a study of 2192 patients with cancer receiving ESA therapy, an Hb increase of greater than or equal to 1 g/dL was attained in 65% of patients.[55] Unlike transfusion, which immediately boosts the Hb level, ESAs can take weeks to elicit

an Hb response, but they are effective at maintaining a target Hb level with repeated administration.

Benefits of ESA Therapy

Elimination of symptoms and avoidance of transfusion are the main goals of ESA therapy. Use of ESAs has been demonstrated to decrease PRBC transfusion requirements in patients with cancer undergoing chemotherapy. In a randomized, placebo-controlled study by Littlewood et al,[56] epoetin alfa (when compared to placebo) was shown to reduce transfusion requirements (24.7% vs. 39.5%, *P* = .0057) and increase Hb levels (2.2 g/dL vs. 0.5 g/dL, *P* < .001) in patients with anemia receiving chemotherapy.[56] A double-blind, placebo-controlled, phase III study randomized 320 patients (Hb ≤ 11 g/dL) to receive darbepoetin alfa at 2.25 mcg/kg/wk or placebo.[57] Results showed that patients receiving darbepoetin alfa required fewer transfusions (27% vs. 52%; 95% CI, 14%–36%; *P* < .001) than patients receiving placebo. 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.[58] A decreased relative risk (RR) for transfusion was observed in patients receiving ESAs (RR, 0.65; 95% CI, 0.62–0.68).[58] Of the patients treated with ESAs, 25 out of 100 subsequently received a transfusion versus 39 out of 100 patients in the untreated group, equating to a one-unit reduction in transfusion in ESA-treated patients.

The first patient-level meta-analysis evaluating the efficacy of darbepoetin alfa treatment when initiated at Hb ≤10 g/dL in patients with CIA found that more patients who received darbepoetin alfa than placebo achieved an Hb increase of ≥1 g/dL (fixed-effects HR = 2.07; 95% CI, 1.62–2.63) or ≥2 g/dL (HR = 2.91; 95% CI, 2.09–4.06).[59] Transfusions were also less common in these patients (HR = 0.58; 95% CI, 0.44–0.77), confirming that darbepoetin alfa is effective at reducing the need for transfusion in patients with CIA when treatment is initiated at Hb ≤10 g/dL.

Risks of ESA Therapy

Risk for Thromboembolism

Increased thromboembolic events, including VTE, have been associated with ESA therapy in patients with cancer. The cause of VTE is complex with a heightened baseline risk related to both the malignancy itself and to chemotherapy (see NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease).[60-63] Other risk factors for VTE in patients with cancer include prior history of VTE, inherited or acquired mutations, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, immobility, steroids, and comorbidities such as hypertension.[64]

Results from meta-analyses established a significant association between ESA usage and increased risk of thrombotic events, with statistically significant risk and odds ratios ranging from 1.48 to 1.69.[58,65-69] A combined analysis of six trials using darbepoetin alfa by Glaspy et al [68] also found an increased trend of thromboembolism for patients with Hb >12 g/dL (RR, 1.66; 95% CI, 0.9–3.04) or in patients achieving a >1 g/dL Hb increase in 14 days (RR, 1.67; 95% CI, 0.96–2.88). An increased risk of stroke was associated with darbepoetin alfa in a clinical trial of patients with chronic kidney disease (CKD) (HR, 1.92; 95% CI, 1.38–2.68).[70] 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.[71]

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

signs and symptoms of thromboembolism in patients with cancer receiving ESAs.

Possible Increased Mortality and Tumor Progression

Since 2007, the FDA has made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa,[72,73] including the addition of black-box warnings. These strengthened FDA restrictions were based mainly on the results of 8 randomized studies that individually showed a decrease in OS and/or locoregional disease control with ESA usage in advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers.[74-81] Of the 8 studies, 4 studies investigated ESA effects in patients who underwent chemotherapy, 2 studies involved patients receiving radiotherapy alone, and 2 studies involved patients receiving neither chemotherapy nor radiotherapy. All 8 trials had an off-label target Hb level over 12 g/dL.

A randomized phase III noninferiority study by Leyland-Jones et al compared epoetin alfa versus best supportive care for the treatment of CIA in women with metastatic breast cancer (n = 2098).[82] The primary endpoint of progression-free survival (PFS) (based on investigator-determined disease progression) did not meet noninferiority criteria. Therefore, non-inferiority of epoetin alfa was not established and transfusions remain the preferred treatment for anemia in patients with metastatic breast cancer.

Worsened health outcomes associated with the use of ESAs have also been observed in 5 meta-analyses of 51 to 91 randomized controlled trials when targeting Hb levels >12 g/dL.[58,65,67,69,83,84] These analyses reported increased mortality in patients receiving ESAs with statistically significant RR/HR of 1.17 (95% CI, 1.06–1.30),[83] 1.15 (95% CI, 1.03–1.29),[69] 1.10 (95% CI, 1.01–1.20),[65] 1.17 (95% CI, 1.06–1.29),[58] and 1.17 (95% CI, 1.04–1.31), respectively.[67] Data from the Cochrane Database also reported increased mortality in patients with Hb >12 g/dL.[58] This suggests that increased mortality could be reduced by more conservative target Hb levels. In keeping with current treatment practice, data from a systematic review by the Agency for Healthcare Research and Quality (AHRQ) determined that delaying ESA treatment until Hb is <10 g/dL resulted in fewer thromboembolic events and a reduced mortality. However, the optimal duration of therapy could not be determined from the limited data set.[67]

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 based on HR/odds ratios of 0.97 (95% CI, 0.85–1.1)[68] and 1.06 (95% CI, 0.97–1.15).[66] Trials with off-label use of rhEpo, in both the adjuvant and neoadjuvant settings, reported no decrease in survival with ESA use in patients with CIA when an Hb target of 13 g/dL was used.[85-87] The PREPARE trial found no difference in 3-year OS (darbepoetin alfa, 88.4% vs. no darbepoetin alfa, 91.5%; HR, 1.26; 95% CI, 0.86–1.85; P = .237), though there was a trend towards decreased disease-free survival in the darbepoetin alfa–treated group that failed to reach statistical significance (darbepoetin alfa, 74.3% vs. no darbepoetin alfa, 80.0%; HR, 1.31; 95% CI, 0.999–1.74; P = .061).[74,87] The phase III WSG-ARA trial that included 1234 patients with early-stage breast cancer receiving adjuvant ESA therapy is the first to evaluate survival as the primary endpoint.[88] In this study, no impact on event-free survival (EFS) (darbepoetin alfa, 89.3% vs. no darbepoetin alfa, 87.5%; $P_{\text{log-rank}}$ = 0.55) or OS (darbepoetin alfa, 95.5% vs. no darbepoetin alfa, 95.4%; $P_{\text{log-rank}}$ = 0.77) was observed. There was an increase in venous thrombosis with darbepoetin alfa (darbepoetin alfa, 3% vs. no darbepoetin alfa, 1%; P = .013), though no increase was seen in pulmonary embolism (0.3%, both groups). The incidence of

grade 2 anemia was higher in patients who were not treated with darbepoetin alfa (darbepoetin, 10.9% vs. no darbepoetin, 23.8%; *P* = .025). These results suggest that the value of darbepoetin alfa may be dependent on other risk factors, including patient comorbidities, type of cancer, type of cancer treatment, and treatment intent. It should be noted that ESAs are not recommended for patients treated with curative intent outside of a clinical trial. There are also data from randomized studies that show no increase in mortality in patients receiving chemotherapy for small cell lung cancer (SCLC) when ESAs are given according to the prescribing label.[89,90]

Another meta-analysis of 3 randomized, placebo-controlled trials in Japanese patients with CIA did not show increased mortality associated with the use of ESAs.[91] In this study, 511 patients with either solid tumors or lymphoma were treated with epoetin beta or darbepoetin alfa. The efficacy endpoints in this study included PRBC transfusion and transfusion trigger (ie, Hb below 8 g/dL) from week 5 until the end of treatment. Safety endpoints were determined by OS and thromboembolic events. The risk of transfusion was reduced by 53% with ESA treatment compared to placebo (RR, 0.47; 95% CI, 0.29–0.76), while OS was equivalent (HR, 1.00; 95% CI, 0.75–1.34; median, 13.3 months). The rates of thromboembolic events were 0.7% in the ESA-treated patients and 1.7% in the placebo group (*P* = NS; no deaths). The study authors highlight several differences between this study and the Cochrane Database report. The first is the time period in which these trials were conducted. The recent analysis included trials occurring between 2006 and 2009, during which there was awareness of the possible association between ESA use and increased mortality. Therefore, patients were more likely to have greater supervision as indicated by the requirement of Hb monitoring at least weekly and the establishment of pre-determined cut-off values for the discontinuation of ESAs.

Risk for Hypertension/Seizures

Seizures have been reported in patients with chronic renal failure receiving ESAs.[72] While it is unclear whether patients with cancer receiving ESA therapy are at risk for seizures, Hb levels should be monitored before and during the use of ESAs to decrease the risk for these adverse events. Additionally, an increased risk for hypertension with ESA usage was reported by a Cochrane review (RR, 1.30; 95% CI, 1.08–1.56).[58]

Risk for Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count and loss of bone marrow erythroblasts caused by the development of neutralizing antibodies against erythropoietin. A marked rise in incidence (191 cases) of PRCA was observed from 1998 to 2004, though 90% of cases occurred with an epoetin alfa product used outside of the United States.[92,93] Causation was attributed to formulations without human serum albumin, subcutaneous (SC) administration, and uncoated rubber stoppers.[94] Interventions, designed accordingly, reduced the incidence of PRCA by 83%. In 2005, the FDA interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia, with or without other cytopenias, resulting in a class label change for all ESAs.[72,73] This toxicity has been reported predominantly in patients with chronic renal failure receiving SC ESAs.

NCCN Recommendations

In 2017, the FDA determined that the ESA Risk Evaluation and Mitigation Strategy (REMS) program is no longer necessary to ensure that the benefits of ESA therapy outweigh its risks of shortened OS and/or increased risk of tumor progression or recurrence in patients with

cancer.[95] 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.[72] 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 and NSCLC, lymphomas, and testicular cancer, among others. An exception to this may be SCLC, for which there are trials demonstrating no negative impact on survival or disease progression with ESA use (see earlier discussion).[89,90] Additionally, ESAs are not recommended for use in patients with cancer who are not receiving therapy, patients receiving non-myelosuppressive therapy, or patients receiving myelosuppressive therapy in whom the anemia can be managed by transfusion. Patients undergoing palliative treatment may consider ESA therapy, transfusion, or participation in a clinical trial, depending on their preferences and personal values. The NCCN Guidelines Panel recognizes that it is not always clear whether a chemotherapy regimen is considered curative. Under these circumstances, given that no other cause of anemia has been identified, physicians should first consider PRBC transfusion or clinical trial enrollment, if available, for anemia management. When considering anemia treatment options, physicians should discuss the risks of ESA use with patients, including the potential for tumor growth, blood clots, serious heart problems, and death. Upon the decision to use an ESA, physicians are advised to use the lowest dose necessary to eliminate symptoms and avoid transfusion.

CKD is an independent indication for ESA therapy. Adverse events occurring with the use of ESAs in these patients appear to be associated with high doses and/or high-target Hb levels. Hence, the FDA label mandates individualized dosing to reduce the need for RBC transfusions. Controlled clinical trials have associated increased risks of mortality and adverse cardiovascular outcomes with ESA use in CKD patients when targeted to Hb levels >11 g/dL.[70,71,96-99] In the study by Pfeffer et al[70] comparing darbepoetin alfa to placebo, a significant increase in cancer-related death was seen in CKD patients with pre-existing cancer at baseline treated with ESA therapy (P = .002). However, another study of patients with CKD stages 4 and 5 did not find an increased incidence of cancer in patients receiving ESAs.[97] Additionally, data from Seliger et al[71] 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.[71] Since almost one-third of patients with end-stage renal disease are also afflicted with cancer, they represent a unique subgroup that requires personalized use of ESAs based on very careful evaluation of risks and benefits (reviewed by Bennett et al[100]). For example, CKD patients not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor carefully dosed ESAs over transfusion to treat severe anemia. In the scenario where the patient with CKD has a curable solid tumor, ESAs should not be administered during chemotherapy. However, they may be used with caution after chemotherapy is complete, keeping in mind the possibility of recurring disease. Risk for thrombosis must be taken into account as part of the risk-benefit ratio.

Most patients receiving a hematopoietic cell transplant will require transfusion support. Nonetheless, ESA therapy may be useful in some instances.[101,102] For example, ESAs may be administered post-transplant to increase the Hct in order to allow phlebotomy to treat

transfusional iron overload. There have also been reports of ESA efficacy in patients who refuse blood transfusions while undergoing autologous cell transplantation.[103-105] Post-transplant use of ESAs for patients undergoing cancer chemotherapy, patients with renal insufficiency, or patients with recurrent/secondary MDS should follow guidelines for chemotherapy-related anemia, CKD, or MDS, respectively.

Iron studies should accompany ESA therapy to monitor the development of iron deficiency. These include serum iron, TIBC, and serum ferritin. The NCCN panel recommends that any patient with cancer who develops a sudden loss of response to ESAs, accompanied by severe anemia and a low reticulocyte count, should be evaluated for the etiology of loss-of-effect. ESAs should be withheld while plasma is sent to ESA-manufacturing pharmaceutical companies for evaluation by assays that measure binding and neutralizing antibodies to erythropoietin. 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.

Dosing Schedules

Epoetin alfa and darbepoetin alfa are considered equivalent by the NCCN panel. Recommended initial dosing schedules for patients receiving chemotherapy are summarized in the algorithm. The most common initial dosing schedules for epoetin alfa evaluated in clinical trials of patients with cancer are 150 units/kg 3 times weekly administered SC[56,106] and 40,000 units once weekly administered SC[77,80,81,107] (see *Erythropoietic Therapy – Dosing and Titration* in the algorithm). Both of these initial dose schedules are listed in the package insert and are recommended by NCCN. Other dosing ranges and schedules of epoetin alfa may be considered, including an extended dosing of 80,000 units administered SC every 2 weeks[108] and a dose of 120,000 units administered SC once every 3 weeks.[109]

Although darbepoetin alfa doses were initially administered at 2.25 mcg/kg SC every week,[57,75,110] there has been interest in implementing either fixed doses or higher doses at decreased frequency. A randomized trial compared weekly dosing at 2.25 mcg/kg versus fixed dosing at 500 mcg every 3 weeks in 705 patients with non-myeloid malignancies and an Hb level <11 g/dL. The percentage of patients achieving the target Hb level (≥11 g/dL) was 77% in the weekly arm and 84% for patients receiving darbepoetin alfa every 3 weeks.[110] Both of these schedules are listed in the package insert. Dosing once every 3 weeks was further refined in 2 studies by reducing the dose to 300 mcg. Initially, a multicenter, open-label study of 1493 patients showed that 79% of patients receiving this ESA dose achieved a target Hb level ≥11 g/dL.[111] A head-to-head comparison with 500 mcg in a phase II, randomized study of patients with nonmyeloid malignancies further confirmed the efficacy of 300 mcg. In this study, patients were given either 300 or 500 mcg of darbepoetin alfa with or without concurrent iron therapy. 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).[112] Other studies have demonstrated the safety and efficacy of alternative dosing schedules for darbepoetin alfa. These include a fixed weekly dose of 100 mcg[57] and a fixed dose of 200 mcg every 2 weeks.[113] In addition to the dosing schedules on the package insert, the NCCN panel recommends these alternative regimens to support the delivery of the lowest ESA dose possible while maintaining efficacy.

Response Assessment and Dose Titration

Response to ESA therapy is assessed to determine whether the initial dose should be reduced, escalated, or withheld. Decisions related to

ESA dose adjustment are based on the goal of maintaining the lowest Hb level sufficient to avoid transfusion.

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

Conversely, the ESA dose should be increased according to the algorithm (see *Erythropoietic Therapy – Dosing and Titration*) for patients receiving chemotherapy who show no response (<1 g/dL Hb increase) following 4 weeks of epoetin alfa or 6 weeks of darbepoetin alfa treatment. A subsequent response at 8 or 9 weeks may necessitate a dose escalation to avoid transfusion. Iron supplementation can be considered to improve response to ESA therapy. ESA therapy should be discontinued and PRBC transfusion should be considered in patients showing no response despite iron supplementation after 8 or 9 weeks of therapy. ESAs should be discontinued when chemotherapy is completed or withdrawn.

Iron Monitoring and Supplementation

Intravenous Iron and Oral Iron

Iron can be administered in oral form or parenteral form (low-molecular-weight iron dextran, ferric gluconate, and iron sucrose).[114] Evidence from 6 published studies utilizing iron in conjunction with an ESA suggest that IV iron is superior to oral iron.[115-120] A recent study indicated that the addition of parenteral iron to ESA therapy for the treatment of CIA improved hematopoietic response, reduced the need for RBC transfusions, and increased Hb levels when compared to oral iron supplementation.[120] Eligibility criteria for these trials varied widely (serum ferritin requirement ranging from >10 ng/mL to <900 ng/mL and a TSAT level requirement ranging from >15% to <60%). Only one study provided guidelines for TSAT monitoring,[118] while 2 studies provided guidelines for ferritin monitoring.[112,117]

A randomized controlled trial comparing the efficacy of IV iron sucrose versus oral ferrous fumarate in patients with gynecologic cancer (n = 64) evaluated the use of IV iron monotherapy for the “primary prevention” of anemia (ie, patients did not present with anemia).[121] 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 blood transfusion was double in the oral iron group compared to the IV iron group (56.3% vs. 28.1%; $P = .02$). Furthermore, patients receiving IV iron required transfusion for a fewer number of treatment cycles versus the oral iron group (0 vs. 0.5 cycle; $P = .04$), with fewer total units of PRBCs (0 vs. 0.5 units; $P = .05$). Neither group experienced hypersensitivity reactions or other serious adverse events. However, constipation occurred in a greater percentage of patients in the control group compared to the IV iron group (40.6% vs. 3.1%; $P < .001$).[121]

A prospective, multicenter, open-label trial randomized 157 patients with CIA receiving epoetin alfa to: 1) no iron; 2) oral iron; 3) iron dextran IV bolus; or 4) iron dextran total dose infusion (TDI).[115] Increases in Hb concentration were greater with IV iron (groups 3 and 4) compared to oral supplementation 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 are equally as efficacious as TDI. In a second open-label study by Henry et al,[118] 187 anemic patients with cancer receiving chemotherapy and epoetin alfa were randomized to no iron, oral ferrous sulfate 3 times daily, or

weekly IV ferric gluconate. The Hb response rate (≥2 g/dL increase) was higher in the IV arm (73%) compared to the oral (45%) or no iron (41%) arms. A third study enrolled 67 patients with lymphoproliferative malignancies not undergoing chemotherapy.[117] Patients were randomized to weekly epoetin beta with or without IV iron sucrose. Although an oral iron arm was not included, IV iron resulted in a higher mean change in Hb level from baseline (2.76 g/dL vs. 1.56 g/dL, *P* = .0002) and a higher Hb level response rate (≥2 g/dL increase; 87% vs. 53%, *P* = .0014) compared to the no iron group.

In a 2008 study, Bastit et al[116] reported their open-label trial evaluating 396 CIA patients with non-myeloid malignancies undergoing chemotherapy (Hb <11 g/dL).[116] Patients were treated with darbepoetin alfa with or without IV iron (iron sucrose or ferric gluconate 200 mg every 3 weeks for 16 weeks). Erythropoietic responses and time to reach the target Hb level were better in the IV iron 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). In a study by Pedrazzoli et al,[119] 149 patients with solid tumors and CIA were randomly assigned to receive weekly darbepoetin alfa with or without ferric gluconate. This was the first trial that excluded patients with absolute iron deficiency; eligibility requirements included a serum ferritin level >100 ng/mL and a TSAT level ≥20%. The ESA/IV iron group showed a higher hematopoietic response rate compared to the control group (93% vs. 70%, respectively; *P* = .0033). Taken together, these studies demonstrated that concurrent IV iron enhanced hematologic response to ESAs. However, there is insufficient evidence to determine whether iron supplementation can allow for an ESA dose decrease. Long-term effects of IV iron supplementation in patients with cancer were not assessed in any of these trials.

In 2011, Steensma et al[122] published findings from the largest trial to date that initially challenged these positive results. Patients with CIA (n = 502) were randomized 1:1:1 to receive IV ferric gluconate, oral ferrous sulfate, or oral placebo in combination with darbepoetin alfa. Initial analysis of this data led the authors to conclude that IV iron failed to confer any benefit in terms of Hb response, transfusion rate, or quality of life compared to oral iron or placebo. However, problems with the study design (including a suboptimal IV iron dosing regimen and a high proportion of participant dropouts) could explain the lack of response to IV iron observed in this study.[123] Another possible reason for the lack of response seen initially may have been that the mean baseline TSAT level for patients in the IV iron group was 22.5%, a value above what is considered to be associated with functional iron deficiency.[122,123] Indeed, further analysis of study data indicated that even though the change in TSAT during the study period did not differ significantly between the 3 arms, the median serum ferritin rose markedly in the IV iron group compared to the other cohorts, suggesting that the total body iron balance was substantively increased in the IV iron arm.[124] However, Steensma et al note that although this positive result suggests that IV iron offers benefits to some patients, it is not yet clear which patients with CIA would benefit most from IV-administered iron. Therefore, developing clearer insight into the parameters that make patients more or less likely to respond to IV iron, as well as studies of alternative dose schedules of IV iron, are warranted.[124]

A systematic review and meta-analysis evaluating the role of iron supplementation included 11 randomized controlled trials analyzing IV iron versus standard of care in patients with CIA.[125] Nine trials incorporated ESAs into treatment, 3 trials compared IV iron to oral iron as the standard of care, and 6 trials compared IV iron to no iron. IV iron supplementation versus no iron in patients treated with ESAs showed a

significantly higher rate of hematopoietic response (n = 7 trials; RR, 1.28; 95% CI, 1.125–1.45; I^2 = 68.1%; random effects model) and significantly reduced transfusion rates compared to standard of care (n = 7 trials; RR, 0.76; 95% CI, 0.61–0.95). Reduction in the number of blood transfusions was also seen in the 2 trials without ESAs (RR, 0.52; 95% CI, 0.34–0.80). IV iron was superior to both no iron (n = 6 trials; RR, 1.21; 95% CI, 1.12–1.31) and oral iron (n = 3 trials; RR, 1.37; 95% CI, 0.92–2.05), and time to response was faster in the IV iron group (range, 36–54 days) versus the standard of care group (range, 46–94 days). IV iron but not oral iron was associated with improved hematopoietic response rates compared to ESAs alone. No difference in adverse events was found (n = 4 trials; RR, 0.99; 95% CI, 0.93–1.04), including thromboembolic events (n = 4 trials; RR, 1.03; 95% CI, 0.59–1.80) and cardiovascular events (n = 6 trials; RR, 1.08; 95% CI, 0.65–1.78). There was also no difference in all-cause mortality at the end of follow-up (n = 7 trials, 1470 patients; RR, 1.13; 95% CI, 0.75–1.70).

Ferric carboxymaltose is FDA-approved for patients with CKD or an intolerance or poor response to oral iron.[126,127] It has also been evaluated for the treatment of iron-deficient anemia in patients with inflammatory bowel disease,[128-130] chronic heart failure,[131,132] and other conditions.[118,133-135] The observational study from Steinmetz et al[136] evaluated its use in patients with cancer. Of the 639 adult patients from 68 cancer centers in Germany, safety data could be obtained for 619 patients. With doses ranging from 600 to 1500 mg of ferric carboxymaltose, adverse drug reactions were seen in 14 (2.3%) patients and were primarily related to the gastrointestinal tract. Of the 233 patients with follow-up Hb measurements, a median increase of 1.4 g/dL (range, 1.3–1.5 g/dL) was observed with an overall increase in median Hb levels to >11 g/dL within 5 weeks of treatment with ferric carboxymaltose.[136] A second observational study of 367 patients with solid tumors or hematologic malignancies demonstrated improved median Hb levels following ferric carboxymaltose alone or in combination with an ESA (1.3 g/dL vs. 1.4 g/dL, respectively) when measured over the 3-month observational period.[137] Stable median Hb levels ≥11 g/dL were reached in patients without signs of iron overload. These data suggest that ferric carboxymaltose may be an effective and well-tolerated treatment for CIA.

There remains a paucity of both safety and efficacy data for the use of ferumoxytol in patients with cancer. Ferumoxytol is a colloidal iron oxide that was FDA-approved in 2009 for the treatment of iron deficiency anemia in patients with CKD. A phase III trial (n = 812 patients) investigating the use of ferumoxytol in patients with anemia due to various causes randomized patients to receive ferumoxytol (n = 608) or placebo (n = 200).[138] Following treatment with ferumoxytol, 81.1% of patients achieved the primary endpoint (Hb increase ≥2.0 g/dL at week 5) compared to only 5.5% of patients given placebo ($P < .0001$). After 5 weeks, Hb levels ≥12 were seen in 50.5% of patients treated with ferumoxytol versus 2.0% of patients receiving placebo ($P < .0001$). The incidence of serious adverse events was similar between the two groups (ferumoxytol, 2.6% vs. placebo, 3.0%). While this ferumoxytol study indicates that the drug is well tolerated and can effectively correct anemia, only a small percentage of patients in this study had cancer (n = 39); ferumoxytol was given to 29 of these patients and placebo was given to 10 patients.[138] 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.[138] In a randomized phase III study of patients with iron deficiency anemia that had not responded to oral iron, ferumoxytol showed noninferiority to iron sucrose as measured by the proportion of patients who had at least a 2 g/dL increase in Hb from baseline to week 5 following treatment with ferumoxytol (84%; n = 406) versus iron sucrose (81.4%; n = 199).[139] In the cancer subgroup (n =

31), there was a trend toward favoring ferumoxytol (54.8%) compared to iron sucrose (38.5%). However, noninferiority was not reached, potentially due to the small sample size. It should be noted that ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.[140] 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.

NCCN Evaluation and Definitions of Iron Status

Iron deficiency is reported in 32% to 60% of patients with cancer, most of whom are also anemic.[141] Iron studies, including serum iron, TIBC, and serum ferritin, should be performed prior to ESA treatment in order to rule out absolute iron deficiency, which may respond to oral or IV iron monotherapy without an ESA. Serum iron and TIBC levels may be falsely elevated by diet (reviewed in Collings et al[142]); therefore, fasting is recommended to provide more accurate measurements. Transferrin saturation should be calculated from these values using the following formula:

- TSAT = (serum iron level x 100)/TIBC

Treatment for iron deficiency is guided by iron status, defined in these guidelines as absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. In the absence of a universal numerical definition of iron deficiency in relevant studies, the NCCN panel recognizes that ferritin and TSAT values defining absolute and functional iron deficiencies represent moving targets.[3] 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 iron, and high TIBC that result in a TSAT level <20% and a ferritin level <30 ng/mL. If the TSAT and ferritin parameters are discordant, a low ferritin value should take precedence in determining whether iron supplementation will be beneficial. The reference interval for serum ferritin depends on the specific laboratory used, but in general, the lower the level, the more probable that true iron deficiency is present.

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. 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. Periodic evaluation of ferritin and TSAT levels is required as some patients, especially those with continued internal bleeding, may suffer a relapse. 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.[143] Hence, IV iron supplementation is not recommended for patients with an active infection.

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

Functional Iron Deficiency

Functional iron deficiency is defined in these guidelines as a ferritin level between 30 ng/mL and 500 ng/mL and a TSAT level <50%. Functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production is deficient. IV iron supplementation with erythropoietic therapy should be

considered. IV iron monotherapy in patients with functional iron deficiency who are not receiving ESA therapy can reduce the number of RBC transfusions. Patients who are receiving ESA therapy are also likely to benefit from IV iron supplementation.

While Hb and TSAT levels will be low, ferritin levels usually remain within normal limits or elevated (laboratory diagnosis of this condition was detailed by Thomas et al[144]). Functional iron deficiency may result from cases where infection or inflammation blocks iron transport to the bone marrow, as seen in anemia of chronic disease. Another form of functional iron deficiency often arises following continued ESA use, resulting in a blunted erythropoietic response to anemia. Hence, iron supplementation will eventually be required in most patients in order to maintain optimal erythropoiesis.[145,146] IV iron supplementation in combination with erythropoietic therapy should be considered.

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

Possible Functional Iron Deficiency

Possible functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production *may* be deficient. These patients are defined by a TSAT level <50% and a ferritin level of >500 ng/mL to 800 ng/mL. Although clinical trials suggest that these patients may have functional iron deficiency, there are insufficient data to support the routine use of IV iron in this setting. Administration of IV iron to these patients should be individualized with the goal of avoiding allogeneic transfusion.

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

No Iron Deficiency

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

NCCN Recommendations for the Management of Iron Deficiency

As previously discussed, most studies show that IV iron is superior over oral iron and should be used in most circumstances.[115-119] Low-molecular-weight iron dextran, ferric gluconate, and iron sucrose are recommended parental iron preparations. Ferric carboxymaltose has not been prospectively evaluated, and therefore should only be considered when other parental iron preparations fail. It is indicated for adult patients when oral iron is not tolerated or there is a limited response. Although ferumoxytol is indicated for the treatment of iron deficiency in adult patients with CKD, it has not been adequately evaluated in patients with cancer and may cause interference with MRI scans causing potential false interpretation of organ iron overload.[140]

Common adverse events following FDA-approved doses of parenteral iron include hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness.[147-149] Most adverse events associated with iron dextran occurred with high-molecular-weight iron dextran.[150] Therefore, the recommended iron dextran product is low-molecular-weight iron dextran.[151] Test doses are required for iron dextran, and are strongly recommended for patients receiving ferric gluconate or iron sucrose who are sensitive to iron dextran or have other drug allergies. As reactions to the IV iron test dose may be severe, pre-medication of the patient should occur prior to the test dose. Anaphylaxis-like reactions occur within minutes of the test dose but respond readily to IV epinephrine, diphenhydramine, and corticosteroids. It should be noted that patients may develop a reaction to IV iron 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.[152] Severe acute adverse reactions include anaphylaxis with dyspnea, hypotension, chest pain, angioedema, or urticaria. Dosage details for administering parenteral iron therapy are listed in the algorithm (see *Recommendations for Administering Parenteral Iron Products*).

Patients with a baseline TSAT level <20% had a higher response rate to IV iron supplementation when given in addition to an ESA. As the TSAT level increases from 20% to 50%, the response rate is diminished, and the time to a response is prolonged. Hence, for this group, IV iron should only be offered if benefits are likely to outweigh risks.

None of the 6 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.

For patients with anemia that fails to respond to iron supplementation 4 to 6 weeks after administration of the total intended dose, repeat iron studies may be considered.[117,122] 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 level exceeds 50%.[116-118]

Individuals with a ferritin level >800 ng/mL or a TSAT level ≥50% do not require iron supplementation as they are not considered iron-deficient.

Clinical Examples of Iron Status

The following clinical scenarios illustrate how iron studies may guide iron and ESA treatment of anemia in patients with cancer.

Patient Case

FM is a 59-year-old female with no significant past medical history. In addition to a 2-month history of early satiety and 9 kg weight loss, she presented to her primary care provider after acute onset of bloody stools. Abdominal imaging revealed a colon mass and mesenteric lesions. She was referred to an oncologist. Biopsy of the colon mass demonstrated a poorly differentiated adenocarcinoma. Her oncologist has begun palliative treatment with FOLFOX plus bevacizumab, a myelosuppressive regimen. After 2 cycles of chemotherapy, her CBC results are as follows: Hb 8.8 g/dL, Hct 26.7%, MCV 73 fL, reticulocytes 0.8%, mean corpuscular Hb 25 pg, red cell distribution width 18.2%, and platelets 398,000/µL. She does not have CKD. Serum folate and vitamin B_{12} levels are within normal limits. Indirect bilirubin and serum LDH are within normal limits. Bleeding has ceased, but given her baseline anemia and red cell indices, iron studies have also been ordered. Five different scenarios are provided below to illustrate the potential management of this patient depending on various ferritin and TSAT combinations.

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

With a ferritin level <30 ng/mL and a TSAT level <20%, this patient has absolute iron deficiency and would benefit from iron repletion. Reducing transfusion requirements remains the goal of therapy. With a baseline Hb of 8.8 g/dL, imminent chemotherapy initiation, and very low iron stores, IV iron repletion is preferred. Oral iron may not supply bioavailable iron rapidly enough in certain patients.[115]

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

With low ferritin and normal TSAT levels, we can postulate that iron stores are becoming depleted. Iron is being mobilized, but signs of iron-restricted erythropoiesis are beginning to emerge. If the ferritin and

TSAT levels are discordant, the low ferritin level should take precedence to determine if IV iron therapy would be beneficial to the patient. Iron would be beneficial in this patient as these laboratory values potentially reflect a transition from an iron-replete to an iron-deficient state. For the same reasons as discussed in scenario 1, IV iron is preferred. 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 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 in excess of 100 ng/mL could be treated with IV iron, as discussed in scenario 2. However, in this instance, an ESA should be considered first. This is because as the ferritin level moves across the spectrum from absolute iron deficiency to iron overload, the response to either an ESA or iron will diminish. As a result of limited data to currently support IV iron added to an ESA for patients with a ferritin greater than 800 ng/mL,[153] iron should be withheld until hyporesponsiveness to the ESA is noted, or until other signs or symptoms of iron deficiency arise. 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 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 of therapy and 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 he or she is iron replete. In this scenario, an ESA may be considered. ESA use induces functional iron deficiency by increasing iron utilization without the compensatory ability to mobilize storage iron in a timely manner. Therefore, iron repletion can be initiated if a response to ESA 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.

Future Development

In the face of current controversy in various aspects of anemia management, well-designed trials are required to answer questions regarding the safety of ESAs for lower-target Hb levels, the role of IV iron in reducing transfusion needs, the optimal dose and frequency of IV iron, and both short- and long-term effects of iron supplementation, among others.

Several novel IV iron agents are currently being studied as monotherapy (without an ESA) in patients with CIA. More information

about these agents can be found at www.clinicaltrials.gov. Other areas for future development include identification of iron deficiency markers. Soluble transferrin receptor level has been suggested as a marker of iron deficiency that can aid in differential diagnosis.[154] However, studies are still needed to evaluate the role of this marker in patients with CIA.

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