National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer- and Chemotherapy-Induced Anemia

Version 2.2016

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NCCN Guidelines Version 2.2016 Panel Members
Cancer- and Chemotherapy-Induced Anemia

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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 specified.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2016 Updates Cancer- and Chemotherapy-Induced Anemia

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Updates in Version 2.2016 of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from Version 1.2016 include:

MS-1

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

Updates in Version 1.2016 of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from Version 2.2015 include:

ANEM-3

- **"Benefits" was changed to "goals" in the page title and in the table: "Comparison of Risks and Goals ~~Benefits~~ of ESA Use Versus Red Blood Cell Transfusion."**

ANEM-4

- **Under "Special Categories in Considering ESA Use," the following category was added: "Patients not receiving therapy or palliative treatment, or those on non-myelosuppressive therapy." For that category, ESA use is not recommended.**

ANEM-A

- **Under "Asymptomatic Anemia," the first bullet was revised: "Hemodynamically stable chronic anemia ~~without acute coronary syndrome~~"**
- **Under "Sympotmatic Anemia," the last sub-bullet was revised: "Transfusion goal ~~to maintain Hb ≥10 g/dL~~ *is unclear and is being evaluated. Consider clinical context and published guidelines."***

ANEM-B (2 of 5)

- **The following reference was added to footnote "1": "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."**

ANEM-B (5 of 5)

- **References were updated.**

ANEM-D (1 of 3)

- **Footnote "b" was added: "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."**
- **The second bullet was revised: "Five of six studies have shown that parenteral iron products ~~are helpful~~ *show improved Hb response rates* in treating absolute..."**
- **Footnote "a" was revised: "Ferric carboxymaltose *has not been prospectively evaluated and therefore* ~~may be~~ *should only* be considered when other parenteral iron preparations fail. 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. (Also on ANEM-D 2 of 3)**

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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 and mean corpuscular volume (MCV)**
- **Then consider**
  - **Hemorrhage (stool guaiac, endoscopy)**
  - **Hemolysis (Coombs test, disseminated intravascular coagularion [DIC] panel, haptoglobin, indirect bilirubin, lactate dehydrogenase)**
  - **Nutritional (iron, total iron-binding capacity, ferritin, B_{12}, folate)[c]**
  - **Inherited (prior history, family history)**
  - **Renal dysfunction (Glomerular filtration rate [GFR] <60 mL/min/1.73 m^2, low Epo)**
  - **Radiation-induced myelosuppression**
- **See Evaluation of Iron Deficiency (ANEM-5)**

→ **Treat as indicated**

→ **No cause identified** → **Consider anemia of chronic inflammation or anemia due to myelosuppressive chemotherapy** → **See 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]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 iron studies are not performed while the patient is fasting they may be falsely elevated.

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RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING

Anemia of chronic inflammation or anemia due to myelosuppressive chemotherapy for lymphoid malignancies and solid tumors

Asymptomatic without significant comorbidities[d] → **Observe** → **Periodic re-evaluation**

Asymptomatic with comorbidities[d] or high risk
- **Comorbidities:**
  - **Cardiac including transfusion-associated circulatory overload (TACO) and coronary heart disease**
  - **Chronic pulmonary disease**
  - **Cerebral vascular disease**
- **High risk:**
  - **Progressive decline in Hb with recent intensive chemotherapy or radiation**

→ **Consider red blood cell transfusion per guidelines[f]** See Indications for Red Blood Cell Transfusion in Patients with Cancer (ANEM-A)

Symptomatic
- **Physiologic:**
  - **Sustained tachycardia, tachypnea, chest pain, dyspnea on exertion, lightheadedness, syncope, severe fatigue[e] preventing work and usual activity**

→ **Red blood cell transfusion per guidelines[f]** See Indications for Red Blood Cell Transfusion in Patients with Cancer (ANEM-A)

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)

[d]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.
[e]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.
[f]See Discussion for further details on treating patients who may refuse blood transfusions (eg. Jehovah's Witnesses).

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COMPARISON OF RISKS AND GOALS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION[g]

If anemia is not due to absolute or functional iron deficiency, there are currently only two proven methods of improving Hb: ESAs and red blood cell transfusion. Listed below are risks and goals of each method.

	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) • TACO • Virus transmission (eg, hepatitis, HIV) • Bacterial contamination • Iron overload • Increased thrombotic events • Possible decreased survival
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)

See REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis-Stimulating Agents (ESAs) (ANEM-C)

[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 indications/dosing/dosing adjustments for chronic kidney disease, under REMS guidelines, with informed consent of patient[j,k,l,m]** →
- **Patient undergoing palliative treatment[i]** → **Consider based on patient preferences:**
  - **ESAs by FDA indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient[j,k,l]**
  - **or**
  - **Red blood cell transfusion per guidelines (See ANEM-A)**
- **Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia[i]** → **Consider based on patient preferences:**
  - **ESAs by FDA indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient[j,k,l]**
  - **or**
  - **Red blood cell transfusion per guidelines (See ANEM-A)**
  - **or**
  - **Clinical trial**

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

- **Myelosuppressive chemotherapy with curative intent[h]**
  - **Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin's lymphoma, testicular cancer, early-stage non-small cell lung cancer, small cell lung cancer, etc.**
- **Patients not receiving therapy or palliative treatment, or those on non-myelosuppressive therapy**

→ **ESAs not recommended**

[h]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.

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

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

[k]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).

[l]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, 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).

[m]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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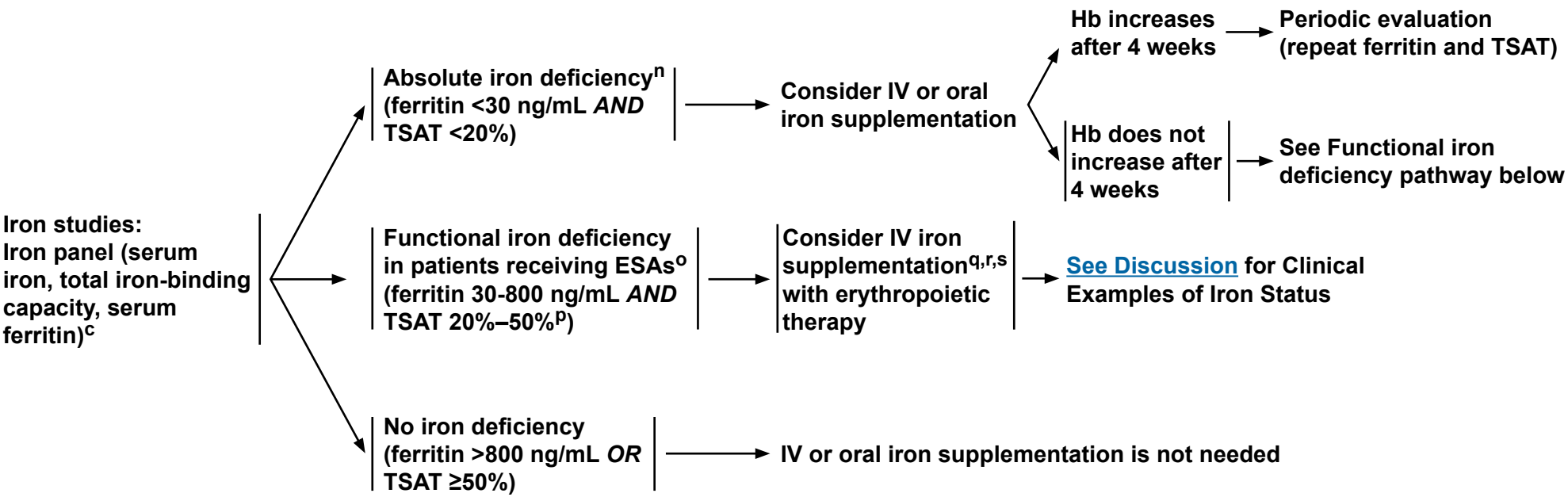
EVALUATION OF IRON DEFICIENCY



See Parenteral Iron Preparations (ANEM-D)

[c]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 iron studies are not performed while the patient is fasting they may be falsely elevated.

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

[o]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 the benefits are likely to outweigh the risks.

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

[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-D).

[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 WITH CANCER[a,b]

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

Asymptomatic Anemia

- **Hemodynamically stable chronic anemia:**
  - **Transfusion goal to maintain Hb 7–9 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 (Hb <10 g/dL):**
  - **Transfusion goal to maintain Hb 8–10 g/dL as needed for prevention of symptoms**

- **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.**

[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.

[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.

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

INITIAL DOSING

PACKAGE INSERT DOSING SCHEDULE

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

ALTERNATIVE REGIMENS

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]		

TITRATION FOR NO RESPONSE

- 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.

TITRATION FOR RESPONSE

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-D).

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)

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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).

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)

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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.[23] 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.[24] 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 permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESA products as antibodies may cross-react.

See References (ANEM-B 5 of 5)

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 OF 5)

ADVERSE EFFECTS REFERENCES

[1]Leyland-Jones B, BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol 2003;4:459-460.
[2]Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255-1260.
[3]Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol 2007;25:1027-1032.
[4]Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. Br J Haematol 2003;122:394-403.
[5]Overgaard J, Hoff C, Sand Hansen, H, et al. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of head and neck (HNCSS): The Danish Head and Neck Cancer Group DAHANCA 10 rand [abstract] Eur J Cancer Suppl 2007;5:7.
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REMS: RISK EVALUATION AND MITIGATION STRATEGY FOR ERYTHROPOIESIS-STIMULATING AGENTS (ESAs)

- The FDA requires that ESAs be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure that patients have been counseled on the risks and benefits of therapy and that therapy is not initiated until the patient's signature is recorded acknowledging acceptance of the known risks.
- As part of REMS for ESAs[1]:
  - Health care providers who prescribe ESAs to patients with cancer are required to enroll in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program.
  - Health care providers who prescribe ESAs should counsel each patient on the risks and benefits of ESAs prior to each new course of ESA therapy.
  - The patient or patient representative must sign an ESA APPRISE Oncology Program Patient and Healthcare Provider Acknowledgment Form (https://www.esa-apprise.com/ESAAppriseUI/public/ESA_APPRISE_Oncology_Program_Acknowledgment_Form_PATIENT.pdf) in the presence of the health care provider to document that a risk:benefit discussion related to ESAs has occurred.
    - ◊ The form must be signed before the patient begins a course of treatment with an ESA.
    - ◊ Each patient must be provided with a copy of the signed form.
    - ◊ Completed forms should be retained by the health care provider or hospital and must be made available to the ESA APPRISE Oncology Program for auditing purposes.
- Patients with cancer using ESAs should[2]:
  - Understand the risks associated with use of ESAs. These risks include:
    - ◊ ESAs may cause tumors to grow faster.
    - ◊ ESAs may cause some patients to die sooner.
    - ◊ ESAs may cause some patients to develop blood clots and serious heart problems such as a heart attack, heart failure, or stroke.
  - Be aware that their health care professional has received special training about the use of ESAs in patients with cancer.
  - Read the Medication Guide (See Epoetin Alfa Medication Guide and See Darbepoetin Alfa Medication Guide) to understand the benefits and risks of using an ESA.
  - Talk with their health care professional about any questions they may have about using ESAs.
  - Be aware that they must sign the Acknowledgment Form that says he or she has talked with his or her health care professional about the risks of ESAs before the first dose of an ESA can be received.
- For selected safety information for health care providers, see https://www.esa-apprise.com.

[1]Adapted from: https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp#isi.
[2]Adapted from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm.

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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 <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 active infection should not receive IV iron therapy.**

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

See References (ANEM-D 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]

[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.

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

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran[13,c]	Ferric Gluconate[14,c]	Iron Sucrose[15,c]
Test dose[d]	Required 25 mg slow IV push and wait 1 h before giving remainder of dose	MD discretion 25 mg slow IV push or infusion	MD discretion 25 mg slow IV push
Dosage[12,e]	100 mg IV over 5 min[3] • Repeated dosing once weekly for 10 doses to achieve total dose of 1 g or • Total dose infusion given over several hours[16,f]	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[17] • 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- D 3 of 3)

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

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Anemia 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 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, is also FDA approved for this indication. Newer ESAs with novel mechanisms of action may be approved in the future. However, for the purposes of these guidelines, the use of the term ESA is used synonymously with rhEpo.

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 NCI (Table 1).

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 the individual patient condition.

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.

Etiology

Causes of anemia in patients with cancer are often multifactorial, adding to the complexity of evaluation.[2] Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, hereditary disease, renal insufficiency, nutritional deficiencies, anemia of chronic disease, or a combination of these factors.[3,4] The malignancy itself can lead to or exacerbate anemia in a number of ways.[5] Cancer cells may directly suppress hematopoiesis through bone marrow infiltration. They may 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 in patients with cancer, 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 have anemia at diagnosis,[6] and 49% of patients with gynecologic cancer are anemic at diagnosis.[7] In addition, the myelosuppressive effect of chemotherapy is a significant

contributing factor to anemia for patients undergoing cytotoxic treatment.[8,9] Radiation therapy to the skeleton is also associated with hematologic toxicity. In a retrospective analysis, approximately one-third of the 210 patients undergoing cranio-spinal radiotherapy for treatment of primary tumors of the central nervous system developed grades 3 and 4 hematologic side effects.[10]

Anemia Associated with Myelosuppressive Chemotherapy

Chemotherapeutic agents induce anemia by directly impairing hematopoiesis in the bone marrow, including disruption of RBC precursor synthesis.[5] Nephrotoxic effects of particular cytotoxic agents (eg, platinum-containing agents) can lead to anemia through decreased production of erythropoietin by the kidney.[5]

Studies have identified patients with lung cancer and gynecologic malignancies as having a very high incidence of chemotherapy-induced anemia (CIA).[7,8] Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to the combined bone marrow and kidney toxicity.[8] 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 the single agents cabazitaxel, docetaxel, and enzalutamide, which have been shown to cause grade III to IV anemia in 11%, 9%, and 0% of patients, respectively.[11-13]

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 Anemia Survey (ECAS)[7], 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.[7] An increase in the fraction of grades 2 to 3 anemia was also associated with a greater number of chemotherapy cycles. Other factors for consideration when evaluating 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.[5]

Guideline Overview

The revised 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 in the sections on RBC transfusion, erythropoietic therapy, and iron monitoring and supplementation.

The guideline algorithms 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 Table of Contents.

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 07/08/2014 and 03/01/2015**,** 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.[14]

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 109 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.

Screening Evaluation

Given the wide variation in the Hb level among healthy subjects, a universal "normal" value is difficult to define. For patients with cancer, NCCN Panel Members are in agreement that an Hb level of 11 g/dL or below should prompt an evaluation of anemia. 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[2]). The overall goals of evaluation are to characterize the anemia and identify any underlying comorbidity that potentially can be corrected 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 is critical to confirm the size, shape, and Hb content of the 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 and 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. Cancer-related fatigue is defined in the NCCN Guidelines as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (see NCCN Guidelines for Cancer-Related Fatigue). A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that it is less likely to be ameliorated by rest.[15] 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 categorized 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 common causes of macrocytosis are medications[16] 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 reticulocytes 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 the circulation for 2 to 3 days before converting to erythrocytes, thereby giving a falsely high value to the RI. 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, B12/folate deficiency, aplastic anemia, or bone marrow dysfunction due to cancer or cancer-related therapy (ie, radiation, myelosuppressive chemotherapy).

- High RI/RPI ratio (>1) indicates normal or increased 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 B12 or red cell folate levels (commonly tested together with iron studies). Ferritin values are also useful in evaluating iron stores.
- Hemorrhage—stool guaiac positive, endoscopy findings
- Hemolysis—Coombs test positive, disseminated intravascular coagulation panel positive, low haptoglobin levels, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH)
- Renal dysfunction—glomerular filtration rate less than 60 mL/min/1.73 m^2 for three or more consecutive months, low erythropoietin level
- Inherited anemia—personal and family history
- Sideroblastic anemia—sideroblasts present in bone marrow biopsy

Clinicians are advised to consult the section *Iron Monitoring and Supplementation* 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 is warranted for the long-term management of anemia as determined by risk assessment.

Red Blood Cell Transfusion

When considering the decision to offer PRBC transfusion, it 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) asymptomatic with comorbidities or high risk, for which transfusion should 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 to 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 comorbidity, 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.[17]

Benefits of Transfusion

The major benefit of transfusion with PRBCs, offered by no other treatment of anemia, 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 of 1 g/dL or in Hct by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.[17,18] 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).[19] A retrospective study of data collected from 605 patients with carcinoma of the cervix evaluated Hb levels prior to therapy 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. Data suggest that blood transfusion reduced the negative prognostic implication of low Hb.[20]

Risks of Transfusion

Risks associated with PRBC transfusion include transfusion-related reactions, transfusion-associated circulatory overload, bacterial contamination and viral infections, and iron overload (reviewed by Spivak, Gascon, and Ludwig[21]). 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.[22,23] 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.[23] 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 reaction.[24,25] Khorana et al[26] 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.[26] However, the increased

thrombotic events and decreased survival may reflect a bias of more severe anemia and/or more advanced cancer in patients who require 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.

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).[27] 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.[17] When iron stores become saturated, iron remains as non-transferrin–bound iron.[28] 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 cumulative cardiac and hepatic toxicity.[29,30]

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.[31,32]

Transfusion Goals and Basic Principles

There is wide variation in reported PRBC transfusion practice,[22,33] but institutional and clinical practice guidelines are often “restrictive” regarding limiting exposure to allogeneic blood. The overall goal of transfusion is to treat or prevent the deficiencies in the oxygen-carrying capacity of the blood, in order to improve oxygen delivery to body tissues. Target Hb ranges for specific conditions recommended by the NCCN Panel are outlined in the algorithm (see *Indications for Red Blood Cell Transfusion in Patients with Cancer* on page ANEM-A). Transfusion is rarely indicated when the Hb level is above 10 g/dL.[34] 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.[33] AABB recommendations include: 1) using an Hb level between 7 and 8 g/dL as a threshold for hospitalized patients who are 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. During NCCN panel discussion, concerns were raised regarding the implications of current ESA restrictions on the transfusion burden. Panelists agree that no single target Hb level is appropriate for all cases and that the balance between 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

antihistamine to prevent allergic and febrile nonhemolytic transfusion reactions.[35,36] 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 who refuse blood transfusions (eg, Jehovah's Witnesses) 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 utilize specific strategies. 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.[37-39] Strategies include minimizing blood loss by restricting 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. Baseline coagulation abnormalities should be fully evaluated and corrected prior to myelosuppressive treatment. Nutritional deficiencies have a low prevalence in both the general population[40,41] and in patients with cancer.[2,42] However, in patients with high clinical suspicion of folate and vitamin B12 deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using intravenous (IV) iron. ESAs may be offered; however, prior approval from third-party payers should be sought to prevent increasing the financial burden of the patient. Patients should also be made aware of the potential increased risks of thrombosis and tumor progression, and should know that under these circumstances the drugs are being used off-label. Lastly, in extreme cases with severe, life-threatening anemia, pure oxygen (400 mmHg, S_AO_2 = 1.0) has been used to increase blood oxygenation.[38]

Erythropoietic Therapy

RBC production is normally controlled by erythropoietin, a cytokine produced in the kidneys. First introduced in 1989, rhEpo was shown to stimulate erythropoiesis in patients with low RBC levels. Although other ESAs are in development, at present, two rhEpos are available in the United States: epoetin alfa and darbepoetin alfa. As previously mentioned, for these guidelines, the term ESA is limited to these two agents. Unlike transfusion that 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. Not all patients respond to ESA therapy. In a study of 2192 patients with cancer receiving ESA therapy, an Hb increase of $\geq$1 g/dL was attained in 65% of patients.[43]

Benefits of ESA Therapy

Elimination of symptoms and avoidance of transfusion are the main goals of ESAs. ESA therapy has been demonstrated to decrease PRBC transfusion requirements in patients with cancer undergoing chemotherapy. In a randomized, placebo-controlled study by Littlewood and colleagues,[44] epoetin alfa was shown to reduce transfusion requirements in patients with anemia receiving chemotherapy.[44] Transfusion requirements were significantly decreased in the epoetin alfa arm compared with placebo (24.7% vs. 39.5%, P = .0057), and the Hb level was increased (2.2 g/dL vs. 0.5 g/dL; P < .001).[44] A double blind, placebo-controlled, randomized phase III study enrolled 320 patients (Hb ≤11 g/dL) receiving darbepoetin alfa at 2.25 mcg/kg/week versus placebo.[45] 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.[46] A decreased relative risk (RR) for transfusion was observed in patients receiving erythropoietin (RR, 0.65; 95% CI, 0.62–0.68).[46] 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.

Risks of ESA Therapy

Risk for Thromboembolism

Increased thromboembolic risks have been associated with ESA treatment of 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 Venous Thromboembolic Disease).[47-50] 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.[51]

Results from meta-analyses established a significant association between increased risk of thrombotic events and ESA usage, with statistically significant risk and odds ratios ranging from 1.48 to 1.69.[46,52-56] A combined analysis of six trials using darbepoetin alfa by Glaspy and colleagues[57] also found an increased trend of thromboembolism for patients with Hb greater than 12 g/dL (RR, 1.66; 95% CI, 0.9–3.04) or in patients achieving a greater than 1 g/dL 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).[58] Furthermore, in a retrospective case-controlled study of CKD patients with cancer, ESA use was associated with a significantly increased risk of stroke (OR, 1.83; 95% CI, 1.26–2.65).[59] The increased risk for thromboembolism in patients with cancer receiving ESA therapy is specified in the black-box warnings included in the updated FDA labels. The NCCN Panel cautions physicians to be alert of 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,[60,61] including the addition of a black box label warning and implementation of a risk management program known as Risk Evaluation and Mitigation Strategy (see *REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis Stimulating Agents (ESAs)* on page ANEM-C). The strengthened FDA restrictions were mainly based on the results of 8 randomized studies that individually showed a decrease in OS and/or decreased locoregional disease control with ESA usage in advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers.[62-69] Of the 8 studies, four studies investigated ESA effects in patients who underwent chemotherapy, 2 studies were in patients receiving radiotherapy alone, and 2 studies were in patients receiving neither chemotherapy nor radiotherapy. All 8 trials had an off-label target Hb level over 12 g/dL.

Worsened health outcomes associated with the use of ESAs have been observed in 5 meta-analyses of 51 to 91 randomized controlled trials when targeting Hb levels above 12 g/dL.[46,52,54,56,70,71] These analyses reported increased mortality in patients receiving ESAs with statistically significant RR/HR of 1.17 (95% CI, 1.06–1.30),[70] 1.15 (95% CI, 1.03–1.29),[56] 1.10 (95% CI, 1.01–1.20),[52] 1.17 (95% CI, 1.06–1.29),[46] and 1.17 (95% CI, 1.04–1.31).[54] Data from the Cochrane Database reported increased mortality in patients with Hb over 12 g/dL that also associated

with patients that did not receive concurrent therapy.[46] 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 below 10g/dL resulted in fewer thromboembolic events and a reduced morality. However, the difference with early treatment was not significant and optimal duration of therapy could not be determined from the limited data.[54]

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 progression based on HR/odds ratios of 0.97 (95% CI, 0.85–1.1)[55] and 1.06 (95% CI, 0.97–1.15).[53] Trials with off-label use of rhEpo, in both the adjuvant and neoadjuvant setting, reported no decrease in survival with ESA use in patients with chemotherapy-related anemia when an Hb target of 13 g/dL was utilized.[72-74] The PREPARE trial found no difference in the 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 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).[74,75] The phase III WSG-ARA trial that included 1234 patients with early breast cancer treated with adjuvant ESA is the first to evaluate survival as the primary endpoint.[76] In this study, no impact on 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 for 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). Results suggest that the value of darbepoetin alfa may be dependent on other risk factors, including patient comorbidities, type of cancer, and type of 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.[77,78]

A meta-analysis of three randomized, placebo-controlled trials in Japanese patients with CIA did not show an increased mortality associated with the use of ESAs.[79] In this study, 511 patients with solid tumor or lymphoma were treated with epoetin beta or darbepoetin alfa. The efficacy endpoints in this study included PRBC transfusion and transfusion trigger (ie, transfusion or 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 the placebo group (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 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. Furthermore, only CIA patients were included in the three Japanese studies. In addition to equivalent OS in the ESA treatment arm compared to the placebo arm, quality of life, in terms of patient-reported fatigue, was improved with ESA treatment. This was measured by the inclusion of the Functional Assessment of Cancer Therapy-Anemia in patient evaluations.[79]

Possible Increased Fatigue

A recent systematic review and meta-analysis evaluated the effects of ESAs on fatigue and anemia-related symptoms.[80] The study included 37 randomized controlled trials with a total of 10,581 patients. The evaluation of fatigue was based on determining a clinically important difference (CID) on either the FACT-An or FACT-F scale. Fatigue evaluation was below the threshold for CID established at greater than or equal to 3 (CID = 2.14; 95% CI, 1.39–3.43). However, the FACT-An scale showed a CID above the threshold set at 4 (CID = 4.09; 95% CI, 2.37–5.80; *P* = .001). These results suggest that ESAs provide a small but clinically important improvement in anemia-related symptoms in patients with cancer, particularly those receiving chemotherapy.

Risk for Hypertension/Seizures

Seizures have been reported in patients with chronic renal failure receiving ESAs. There is a 2.5% incidence of seizure in patients on dialysis during the first 90 days of therapy.[81] 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. An increased risk for hypertension with ESA usage was reported by a Cochrane review (RR, 1.30; 95% CI, 1.08–1.56).[46]

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. From 1998 to 2004, however, a marked rise in incidence (191 cases) was observed, though 90% of cases occurred with an epoetin alfa product used outside of the United States.[82,83] Causation was attributed to formulations without human serum albumin, subcutaneous (SC) administration, and uncoated rubber stoppers.[84] 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, associated with neutralizing antibodies.[85] PRCA resulted in a class label change for all ESAs. This toxicity has been reported predominantly in patients with chronic renal failure receiving SC ESAs.

NCCN Recommendations

To promote safety, the FDA requires that ESAs only be administered with informed patient consent under the REMS program for patients with cancer. The REMS program (https://www.esa-apprise.com/ESAAppriseUI/) consists of Medication Guides for patients and the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) program for prescribing physicians (see *REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis Stimulating Agents (ESAs)* on page ANEM-C). Although the ESA APPRISE program does not apply to patients with cancer who are receiving ESA therapy for CKD, the panel still recommends its use.

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.[60] 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 anticipated treatment outcome is cure. This includes primary and adjuvant chemotherapy for malignancies such as early-stage breast cancer and non-small cell lung cancer, 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 (see earlier discussion).[77,78] Hence, patients not receiving concomitant myelosuppressive chemotherapy are not eligible. Additionally, ESAs are not recommended for patients who are not receiving therapy or for patients on non-myelosuppressive therapy. Patients undergoing palliative treatment may consider ESA or transfusion therapy 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, the options for anemia management should first be consideration of PRBC transfusion and clinical trial enrollment if available. 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, and the FDA label mandates individualized dosing to reduce the need for RBC transfusions. Controlled clinical trials have associated increased risk of mortality and adverse cardiovascular outcomes with ESAs in CKD patients when targeted to Hb levels over 11 g/dL.[58,59,86-89] In the study by Pfeffer et al[58] (comparing darbepoetin alfa to placebo), a statistically significant increase in death due to cancer was seen in CKD patients who had pre-existing cancer at baseline (P = .002). Conversely, in a study of patients with CKD stages 4 and 5, an increased incidence in cancer was not observed, and it is highlighted that the average Hb was 10.1 g/dL.[87] Data from Seliger and colleagues[59] 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.[59] Since almost one-third of patients with end-stage renal disease are also afflicted with cancer, they represent a unique group that requires personalized use of ESAs based on very careful weighing of risks and benefits (reviewed by Bennett et al[90]). 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 transfusions to treat severe anemia. In the scenario where the CKD patient 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 residual disease. Risk for thrombosis must be taken into account as part of the risk-benefit ratio.

Most hematopoietic cell transplant patients require transfusion support. Nonetheless, ESA therapy may be useful in some instances.[91,92] For example, ESAs may be administered post-transplant to increase the Hct in order to allow phlebotomy to treat transfusional iron overload. There have been reports of ESA efficacy in patients who refuse blood transfusions while undergoing autologous cell transplantation.[93-95] 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 (see below). 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 permanently discontinued in patients with antibody-mediated anemia. Patients should not be 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 three times weekly administered SC[44,96] and 40,000 units administered once weekly SC[65,68,69,97] (see *Erythropoietic Therapy – Dosing, Titration, and Adverse Effects* on page ANEM-B). 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 SC every 2 weeks[98] and a dose of 120,000 units SC once every 3 weeks.[99]

Although darbepoetin alfa doses were initially administered at 2.25 mcg/kg SC every week,[45,63,100] there has been interest in 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 three weeks in 705 patients with non-myeloid malignancies and an Hb level below 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 three weeks.[100] Both of these schedules are listed in the package insert. Dosing once every three weeks was further refined in two studies by reducing the dose to 300 mcg. Initially, a multicenter, open-label study of 1493 patients showed that 79% of patients achieved a target Hb level greater than or equal to 11 g/dL.[101] 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).[102] Other studies have demonstrated the safety and efficacy of alternative dosing schedules for darbepoetin alfa. These include a fixed weekly dose of 100 mcg,[45] and a fixed dose of 200 mcg every 2 weeks.[103] In addition to the dosing schedule on the package insert, the NCCN Panel recommends these alternative regimens to aim for the smallest yet still effective dose.

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 a gradual increase in Hb level that remains 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%–40%) should be implemented

if the Hb level increases by 1 g/dL or more during a 2-week period, or if Hb reaches a level sufficient to avoid transfusion.

Conversely, the ESA dose should be increased according to the algorithm (see *Erythropoietic Therapy – Dosing, Titration, and Adverse Effects* on page ANEM-B) 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. Iron supplementation can be considered to improve response to ESA therapy. A subsequent response at 8 or 9 weeks for patients on ESA dosing schedules of every 2 or 3 weeks may necessitate a dose titration to avoid transfusion. Individuals receiving weekly doses of ESA therapy can be evaluated for subsequent response at 8 or 9 weeks. The same dose reduction formulas as described above should be followed. ESA therapy should be discontinued in patients showing no response despite iron supplementation after 8 or 9 weeks of therapy, and PRBC transfusion should be considered. ESAs should be discontinued when the chemotherapy cycle is complete or when chemotherapy is discontinued.

Iron Monitoring and Supplementation

Iron deficiency is reported in 32% to 60% of patients with cancer, most of whom are also anemic.[104] Absolute iron deficiency refers to the depletion of total body iron stores. It is characterized by low Hb, TSAT, and ferritin levels. Low iron and high TIBC result in a TSAT level less than 20% and a ferritin level less than 30 ng/mL. 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 (see *Clinical Examples of Iron Status, case scenario 1).*

Functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production is deficient. This includes cases where infection or inflammation blocks iron transport to the bone marrow, as seen in anemia of chronic disease. One form of functional iron deficiency often arises following continued ESA use. The overall result is a blunted erythropoietic response to anemia. Hence, iron supplementation will eventually be required in most patients in order to maintain optimal erythropoiesis.[105,106] While Hb and TSAT levels will be low, ferritin level usually remains within normal limits. Laboratory diagnosis of this condition was detailed by Thomas and colleagues.[107] Functional iron deficiency is defined in these guidelines as a TSAT level between 20% and 50% and a ferritin level between 30 ng/mL and 800 ng/mL (see *Clinical Examples of Iron Status, case scenarios 4 and 5).*

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[108]); therefore, fasting iron studies may provide a more accurate representation of iron deficiency.

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).[109] Evidence from 5 published studies utilizing iron in conjunction with an ESA suggest that IV iron is superior to oral iron.[110-114] 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,[113] while two studies provided guidelines for ferritin monitoring.[102,112] Ferric carboxymaltose may also be considered when infusion reactions preclude use of other parenteral iron preparations.[115]

A recent 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 have presenting anemia). Previously, IV iron was shown to be effective in the treatment of patients with anemia who had a prior blood transfusion.[116] 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 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). Oral iron is the current treatment for anemia in patients with gynecologic cancer, but the gastrointestinal side effects are significant and reduce patient compliance.[116]

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).[110] Increases in Hb concentration were greater with IV iron (groups 3 and 4) compared to oral supplementation or no iron (*P* < .02) while 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 and colleagues,[113] 187 anemic patients with cancer receiving chemotherapy and epoetin alfa were randomized to no iron, oral ferrous sulfate three 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.[112] 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 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.

Two additional studies were published in 2008. Bastit et al[111] reported their open-label trial evaluating 396 patients with nonmyeloid malignancies undergoing chemotherapy (Hb <11 g/dL).[111] Patients were treated with darbepoetin alfa with or without IV iron (iron sucrose or ferric gluconate 200 mg every three weeks for 16 weeks). Erythropoietic responses and time to reach the target Hb level were better in the IV iron arm. Most significantly, this is 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,[114] 149 patients with solid tumors and CIA were randomly assigned to receive weekly darbepoetin alfa with or without ferric gluconate. This is the first trial that excluded patients with absolute iron deficiency; eligibility requirements included a serum ferritin level greater than 100 ng/mL and a TSAT level greater than or equal to 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. 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 five trials.

In 2011, Steensma et al[117] published findings from the largest trial to date that challenged these positive results. Roughly 500 patients with CIA were randomized 1:1:1 to IV ferric gluconate, oral ferrous sulfate, or oral placebo. IV iron failed to confer benefit in terms of Hb response, transfusion rates, or quality of life compared to oral iron or placebo. One possibility for the lack of response may be 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.

A systematic review and meta-analysis evaluating the role of iron supplementation has been reported.[118] Eleven randomized controlled trials analyzed IV iron versus standard of care in patients with CIA. 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 two 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). Time to response was faster in the IV iron group (range, 36–54 days) versus standard-of-care group (46–94 days). IV iron but not oral iron was associated with improved hematopoietic response rates compared to ESA 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). No difference in all-cause mortality was found 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. It has also been evaluated for the treatment of iron-deficient anemia in patients with dialysis-dependent CKD,[119,120] inflammatory bowel disease,[121-123] chronic heart failure,[124,125] and others.[113,126-128] The observational study from Steinmetz et al[115] is the first to evaluate its use in patients with cancer. Of the 639 adult patients from 68 cancer centers in Germany, safety data could be obtained from 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 of median Hb levels greater than 11 g/dL within 5 weeks of treatment with ferric carboxymaltose.[115] Data from this study 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 approved in June 2009 by the FDA for the treatment of iron deficiency anemia in patients with CKD. A recent 812-patient, phase III trial investigating the use of ferumoxytol in patients with anemia due to various causes randomized patients to either the treatment arm (n = 608) or the placebo arm (n = 200).[129] 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 greater than or equal to 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.[129] 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.[129] 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 demonstrated at least a 2 g/dL increase from baseline to week 5 following treatment with ferumoxytol (84%; n = 406) versus iron sucrose (81.4%; n = 199).[130] In the cancer subgroup (n = 31), there was a trend favoring ferumoxytol (54.8%) compared to iron sucrose (38.5%). However, noninferiority was not reached, potentially due to the small sample size.

NCCN Recommendations

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.[2]

Absolute iron deficiency is defined as a ferritin level below 30 ng/mL and a TSAT level below 20%. If the 2 parameters are discordant, a low ferritin value should take precedence in determining whether iron supplementation will be beneficial. 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, patients 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.[131] Hence, iron supplementation is not recommended for patients with an active infection.

A ferritin level between 30 ng/mL and 800 ng/mL and a concurrent TSAT level between 20% and 50% indicate adequate iron stores, unless the patient is receiving an ESA. Patients receiving ESA therapy with a ferritin level between 30 ng/mL and 800 ng/mL and a TSAT level between 20% and 50% will develop functional iron deficiency and will likely benefit from IV iron. Iron monotherapy in patients with functional iron deficiency not receiving ESA therapy can reduce the number of RBC transfusions.

Several studies have focused on the effectiveness of IV iron monotherapy in patients with cancer. Patients with cervical cancer treated with concurrent chemoradiotherapy were given IV iron sucrose to prevent anemia.[132] The study group (n = 30) received 200 mg of IV iron sucrose while the control group (n = 45) did not receive IV iron sucrose. In the study group, 12 patients (40%) required subsequent blood transfusions compared to 29 patients (64%) in the control group (*P* = .04). The mean number of transfusion units was also reduced in the study group compared to the control group (1.87 units vs. 3.58 units; *P* = .04). Similarly, in a study of 44 patients with gynecologic cancer, half of the patients received 200 mg IV iron sucrose while the comparator group received 600 mg oral ferrous sulphate daily.[133] Of the 22 patients receiving IV iron, 5 patients (22.7%) required RBC transfusion compared to 14 of 22 patients (63.6%) in the comparator group (*P* = .01). Significantly improved Hb and Hct levels were seen

with IV iron treatment. Furthermore, there was no difference in adverse events between the two groups and no serious adverse events were seen. A larger observational study of 639 patients with cancer further investigated the effectiveness and tolerability of ferric carboxymaltose.[115] The study population included 347 patients who received ferric carboxymaltose monotherapy. No significant difference was seen in Hb improvement between the ferric carboxymaltose monotherapy group and the ferric carboxymaltose plus ESA group. Tolerability data were also collected for 354 patients following a 12-week observation period. Adverse drug reactions were recorded in 14 patients (2.3%) with only one serious adverse drug reaction possibly related to the ferric carboxymaltose. As previously discussed, most studies show that IV iron is superior over oral iron and should be used.[110-114]

Patients with a baseline TSAT level below 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.

Common adverse events following FDA-approved doses of parenteral iron include hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness.[134-136] Most adverse events associated with iron dextran occur with high-molecular-weight iron dextran.[137] Therefore, the recommended iron dextran product is low-molecular-weight iron dextran.[138] 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 who 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.[139] 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* on page ANEM-D 2 of 3).

None of the six 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.

Should the patient fail to respond to iron after 4 to 6 weeks and after the total intended dose has been administered, repeat iron studies may be considered.[112,117] 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%.[111-113]

Individuals with a ferritin level greater than 800 ng/mL or a TSAT level greater than or equal to 50% do not require iron supplementation as they are not considered iron-deficient and will likely not experience functional iron deficiency, even if an ESA is administered.

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 chemotherapy, 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 B12 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 less than 30 ng/mL and a TSAT level less than 20%, this patient has absolute iron deficiency and would benefit from iron repletion. Reducing transfusion requirements remains the goal of therapy. With a baseline Hb of 8.8 g/dL, imminent chemotherapy initiation, and very low iron stores, IV iron repletion is preferred. Oral iron may not supply bioavailable iron rapidly enough in certain patients.[110]

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 >800 ng/mL,[140] 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 with disease that responds to the ESA as well as reduce the time to response.

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

As the TSAT level increases from 20% to 50%, the percentage of patients with disease 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 because TSAT is typically low in that condition. 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, it is up to the treating clinician 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 CIA such as iron isomaltoside. More information about these agents can be found at www.clinicaltrials.gov. Other areas for future development include markers of iron deficiency. Soluble transferrin receptor level has been suggested as a marker of iron deficiency that can aid in differential diagnosis.[141] However, further studies are still needed to evaluate the role of this marker in patients with CIA.

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