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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Cancer- and Chemotherapy- Induced Anemia**

Version 1.2015

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## Cancer- and Chemotherapy-Induced Anemia

[NCCN Guidelines Index](#)  
[Anemia Table of Contents](#)  
[Discussion](#)

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**Continue**

[NCCN Guidelines Panel Disclosures](#)



# NCCN Guidelines Version 1.2015 Table of Contents

## Cancer- and Chemotherapy-Induced Anemia

### [NCCN Cancer- and Chemotherapy-Induced Anemia Panel Members](#)

### [Summary of the Guidelines Updates](#)

### [Evaluation of Anemia \(ANEM-1\)](#)

### [Risk Assessment and Indications for Initial Transfusion in Acute Setting \(ANEM-2\)](#)

### [Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion \(ANEM-3\)](#)

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

### [Evaluation of Iron Deficiency \(ANEM-5\)](#)

### [Indications for Red Blood Cell Transfusion in Patients with Cancer \(ANEM-A\)](#)

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

### [REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis-Stimulating Agents \(ESAs\) \(ANEM-C\)](#)

### [Parenteral Iron Preparations \(ANEM-D\)](#)

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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 1.2015 Updates

## Cancer- and Chemotherapy-Induced Anemia

Updates in the 1.2015 Version of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from the 3.2014 Version include:

### ANEM-1

- Evaluation of Anemia
  - ▶ "Hemolysis" sub-bullet was revised: "Indirect bilirubin" was added to the tests for hemolysis.
- Footnote
  - ▶ A line was added to footnote "c": "Additionally, if iron studies are not performed while the patient is fasting they may be falsely elevated." (Also on ANEM-5)

### ANEM-2

- Asymptomatic with comorbidities or high risk
  - ▶ First sub-bullet was revised: "Congestive heart failure" was changed to "Transfusion-associated circulatory overload (TACO)." (Also on ANEM-3)

### ANEM-3

- ESA in the Cancer Setting
  - ▶ Under "Benefits," the second bullet was revised: "Gradual improvement in **fatigue anemia-related symptoms**."
- Red Blood Cell Transfusion:
  - ▶ Under "Benefits," the second bullet was revised: "Rapid improvement in **fatigue anemia-related symptoms**."
- A link was added below the table: See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-B).

### ANEM-4

- Myelosuppressive chemotherapy with curative intent
  - ▶ "Small cell lung cancer" was added to the list of examples of cancers for which there is therapy with curative intent.
- For the categories "Patient undergoing palliative treatment" and "Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia," the text was revised as follows: "Consider based on patient preferences and values."
- Footnote
  - ▶ Footnote "m" was revised: "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.**"

### ANEM-B (1 of 5)

- Footnote "\*" was added: "Data indicate that darbepoetin alfa 300 mcg is equivalent in terms of efficacy to darbepoetin alfa 500 mcg for initial dosing."

### ANEM-B (2 of 5)

- Reference was added: "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."

### ANEM-C

- As part of REMS for ESAs: The third sub-bullet regarding the Acknowledgment Form was reorganized to include sub-bullets, and the following text was added: "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."

### ANEM-D (1 of 3)

- Parenteral iron preparations studied in patients with cancer
  - ▶ "Iron dextran" was changed to "low-molecular-weight iron dextran." (Also for ANEM-D 2 of 3)
  - ▶ "Ferric carboxymaltose" was added along with footnote "†": "Ferric carboxymaltose may 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."

[Continued on next page](#)



# NCCN Guidelines Version 1.2015 Updates

## Cancer- and Chemotherapy-Induced Anemia

Updates in the 1.2015 Version of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from the 3.2014 Version (continued):

### ANEM-D (1 of 3) continued

- Under the second bullet, the second sub-bullet was revised: "If the patient fails to respond to treatment with iron fails after 4 to 6 weeks and after the total intended dose has been administered, repeat iron studies may be considered. Patients should be monitored for evidence of iron overload, including signs and symptoms of cardiomyopathy, endocrinopathy, and hepatotoxicity. If evidence exists of iron overload..."
- The third bullet was revised: "Test doses are required for *low-molecular-weight* iron dextran, but not for ferric gluconate, or 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."
- The fourth bullet was added: "High-molecular-weight iron dextran is not recommended."
- Two bullets were removed:
  - ▶ "Most adverse events associated with iron dextran occur with high-molecular-weight iron dextran (Dexferrum)."
  - ▶ "If iron dextran preparation is used, IV low-molecular-weight iron dextran (INFeD®) is recommended."

### ANEM-D (2 of 3)

- Footnotes
  - ▶ Footnote "†" was added: "Ferric carboxymaltose may 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."
  - ▶ Footnote "‡" was revised: "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."
  - ▶ Footnote "¶" was added: "Premedications should be given prior to the IV iron test dose as reactions to the test dose may be severe."

### ANEM-D (3 of 3)

- The following references were added for ferric carboxymaltose:
  - ▶ Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. *Ann Oncol* 2013;24:475-482.
  - ▶ National Institutes of Health. Ferric carboxymaltose package insert. Available at: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=517b4a19-45b3-4286-9f6a-ced4e10447de> Accessed June 18, 2014.
- References were updated.



# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### HEMOGLOBIN CONCENTRATION TO PROMPT AN EVALUATION OF ANEMIA

Hemoglobin (Hb)  $\leq$  11 g/dL or  $\geq$  2 g/dL below baseline

### EVALUATION OF ANEMIA<sup>a,b</sup>

Evaluate anemia for possible cause as indicated ([see MS-3](#)):

- First check
  - Reticulocyte count and mean corpuscular volume (MCV)
- Then consider
  - Hemorrhage (stool guaiac, endoscopy)
  - Hemolysis (Coombs test, DIC panel, haptoglobin, indirect bilirubin, lactate dehydrogenase)
  - Nutritional (iron, total iron-binding capacity, ferritin, B<sub>12</sub>, folate)<sup>c</sup>
  - Inherited (prior history, family history)
  - Renal dysfunction (GFR  $<$  60 mL/min/1.73 m<sup>2</sup>, 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](#)

<sup>a</sup>The NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia were formulated in reference to adult patients.

<sup>b</sup>This is a basic evaluation for possible causes of anemia.

<sup>c</sup>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.

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

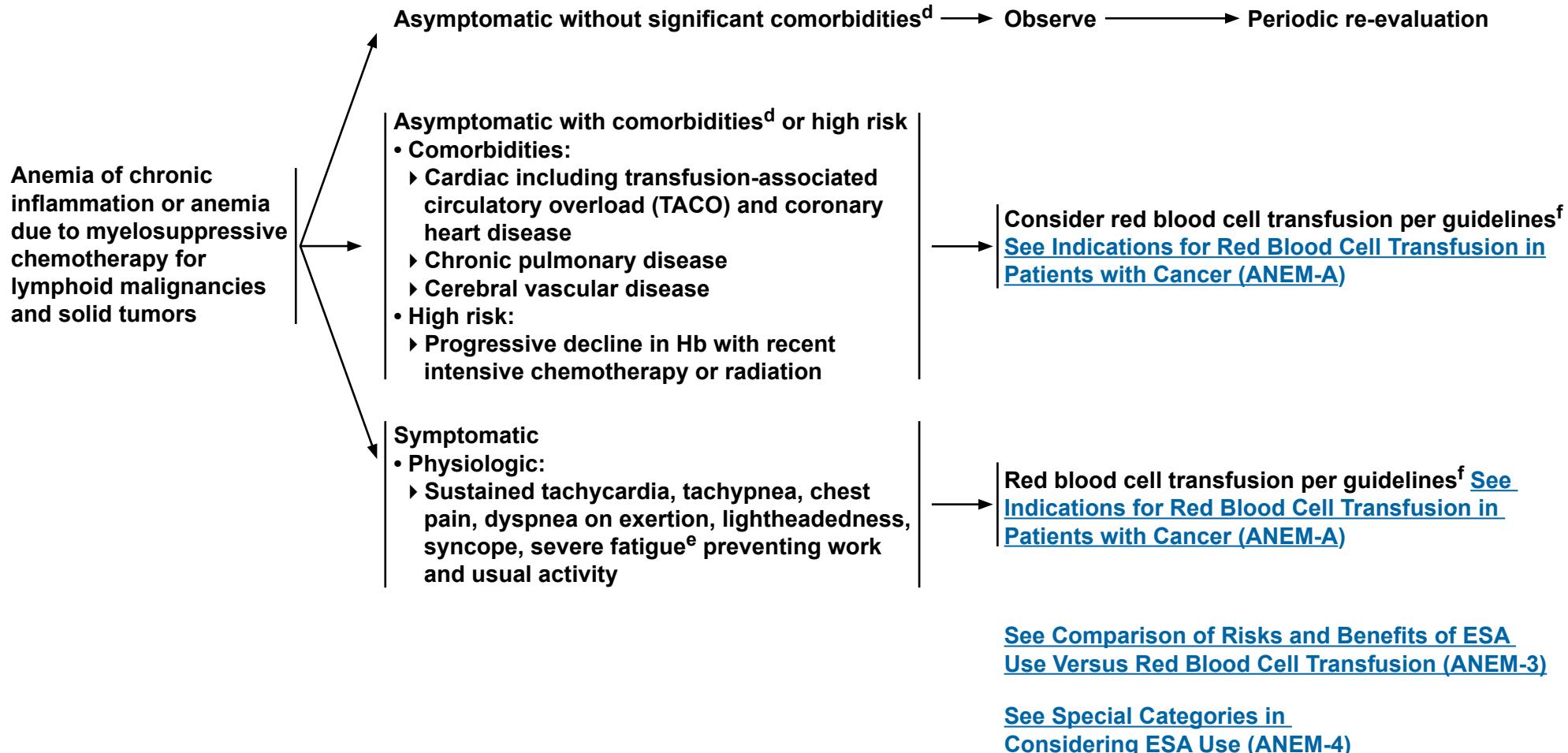
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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING



<sup>d</sup>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.

<sup>e</sup>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.

<sup>f</sup>See Discussion for further details on treating patients who may refuse blood transfusion (eg, Jehovah's Witnesses).

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### COMPARISON OF RISKS AND BENEFITS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION<sup>9</sup>

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 benefits of each method.

ESA in the Cancer Setting		Red Blood Cell Transfusion
<b>Risks</b>	<ul style="list-style-type: none"> <li>• Increased thrombotic events</li> <li>• Possible decreased survival</li> <li>• Time to tumor progression shortened</li> </ul>	<ul style="list-style-type: none"> <li>• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury)</li> <li>• TACO</li> <li>• Virus transmission (eg, hepatitis, HIV)</li> <li>• Bacterial contamination</li> <li>• Iron overload</li> <li>• Increased thrombotic events</li> <li>• Possible decreased survival</li> </ul>
<b>Benefits</b>	<ul style="list-style-type: none"> <li>• Transfusion avoidance</li> <li>• Gradual improvement in anemia-related symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Rapid increase of Hb and hematocrit levels</li> <li>• Rapid improvement in anemia-related symptoms</li> </ul>

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

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

<sup>9</sup>[See Discussion](#) for detailed information regarding the risks and benefits of ESA use and red blood cell transfusion.

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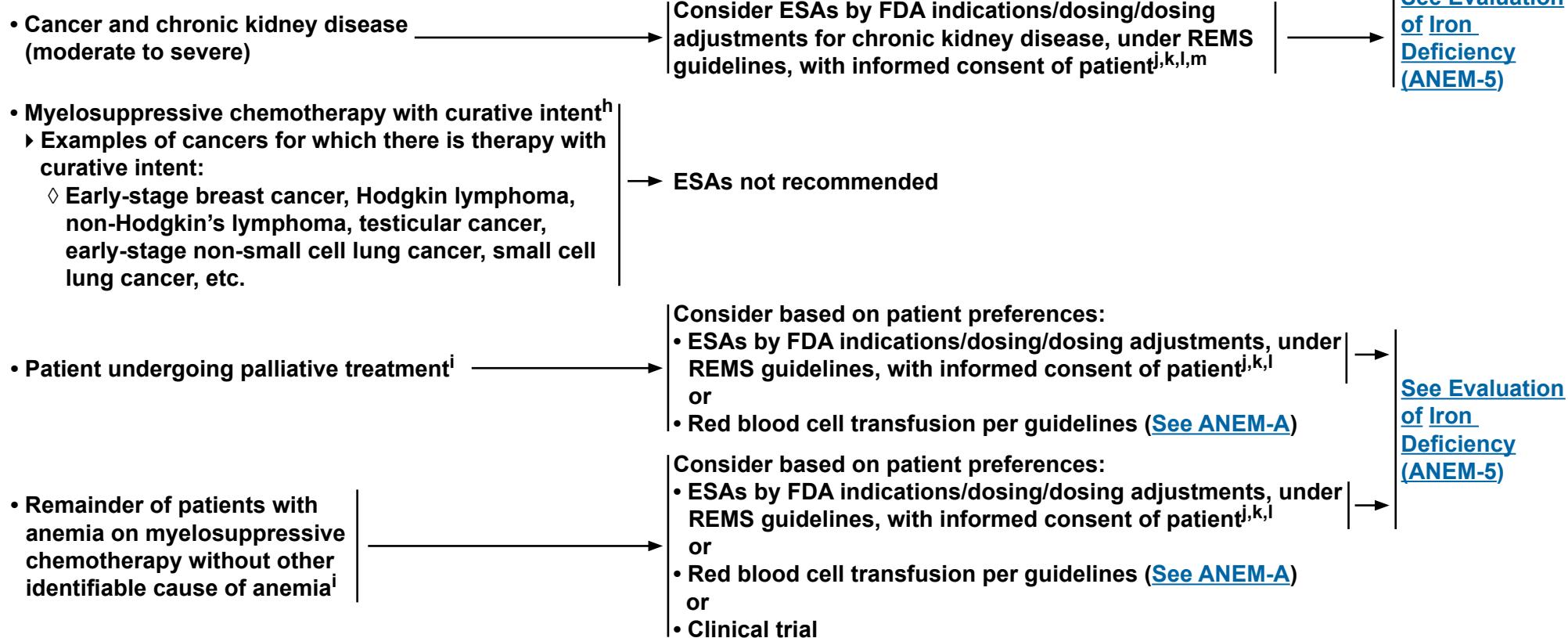
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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

[NCCN Guidelines Index](#)  
[Anemia Table of Contents](#)  
[Discussion](#)

### SPECIAL CATEGORIES IN CONSIDERING ESA USE



<sup>h</sup>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.

<sup>i</sup>[See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion \(ANEM-3\).](#)

<sup>j</sup>[See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects \(ANEM-B\).](#)

<sup>k</sup>Health care providers prescribing ESAs need to enroll in the ESA APPRISE program. See [REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis-Stimulating Agents \(ESAs\) \(ANEM-C\)](#).

<sup>l</sup>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](#)).

<sup>m</sup>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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## Cancer- and Chemotherapy-Induced Anemia

[NCCN Guidelines Index](#)  
[Anemia Table of Contents](#)  
[Discussion](#)

### EVALUATION OF IRON DEFICIENCY

#### EVALUATION

#### IRON STATUS

#### MANAGEMENT

Iron studies:  
Iron panel (serum iron, total iron-binding capacity, serum ferritin)<sup>c</sup>

Absolute iron deficiency<sup>n</sup>  
(ferritin <30 ng/mL AND TSAT <20%)

Consider IV or oral iron supplementation

Hb increases after 4 wks → Periodic evaluation (repeat ferritin and TSAT)

Functional iron deficiency in patients receiving ESAs<sup>o</sup>  
(ferritin 30-800 ng/mL AND TSAT 20%-50%<sup>p</sup>)

Consider IV iron supplementation<sup>q,r,s</sup> with erythropoietic therapy

Hb does not increase after 4 wks → See Functional iron deficiency pathway below

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

IV or oral iron supplementation is not needed

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

<sup>c</sup>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.

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

<sup>o</sup>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.

<sup>p</sup>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.

<sup>q</sup>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 \(ANEM-D\)](#)

<sup>r</sup>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.

<sup>s</sup>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 <sup>a,b</sup>

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

#### Asymptomatic Anemia

- Hemodynamically stable chronic anemia without acute coronary syndrome:
  - ▶ 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 to maintain Hb  $\geq$ 10 g/dL

<sup>a</sup>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.

<sup>b</sup>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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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

[NCCN Guidelines Index](#)  
[Anemia Table of Contents](#)  
[Discussion](#)

### ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (1 of 5)<sup>1-4</sup>

#### INITIAL DOSING

#### TITRATION FOR NO RESPONSE

#### TITRATION FOR RESPONSE

##### PACKAGE INSERT DOSING SCHEDULE

Epoetin alfa 150 units/kg 3 times wk by subcutaneous injection | → Increase dose of epoetin alfa to 300 units/kg 3 times 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

- 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-week period, reduce dose by 25% for epoetin alfa and by 40% for darbepoetin alfa.

##### ALTERNATIVE REGIMENS

Darbepoetin alfa 100 mcg fixed dose | → Increase darbepoetin alfa to up to 150-200 mcg fixed dose every wk by subcutaneous injection<sup>5</sup>  
or  
Darbepoetin alfa 200 mcg fixed dose | → Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection<sup>7</sup>  
or  
Darbepoetin alfa 300 mcg\* fixed dose | → Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection<sup>7</sup>  
or  
Epoetin alfa 80,000 units every 2 wks by subcutaneous injection<sup>8</sup>  
or  
Epoetin alfa 120,000 units every 3 wks by subcutaneous injection<sup>9</sup>

[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.<sup>10</sup>

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 OF 5)

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

##### Footnotes

<sup>1</sup>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.

<sup>2</sup>Less-frequent dosing regimens could be considered as an alternative to dose reduction.

<sup>3</sup>The dosages and regimens included in this table have been evaluated in patients with cancer receiving chemotherapy.

<sup>4</sup>IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See manuscript for detailed discussion.) [See Parenteral Iron Preparations \(ANEM-D\)](#).

##### References

<sup>5</sup>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.

<sup>6</sup>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.

<sup>7</sup>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.

<sup>8</sup>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.

<sup>9</sup>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.

<sup>10</sup>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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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 OF 5)

#### Survival of Patients with Cancer

- Studies have reported possible decreased survival in patients with cancer receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in patients receiving erythropoietic drugs for correction of anemia and target Hb levels of > 12 g/dL.<sup>1-8</sup> One analysis in patients with cancer not receiving active therapy found decreased survival in patients treated with ESAs.<sup>6</sup> 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,<sup>9,10,11,12</sup> two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.<sup>13,14</sup>
- Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.<sup>15-17</sup>
- 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 Benefits 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.<sup>18</sup> 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](#))
- Four meta-analyses reported an increase in relative risk of thrombotic events ranging from 48% to 69% with ESA use.<sup>9,12,13,14</sup> The absolute risk of venous thromboembolism was 7.5% in patients treated with ESAs compared to 4.9% in control patients.<sup>9</sup>
- 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.<sup>19</sup>

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

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

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

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



### 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.<sup>20</sup> 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.<sup>21</sup>
- In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia.<sup>22</sup> 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.<sup>23</sup> 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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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 OF 5)

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### 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<sup>1</sup>:
  - ▶ 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/ESAApraiseUI/public/ESA\\_APPRISE\\_Oncology\\_Program\\_Acknowledgment\\_Form\\_PATIENT.pdf](https://www.esa-apprise.com/ESAApraiseUI/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<sup>2</sup>:
  - ▶ 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 they have talked with their health care professional about the risks of ESAs before they can receive their first dose of an ESA.
- For selected safety information for health care providers, see <https://www.esa-apprise.com>.

<sup>1</sup>Adapted from: <https://www.esa-apprise.com/ESAApraiseUI/ESAApraiseUI/default.jsp#isi>

<sup>2</sup>Adapted from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm>

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### PARENTERAL IRON PREPARATIONS<sup>1-7</sup> (1 of 3)

- Parenteral iron preparations studied in patients with cancer:
  - ▶ Low-molecular-weight iron dextran
  - ▶ Ferric gluconate
  - ▶ Iron sucrose
  - ▶ Ferric carboxymaltose<sup>†</sup>
- Five<sup>2-6</sup> of six<sup>8</sup> studies have shown that parenteral iron products are helpful 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 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.<sup>5,8</sup> 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<sup>5,6</sup> or TSAT exceeds 50%.<sup>2</sup>
- 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.<sup>9,10</sup>
- Patients with active infection should not receive IV iron therapy.

[See Recommendations for Administering Parenteral Iron Products \(ANEM-D 2 of 3\)](#)

[See References \(ANEM-D 3 of 3\)](#)

<sup>†</sup>Ferric carboxymaltose may be considered when other parenteral iron preparations fail.<sup>7</sup> 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.<sup>11</sup>

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

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### PARENTERAL IRON PREPARATIONS<sup>1-6</sup> (2 of 3)<sup>†</sup>

#### RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

		Low-Molecular-Weight Iron Dextran <sup>13,‡</sup>	Ferric Gluconate <sup>14,‡</sup>	Iron Sucrose <sup>15,‡</sup>
Test dose <sup>¶</sup>	<b>Required</b>  <b>25 mg slow IV push and wait 1 hr before giving remainder of dose</b>	MD discretion	MD discretion	MD discretion
Dosage <sup>12,*</sup>	<b>100 mg IV over 5 min<sup>3</sup></b> <ul style="list-style-type: none"> <li>Repeated dosing once weekly for 10 doses to achieve total dose of 1 g or</li> <li>Total dose infusion given over several hours<sup>16,**</sup></li> </ul>	<b>125 mg IV over 60 min<sup>2,4,5,8</sup></b> <ul style="list-style-type: none"> <li>Repeated dosing given once weekly for 8 doses</li> </ul> <hr/> <ul style="list-style-type: none"> <li>Individual doses above 125 mg are not recommended based on published trial results<sup>8</sup></li> <li>Total treatment course = 1000 mg</li> </ul>	<b>200 mg IV over 60 min<sup>6</sup></b> <ul style="list-style-type: none"> <li>Repeated dosing given every 2-3 weeks or</li> <li>200 mg IV over 2-5 min</li> <li>Repeated dosing given every 1-4 weeks</li> </ul> <hr/> <ul style="list-style-type: none"> <li>Individual doses above 300 mg are not recommended<sup>17</sup></li> <li>Total treatment course = 1000 mg</li> </ul>	
Routes	<b>IV infusion</b>  <b>IM (not recommended)</b>	IV injection/infusion	IV injection/infusion	

<sup>†</sup>Ferric carboxymaltose may be considered when other parenteral iron preparations fail.<sup>7</sup> 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.<sup>11</sup>

<sup>‡</sup>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.

<sup>¶</sup>Premedications should be given prior to the IV iron test dose as reactions to the test dose may be severe.

\*For additional details about iron dosing, see prescribing information.

\*\*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 wks if inadequate hemoglobin response.

[See References \(ANEM-D 3 of 3\)](#)

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**ANEM-D  
2 OF 3**



# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

### PARENTERAL IRON PREPARATIONS<sup>1-6</sup> (3 of 3)

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### Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/11/14

### 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](#).....MS-2

Etiology .....MS-2

Anemia Associated with Myelosuppressive Chemotherapy....MS-2

#### [Table 1. National Cancer Institute Anemia Scale](#).....MS-3

Guideline Overview .....MS-3

#### [Screening Evaluation](#) .....MS-3

Initial Assessment .....MS-3

Approaches to Evaluation.....MS-4

#### [Follow-up Risk Assessment](#) .....MS-5

#### [Red Blood Cell Transfusion](#) .....MS-6

Benefits of Transfusion.....MS-6

Risks of Transfusion .....	MS-6
Iron Overload .....	MS-6
Transfusion Goals and Basic Principles .....	MS-7
Cancer Patients Who Refuse Blood Transfusions .....	MS-7
<b>Erythropoietic Therapy</b> .....	<b>MS-8</b>
Benefits of ESA Therapy .....	MS-8
Risks of ESA Therapy .....	MS-8
Possible Increased Mortality and Tumor Progression .....	MS-8
Risk of Thromboembolism .....	MS-9
Risk of Hypertension/Seizures .....	MS-9
Risk of Pure Red Cell Aplasia .....	MS-9
NCCN Recommendations .....	MS-10
Dosing Schedules .....	MS-11
Response Assessment and Dose Titration .....	MS-11
<b>Iron Monitoring and Supplementation</b> .....	<b>MS-12</b>
Functional Iron Deficiency and ESA Therapy .....	MS-12
Intravenous Iron and Oral Iron.....	MS-12
NCCN Recommendations .....	MS-13
Clinical Examples of Iron Status .....	MS-14
Patient Case .....	MS-14
Scenario 1: Serum ferritin 5 ng/mL & TSAT 4% .....	MS-15
Scenario 2: Serum ferritin 10 ng/mL & TSAT 22% .....	MS-15
Scenario 3: Serum ferritin 580 ng/mL & TSAT 12% .....	MS-15
Scenario 4: Serum ferritin 100 ng/mL & TSAT 30% .....	MS-15
Scenario 5: Serum ferritin 500 ng/mL & TSAT 40% .....	MS-15
<b>Future Development</b> .....	<b>MS-16</b>
<b>References</b> .....	<b>MS-17</b>

### Overview

Anemia is prevalent in 30% to 90% of cancer patients.<sup>1</sup> Correction of anemia can be achieved by either treating the underlying etiology or providing supportive care by transfusion with packed red blood cells (PRBC) or administration of erythropoiesis-stimulating agents (ESAs), with or without iron supplementation. The purpose of these NCCN Guidelines is two-fold: 1) to operationalize the evaluation and treatment of anemia in adult cancer patients, with an emphasis on those patients with anemia who are receiving concomitant chemotherapy; and 2) to enable the patient and clinician to assess anemia treatment options based upon the individual patient condition.

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 packed cell volume to subnormal levels. An anemia scale by grade is provided by the NCI (Table 1).

### Etiology

Causes of anemia in cancer patients are often multifactorial, adding to the complexity of the problem in evaluation. 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.<sup>2,3</sup> The malignancy itself can lead to or exacerbate anemia in a number of ways.<sup>4</sup> 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 vessel or organ damage can further exacerbate anemia from cancer. Additional indirect effects may include nutritional

deficiencies caused by loss of appetite in the cancer patient, hemolysis by immune-mediated antibodies, or changes in coagulation capability. For this myriad of reasons, anemia is prevalent among cancer patients at initial presentation. For example, 32% of non-Hodgkin's lymphoma patients have anemia at diagnosis,<sup>5</sup> while 49% of patients are anemic when diagnosed with gynecologic cancer.<sup>6</sup> In addition, the myelosuppressive effect of chemotherapy is a significant contributing factor to anemia for patients undergoing cytotoxic treatment.<sup>7</sup> Radiation therapy to the skeleton is also associated with hematologic toxicity. In a retrospective analysis, approximately one-third of 210 patients undergoing radiotherapy to the cranium and/or spine for treatment of primary tumors of the central nervous system developed grades 3 and 4 hematologic side effects.<sup>8</sup>

#### ***Anemia Associated with Myelosuppressive Chemotherapy***

Chemotherapeutic agents induce anemia by directly impairing hematopoiesis, including synthesis of RBC precursors, in the bone marrow.<sup>4</sup> In addition, nephrotoxic effects of particular cytotoxic agents (eg, platinum-containing agents) can also lead to anemia through decreased production of erythropoietin by the kidney.<sup>4</sup>

Studies have identified patients with lung cancer and gynecologic malignancies as having a very high incidence of chemotherapy-induced anemia (CIA).<sup>6,7</sup> Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity.<sup>7</sup> It is important to review the toxicity profile of each agent as newer regimens may or may not cause anemia. Consider the single agents cabazitaxel, docetaxel, and enzalutamide, which have been shown to cause grade III to IV anemia in 11%, 5%, and 0% of patients, respectively.

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, for patients in the European Cancer Anemia Survey (ECAS)<sup>6</sup>, 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. 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 of CIA include the nadir Hb level, the time to the nadir Hb level (roughly estimated at 2 weeks, but time can vary), and whether a Hb measurement is considered to be pre- or post-nadir.<sup>4</sup>

**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>.

### 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. Special categories are outlined in considering the use of ESAs for long-term management. Further

information is provided on transfusion, erythropoietic therapy, and iron supplementation.

This guideline algorithm is 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 from the [NCCN Guidelines Table of Contents](#).

### Screening Evaluation

Given the wide variation in the Hb level among healthy subjects, a universal “normal” value is difficult to define. For cancer patients, 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 cancer patient may suffer from anemia as the result of a combination of causes, some of which may not be directly related to cancer. The overall goals of evaluation are to characterize the anemia and identify any underlying comorbidity that can be potentially corrected.

### Initial Assessment

Initial broad characterization involves a complete blood count (CBC) with indices that will reveal if other cytopenias are present. A visual review of the peripheral blood smear is critical to confirm the size, shape, and color of RBCs. A detailed history and physical exam must be taken. The history should include the duration and time of onset of symptoms, comorbidities, family history, and exposure to antineoplastic drugs and radiation. Common complaints are syncope, exercise dyspnea, headache, vertigo, chest pain, fatigue (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 tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with normal 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.<sup>9</sup> 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 stool, petechiae, and heart murmur, among others.

### Approaches to Evaluation

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

- Microcytic (<80 fL)—most commonly caused by iron deficiency; other etiologies include thalassemia, anemia of chronic disease, and sideroblastic anemia.
- Macrocytic (>100 fL)—the majority of which is megaloblastic, pointing towards B12 or folate deficiency caused by insufficient uptake or inadequate absorption through lack of intrinsic factor. Non-megaloblastic anemia is less common and may be the result of alcoholism. MDS and certain drugs such as hydroxyurea or trimethoprim/sulfamethoxazole can also cause macrocytosis.
- 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 count (see below).

The kinetic approach focuses on the underlying mechanism of anemia, distinguishing among the production, destruction, and loss of RBCs. The main starting point is the reticulocyte count corrected against the degree of anemia (reticulocyte index, RI), a measurement of the fraction of reticulocytes (immature RBC) in blood that provides an indication of the RBC production capacity by the bone marrow. The normal RI ranges between 1.0 and 2.0.

- Low RI indicates decreased RBC production, suggesting iron deficiency, B12/folate deficiency, aplastic anemia, or bone marrow dysfunction due to cancer or cancer-related therapy (radiation or myelosuppressive chemotherapy).
- High RI indicates normal or increased RBC production, suggesting blood loss or hemolysis in the anemic patient.

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. Below is a summary of additional cues or tests for common underlying ailments:

- Absolute iron deficiency—low iron and high total iron binding capacity (TIBC) resulting in transferrin saturation (TSAT) less than 20% and ferritin less than 30 ng/mL. The reference interval for serum ferritin depends on the specific laboratory used. 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 discussed within the context of ESA therapy in a later section.

- B12/folate deficiency—low vitamin B12 or folate levels (commonly tested together with iron studies)
- Hemorrhage—stool guaiac positive, endoscopy findings
- Hemolysis—Coombs test positive, disseminated intravascular coagulation (DIC) panel positive, low haptoglobin levels, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH)
- Chronic kidney disease (CKD)—glomerular filtration rate (GFR) less than 60 mL/min/1.73 m<sup>2</sup> 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 or myelosuppressive chemotherapy (if applicable) should be considered as the cause of anemia in the cancer patient.

### Follow-up Risk Assessment

If the likely cause of anemia is cancer-related inflammation or myelosuppressive chemotherapy (for solid tumors or lymphoid malignancies), a risk assessment of the anemia is necessary to determine the initial intervention plan—whether the patient requires an immediate boost in Hb levels by PRBC transfusion. Consideration of

ESA therapy is generally a long-term management decision given its onset of action and potential risks.

It is important to note that the decision to offer PRBC transfusion should not be made strictly on the basis of whether the Hb level of the patient has reached a certain threshold or “trigger.” 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, since physiologic adjustments to compensate for lower oxygen-carrying capacity of the blood can occur with 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, degree of 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 a progressive decline in Hb level following anti-cancer treatment.



### Red Blood Cell Transfusion

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, irradiation, freezing, and washing. Patients who are immunocompromised may need PRBCs that are cytomegalovirus (CMV) negative. One unit of PRBC (300 cc) can have a hematocrit 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.<sup>10</sup>

### Benefits of Transfusion

The major benefit of transfusion with PRBC, offered by no other treatment of anemia, is a rapid increase in Hb and hematocrit levels. Hence, PRBC transfusion is the only intervention option for patients who require immediate correction of anemia. Transfusion of 1 unit (300 cc) of PRBC has been estimated to result in an average increase in Hb level of 1 g/dL or hematocrit by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.<sup>10,11</sup> Additionally, patients receiving concomitant fluid resuscitation may not experience an Hb increase of 1 g/dL per unit of blood transfused.

Results of a number of studies evaluating the impact of transfusion on mortality in critically ill patients 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 (HR, 0.26; 95% CI, 0.09–0.75,  $P = .01$ ).<sup>12</sup>

### Risks of Transfusion

Risks associated with PRBC transfusion include transfusion-related reactions, congestive heart failure, bacterial contamination and viral infections, and iron overload (reviewed by Spivak, Gascon, and Ludwig<sup>13</sup>). 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.<sup>14,15</sup> Bacterial infection is the most common form, occurring as frequently as 1 in 3000 random-donor samples before the mandate of bacterial screening since 2004.<sup>15</sup> 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.<sup>16,17</sup> However, Khorana et al analyzed data from discharge summaries of cancer patients admitted to 60 U.S. medical centers between 1995 and 2003 and found increased risks ( $P < .001$ ) of venous thromboembolism (VTE) (OR, 1.60; 95% CI, 1.53–1.67), arterial thromboembolism (OR, 1.53; 95% CI, 1.46–1.61) and in-hospital mortality (OR, 1.34; 95% CI, 1.29–1.38) associated with PRBC transfusions.<sup>18</sup>

### Iron Overload

The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anemia (ie, patients with MDS).<sup>19</sup> However, iron overload is unlikely to occur in patients receiving transfusions that are restricted to the limited time period corresponding to chemotherapy treatment (usually <1 year). Full reliance on PRBC transfusion as a treatment for CIA may exacerbate the limited supply of blood in the United States, in addition to contributing to inconvenience and discomfort experienced by patients. A recent analysis that modeled the impact of reducing ESA

use in this population indicated that approximately 202,000 additional units of PRBC would be required to treat anemia in patients undergoing chemotherapy if ESA use was reduced by 75%.<sup>20</sup>

### Transfusion Goals and Basic Principles

There is wide variation in reported RBC transfusion practice,<sup>14,21,22</sup> but institutional and clinical practice guidelines are often “restrictive” in that they are based on limiting exposure to allogeneic blood. The overall goal of transfusion is to treat or prevent deficit of oxygen-carrying capacity in 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 Cancer Patients*). Transfusion is rarely indicated when the Hb level is above 10 g/dL.<sup>23</sup> The AABB (formerly the American Association of Blood Banks) recently published guidelines based on a systematic review of randomized trials evaluating transfusion thresholds and using GRADE guidelines methodology.<sup>22</sup> AABB recommendations include: 1) using a Hb level of 7 to 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 on the cancer population. During 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 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.<sup>24,25</sup> However, if repeated transfusions are required, leukocyte-reducing blood and use of premedication may be used to minimize adverse transfusion reactions. In most instances, PRBCs should be transfused by the unit and reassessment should be conducted after each transfusion.

### Cancer Patients Who Refuse Blood Transfusions

Cancer patients 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 cancer patients, but investigators have outlined strategies to permit such treatment to be given without transfusion.<sup>26-28</sup> These strategies include minimizing blood loss by restricting routine laboratory testing, using pediatric blood collection tubes, using anti-fibrinolytic drugs for oral bleeding, aggressive treatment of mucositis, suppressing menses, and minimizing gastrointestinal bleeding by using proton pump inhibitors, stool softeners, etc. Any baseline coagulation abnormalities should be fully evaluated and corrected prior to myelosuppressive treatment. Pre-existing absolute iron deficiency should be corrected, and intravenous (IV) iron should be used if functional iron deficiency is present. ESAs may be offered after chemotherapy; however, prior approval from third party payers may be necessary 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,  $SaO_2 = 1.0$ ) has been used to increase dissolved oxygen in patient's blood.<sup>27</sup>

### Erythropoietic Therapy

RBC production is normally controlled by erythropoietin, a cytokine produced in the kidneys. First introduced in 1989, ESAs are synthetic, recombinant human erythropoietin that can stimulate erythropoiesis in patients with low RBC levels. At present, two ESAs are available in the United States: epoetin alfa and darbepoetin alfa. 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 cancer patients treated with ESA therapy, an Hb increase of  $\geq 1$  g/dL was attained in 65% of patients.<sup>29</sup>

Popularity of ESAs reached a peak in 2003 to 2004, when their use for cancer patients alone accounted for 17% of all Medicare Part B spending.<sup>30</sup> However, this paradigm has shifted dramatically after evidence of increased VTE, and mortality has emerged with certain Hb targets in certain cancer subtypes in recent years (see below).

### Benefits of ESA Therapy

Avoidance of transfusion is the main benefit of ESAs. Administration of ESA therapy has been demonstrated to decrease PRBC transfusion requirements in cancer patients undergoing chemotherapy. In a randomized, placebo-controlled study by Littlewood and colleagues, epoetin alfa was shown to reduce transfusion requirements in patients with anemia receiving chemotherapy.<sup>31</sup> Transfusion requirements were significantly decreased in the epoetin arm compared with placebo

(24.7% vs. 39.5%,  $P = .0057$ ), and rise in Hb level was increased (2.2 g/dL vs. 0.5 g/dL;  $P < .001$ ).<sup>31</sup> A double blind, placebo-controlled, randomized phase III study of darbepoetin alfa enrolled 320 patients ( $Hb \leq 11$  g/dL) receiving darbepoetin alfa at 2.25 mcg/kg/week versus placebo.<sup>32</sup> 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 of 91 randomized, controlled clinical trials involving use of ESA therapy that enrolled a total of 20,102 patients undergoing treatment for cancer.<sup>33</sup> A decreased relative risk for transfusion was observed in the patients receiving erythropoietin (RR, 0.65; 95% CI, 0.62–0.68).

### Risks of ESA Therapy

#### *Possible Increased Mortality and Tumor Progression*

Starting from 2007, the FDA made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa,<sup>34,35</sup> including addition of a "Black Box" label warning and implementation of a risk management program known as Risk Evaluation and Mitigation Strategy (REMS, see algorithm). The strengthened FDA restrictions were mainly based on the results of 8 randomized studies that individually showed a decrease in overall survival and/or decreased locoregional disease control with ESA usage for advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers (NSCLC).<sup>36–43</sup> Of the 8 studies, three investigated ESA effects in patients who underwent chemotherapy. All 8 trials had an off-label target Hb level of over 12 g/dL.

Worsened health outcomes associated with the use of ESAs have been confirmed in 5 meta-analyses of 51 to 91 randomized controlled trials when targeting Hb levels above 12 g/dL.<sup>33,44–48</sup> These analyses reported increased mortality in patients receiving ESAs with statistically

significant relative risks/hazard ratios of 1.17 (95% CI, 1.06–1.30),<sup>45</sup> 1.15 (95% CI, 1.03–1.29),<sup>46</sup> 1.10 (95% CI, 1.01–1.20),<sup>44</sup> 1.17 (95% CI, 1.06–1.29),<sup>33</sup> and 1.17 (1.04–1.31).<sup>48</sup> However, this association has been refuted by two other meta-analyses by Ludwig et al<sup>49</sup> (HR, 0.97; 95% CI, 0.85–1.1) and Glaspy et al<sup>50</sup> (OR, 1.06; 95% CI, 0.97–1.15) reporting no statistically significant effect of ESAs on mortality or progression. In addition, several recent pharmacovigilance trials reported no decrease in survival with ESA use in patients with chemotherapy-related anemia when an Hb target range of 13 g/dL was utilized.<sup>51–53</sup> One of these is an update on the PREPARE trial that originally reported increased deaths among breast cancer patients receiving darbepoetin compared to no darbepoetin.<sup>36</sup> The update found no difference in overall survival; there was a trend towards decreased disease-free survival that failed to reach statistical significance.<sup>53</sup> There are also data from randomized studies that showed no increase in mortality with ESA use according to prescribing label specifically in patients receiving chemotherapy for small cell lung cancer (SCLC).<sup>54,55</sup>

### Risk of Thromboembolism

Increased thromboembolic risks have been associated with ESA treatment of cancer patients. The cause of VTE is complex; a heightened baseline risk is related to the malignancy itself as well as to chemotherapy (see [NCCN Guidelines for Venous Thromboembolic Disease](#)).<sup>56–59</sup> Other risk factors for VTE in cancer patients include prior history of VTE, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, prolonged inactivity by hospitalization, steroids, and comorbidities such as hypertension.<sup>60</sup>

Overall, results from meta-analyses established significant association between increased risk of thrombotic events and ESA usage, with

statistically significant risk ratio or odds ratio ranging from 1.48 to 1.69.<sup>33,44,46,48–50</sup> A combined analysis of six trials on darbepoetin alfa by Glaspy and colleagues<sup>61</sup> also found an increased trend of thromboembolism for patients with Hb over 12 g/dL (RR, 1.66; 95% CI, 0.9–3.04) or patients achieving over a 1 g/dL increase in 14 days (RR, 1.67; 95% CI, 0.96–2.88). Also, an increased risk of stroke was associated with darbepoetin alfa in a clinical trial of patients with CKD (HR, 1.92; 95% CI, 1.38–2.68).<sup>62</sup> The increased risk of thromboembolism in cancer patients 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 cancer patients receiving ESAs.

### Risk of 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.<sup>63</sup> While it is unclear whether cancer patients receiving ESA therapy are at risk for seizures, Hb levels should be monitored before and during the use of ESAs to decrease the risk of 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).<sup>33</sup>

### Risk of Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count, a loss of bone marrow erythroblasts, neutralizing antibodies against erythropoietin, and resistance to ESA therapy. From 1998 to 2004, however, a marked rise in incidence (191 cases) was observed, 90% of which occurred with Eprex®, an epoetin alfa product used outside of the United States.<sup>64,65</sup> Causation was attributed to formulations without human serum albumin, subcutaneous (SC) administration, and uncoated rubber stoppers.<sup>66</sup>

Interventions designed accordingly reduced the incidence 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.<sup>67</sup> PRCA resulted in a class label change for all ESAs. Toxicity has been reported predominantly in patients with chronic renal failure receiving SC ESAs.

The NCCN Panel recommends that any cancer patient who develops a sudden loss of response to ESA, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect. ESAs should be withheld while plasma is sent to ESA-producing pharmaceutical companies for evaluation of assays for 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.

### 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 section of algorithm). Although the ESA APPRISE program does not apply to cancer patients who are receiving ESA therapy for CKD, the panel still recommends its use.

For cancer patients, 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.<sup>34</sup> Hence,

patients not receiving concomitant myelosuppressive chemotherapy are not eligible. As discussed above, 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. These include primary and adjuvant chemotherapy for malignancies such as early-stage breast cancer and NSCLC, lymphomas, and testicular cancer, among others. An exception to this may be SCLC, for which there are trials demonstrating no negative impact on survival or disease progression (see above). Patients undergoing palliative treatment may consider ESA therapy or transfusion depending on their preference and values. The NCCN Guidelines Panel recognized 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 be: consideration of RBC transfusion, clinical trial enrollment if available, and consideration of ESAs. Upon decision of ESA use, physicians are advised to use the lowest dose necessary to avoid transfusion.

CKD is an independent indication for ESA therapy. Risks 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 of over 11 g/dL.<sup>62,68-70</sup> 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<sup>71</sup>). For example, CKD patients not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor

ESAs over transfusions to treat severe anemia by careful dosing. In the scenario where the CKD patient has a curable solid tumor, ESAs should not be administered during chemotherapy, but may be used with caution after chemotherapy is complete, keeping in mind the possibility of residual disease. Risk of thrombosis must be taken into account in weighing the risk-benefit ratio.

Most hematopoietic stem cell transplant patients require transfusion support. Nonetheless, ESA therapy may be useful in some instances. For example, ESA may be administered post-transplant to increase the hematocrit in order to allow phlebotomy in cases of transfusional iron overload. There have been reports of ESA efficacy in patients who refuse blood transfusions while undergoing autologous stem cell transplantation.<sup>72-74</sup> 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.

### 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 cancer patients are 150 units/kg three times weekly administered SC<sup>31,75</sup> and 40,000 units once weekly SC.<sup>39,42,43,76</sup> Both of these initial dose schedules are currently recommended. Other dosing ranges and schedules of epoetin alfa may be considered, including an

extended dosing of 80,000 units SC every 2 weeks<sup>77</sup> and a dose of 120,000 units SC once every 3 weeks.<sup>78</sup>

Although darbepoetin doses were initially administered at 2.25 mcg/kg SC every week,<sup>32,37,79</sup> there has been interest in using fixed doses and 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 ( $\geq 11$  g/dL) was 77% in the weekly arm and 84% for patients receiving darbepoetin alfa every three weeks.<sup>79</sup> Currently the NCCN Panel recommends both schedules. A number of studies have demonstrated the safety and efficacy of alternative dosing schedules for darbepoetin alfa. These include a fixed weekly dose of 100 mcg,<sup>32</sup> a fixed dose of 200 mcg every 2 weeks,<sup>80</sup> and 300 mcg every 3 weeks.<sup>81</sup>

### 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 to avoid transfusion.

ESAs require at least 2 weeks of treatment before there is an increase in the number of RBCs. Hb levels should be measured weekly until they stabilize. 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 and titration*) for patients receiving chemotherapy who show no response (<1 g/dL in Hb increase) in Hb level following 4 weeks of epoetin alfa or 6 weeks of



darbepoetin alfa. Iron supplementation can be considered to improve response to ESA therapy (see below). 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 with the goal 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 chemotherapy is complete and anemia has resolved, usually within 6 weeks.

### Iron Monitoring and Supplementation

Iron deficiency is reported in 32% to 60% of cancer patients, most of whom are also anemic.<sup>82</sup> Absolute iron deficiency refers to the depletion of total body iron stores. It is characterized by low Hb level, TSAT, and ferritin level. Functional iron deficiency is a condition in which stored iron is apparently sufficient but bioavailable iron is deficient. While Hb level and TSAT will be low, ferritin level usually remains within normal limits. Laboratory diagnosis of this condition was detailed by Thomas and colleagues.<sup>83</sup>

### Functional Iron Deficiency and ESA Therapy

Functional iron deficiency occurs when there is a failure to release iron rapidly enough to keep pace with erythropoiesis. 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.<sup>84,85</sup> 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.

### 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).<sup>86</sup> Evidence from 5 published studies utilizing iron in conjunction with an ESA suggests that IV iron is superior to oral iron.<sup>87-91</sup> Eligibility criteria for these trials varied widely (serum ferritin requirement ranging from >10 ng/mL to less than 900 ng/mL and TSAT requirement ranging from >15% to <60%). Only one study provided guidelines for TSAT monitoring,<sup>90</sup> while two studies provided guidelines for ferritin monitoring.<sup>89,92</sup>

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).<sup>87</sup> 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 as equally efficacious as TDI. In a second open-label study by Henry and colleagues,<sup>90</sup> 187 anemic cancer patients receiving chemotherapy and epoetin alfa were randomized to no iron, oral ferrous sulfate three times daily, or weekly IV ferric gluconate. IV iron produced a significantly greater Hb response than oral or no iron. The Hb response rate ( $\geq 2$  g/dL increase) was also higher in the IV arm (73%) compared to oral (45%) or no iron (41%). A third study was conducted on 67 patients with lymphoproliferative malignancies not undergoing chemotherapy.<sup>89</sup>



# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

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 higher mean change in Hb level from baseline (2.76 vs. 1.56 g/dL,  $P = .0002$ ) and in a higher Hb level response rate ( $\geq 2$  g/dL increase) (87% vs. 53%,  $P = .0014$ ) compared to the no iron group.

Two additional studies were published in 2008. Bastit et al reported their open-label trial on 396 patients with nonmyeloid malignancies undergoing chemotherapy (Hb less than 11 g/dL).<sup>88</sup> These were treated with darbepoetin alfa with or without IV iron (iron sucrose or ferric gluconate, proportion of patients receiving each preparation has not been reported) 200 mg every three weeks for 16 weeks. Again, hematopoietic responses and time to reach target Hb level was improved in the IV iron arm. Most significantly, this is the first and only 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,<sup>91</sup> 149 patients with solid tumors and CIA were randomly assigned to weekly darbepoetin alfa with or without ferric gluconate. This is the first trial that excluded patients with absolute or functional iron deficiency; eligibility requirements included serum ferritin levels  $>100$  ng/mL and TSATs  $\geq 20\%$ . The ESA/IV iron group showed a higher hematopoietic response rate (93% vs. 70%,  $P = .0033$ ) compared to the control group. These studies demonstrated that concurrent IV iron enhanced hematologic response to ESAs, although there is insufficient evidence to determine whether iron supplementation can allow an ESA dose decrease. Long-term effects of IV iron supplementation in cancer patients were not assessed in any of these five trials.

In 2011, Steensma et al<sup>93</sup> published findings from the largest trial to date that challenged results from the above studies. 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 lack of response may be that the mean baseline TSAT for patients in the IV iron group was 22.5%, a value above what is considered to be associated with functional iron deficiency.

A meta-analysis evaluating the role of iron supplementation has been reported in abstract form.<sup>94</sup> This includes seven randomized controlled trials involving 1777 patients with CIA. Oral or IV iron supplementation with ESAs reduced transfusion rates compared to no iron. IV iron but not oral iron was associated with improved hematopoietic response rates compared to ESA alone. No difference in adverse events was found.

### NCCN Recommendations

In the absence of a universal numerical definition of iron deficiency used in relevant studies, the NCCN Panel recognized that ferritin and TSAT values were used to define absolute and functional iron deficiencies represent moving targets.

Absolute iron deficiency is defined as ferritin level below 30 ng/mL and TSAT below 20%. If the 2 parameters are discordant, a low ferritin value should take precedence in determining whether iron supplementation will be beneficial. IV or oral iron products alone (without an ESA) are recommended for cancer patients with 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 is required as some patients, especially those with continued internal bleeding, may suffer a relapse.

A ferritin level of 30 to 100 ng/mL and concurrent TSAT of 20% to 50% indicate adequate iron stores, unless the patient is receiving an ESA.



# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

Patients receiving ESA therapy with a ferritin between 30 and 100 ng/mL and TSAT 20% to 50% will develop functional iron deficiency and will likely benefit from IV iron. Iron monotherapy has not been studied specifically in patients with functional iron deficiency not receiving ESA therapy. As previously discussed, most studies showed that IV iron is superior over oral iron and should be used.<sup>87-91</sup> Based on these studies, patients with a baseline TSAT below 20% had a higher response rate to IV iron supplementation in addition to ESA. Response rate is diminished and prolonged as TSAT increased from 20% to 50%. 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.<sup>95-97</sup> Most adverse events associated with iron dextran occur with high-molecular-weight iron dextran (Dexferrum®).<sup>98</sup> The recommended iron dextran product is low-molecular-weight iron dextran (INFed®).<sup>99</sup> 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. Dosage details for administering parenteral iron therapy are listed in the algorithm (see *Recommendations for administering parenteral iron products*). Although data are conflicting in the literature, concerns exist regarding IV iron possibly promoting inflammation and bacterial growth.<sup>100</sup> Hence, iron supplementation is not recommended for patients with an active infection.

None of the six studies on iron supplementation in conjunction with ESAs 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 or when the MCV <80 fL or evidence of hypochromic RBCs are seen in 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.<sup>89,93</sup> 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 or if TSAT exceeds 50%.<sup>88-90</sup>

Individuals with ferritin level above 800 ng/mL or TSAT over 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 cancer patients.

#### 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 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, hematocrit 26.7%, MCV 73 fL, 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



# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

[NCCN Guidelines Index](#)  
[Anemia Table of Contents](#)  
[Discussion](#)

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 ferritin <30 ng/mL and TSAT <20%, this patient has absolute iron deficiency and would benefit from iron repletion. Reducing transfusion requirements remains a 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.<sup>87</sup>

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

With a low ferritin and normal TSAT, 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 level and TSAT are discordant, the low ferritin should take precedence to determine if IV iron therapy would be beneficial to the patient. Iron would be beneficial as these laboratory values potentially reflect transition from an iron replete to an iron deficient state. For the same reasons as discussed above, IV iron is preferred. It is also possible for TIBC to be low secondary to malnutrition, resulting in a normal TSAT despite definitive absolute iron deficiency. ESA use should be considered only after iron repletion.

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

With a normal or elevated ferritin and low TSAT, 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 is low. Thus, patients with ferritin levels in excess of 100 ng/mL could be treated the same with IV iron, as discussed above. However, in this instance, an ESA should be considered first. This is because as the ferritin 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 little data to currently support IV iron added to an ESA for patients with a ferritin >500 ng/mL,<sup>101</sup> 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 percent of patients responding to the ESA as well as reduce the time to response.

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

As TSAT increases from 20% to 50%, the percentage of patients responding to iron decreases; therefore, this patient may not necessarily require IV iron until TSAT 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 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 red cell transfusion.

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

These ferritin and TSAT parameters suggest functional iron deficiency is unlikely because TSAT is typically low in that condition. Therefore, this patient is unlikely to benefit from iron therapy since they are iron replete. In this scenario, an ESA may be considered. Because ESA use induces functional iron deficiency by increasing iron utilization without the compensatory ability to mobilize storage iron in a timely manner, iron repletion can be initiated if response to ESA is not seen and the patient remains transfusion-dependent. Of note, improved response is

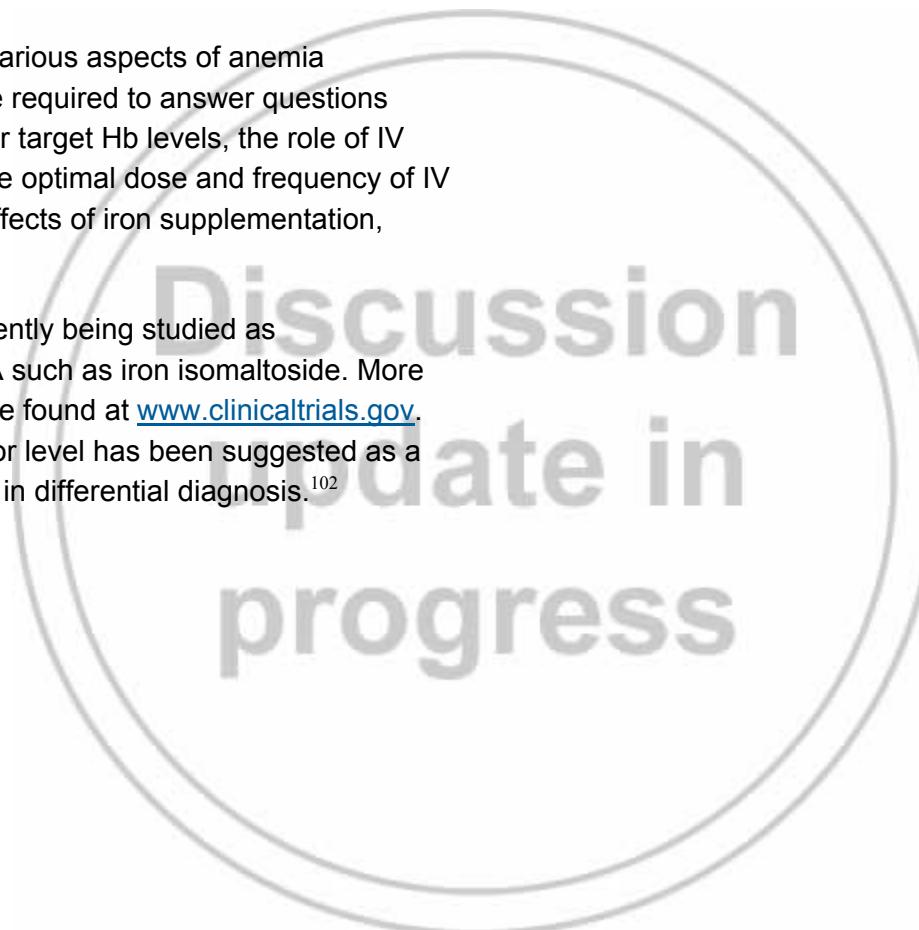


generally expected as TSAT decreases from 50% to 20%. Ultimately, it is up to the treating clinician to determine whether the potential benefits of iron administration are likely to outweigh the risks.

### 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](http://www.clinicaltrials.gov). In addition, soluble transferrin receptor level has been suggested as a marker of iron deficiency that can aid in differential diagnosis.<sup>102</sup>



Discussion  
Update in  
progress

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

[NCCN Guidelines Index](#)  
[Anemia Table of Contents](#)  
[Discussion](#)

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

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# NCCN Guidelines Version 1.2015

## Cancer- and Chemotherapy-Induced Anemia

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# NCCN Guidelines Version 1.2015

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## Cancer- and Chemotherapy-Induced Anemia

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Discussion  
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progress