

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer- and Chemotherapy- Induced Anemia

Version 1.2013

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NCCN Guidelines Version 1.2013 Panel Members Cancer- and Chemotherapy-Induced Anemia

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

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical_trials/physician.html](#).

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

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NCCN Guidelines Version 1.2013 Updates

Cancer- and Chemotherapy-Induced Anemia

Updates in the 1.2013 Version of the Cancer- and Chemotherapy-Induced Anemia Guidelines from the 2.2012 Version include:

ANEM-1

- Myeloid malignancies or Acute lymphoblastic leukemia:
 - “Appropriate therapy for Acute Lymphoblastic Leukemia (ALL)” was removed and is directed to “Treat underlying disease per NCCN guideline. See NCCN Guidelines Table of Contents” where the new NCCN ALL guidelines are located.

ANEM-2

- Footnote “f” was added: “See Discussion for further details on treating patients who may refuse blood transfusion (eg, Jehovah's Witnesses).”

ANEM-3

- Risks of red blood cell transfusion: “Decreased survival” was added.

ANEM-4

- Remainder of patients with anemia on...: “Clinical trial” was moved from second option to third option.

ANEM-5

- Management of functional iron deficiency in patients receiving ESAs:
 - The transferrin saturation for functional iron deficiency was changed from “<20%” to “<50%.”
- Footnotes:
 - Footnote “n” was added: “If absolute iron deficiency is present (ferritin <30 ng/mL and transferrin saturation <15%), consider IV or oral iron supplementation... However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin.”
 - Footnote “o” was added: “Only 1 of 6 studies (Henry DH, Dahl NV, Auerbach M, et al. *Oncologist* 2007;12:231-242) of IV iron therapy in cancer patients provided a TSAT guideline for monitoring.”
 - Footnote “r” was modified as: “There is insufficient data to ~~consider recommend~~ IV iron as monotherapy *without an ESA* for the treatment of functional iron deficiency anemia.”

ANEM-A

- Footnote “a” was added: “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 Mar 26. [Epub ahead of print].”

ANEM-C

- Selected safety information for healthcare providers:
 - 2nd bullet was revised: “To decrease these risks, as well as the risk of serious cardiovascular and ~~thrombovascular events~~ *thromboembolic reactions*, use the lowest dose needed to avoid red blood cell transfusion.”
 - 3rd bullet was revised: “Use ESAs only for ~~treatment of anemia due to concomitant~~ *from* myelosuppressive chemotherapy.”
 - 5th bullet was revised: “Discontinue ESA therapy following the completion of a chemotherapy course ~~when anemia resolves (usually 6-8 weeks after the last cycle).~~”

ANEM-D 1 of 3

- 2nd bullet, two new subbullets were added:
 - 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 3-4 weeks of administration. Clinicians may consider repeating iron studies if/when the mean corpuscular volume (MCV) <80 fL, or evidence of hypochromic red blood cells are seen in the peripheral blood.
 - If the patient fails to respond to iron after 4-6 weeks and after the total intended dose has been administered, repeat iron studies may be considered. If evidence exists of iron overload, do not administer IV iron. Subsequent doses of iron should be withheld if the serum ferritin exceeds 1000 mg/mL or TSAT exceeds 50%.

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- Prescribing information added as references to the table.
- Footnote ‡ added to dosage: “For additional details about iron dosing, see prescribing information.”
- Ferric gluconate and iron sucrose, “Maximum total dose = 1000 mg” was clarified as “*Total treatment course = 1000 mg.*”

UPDATES

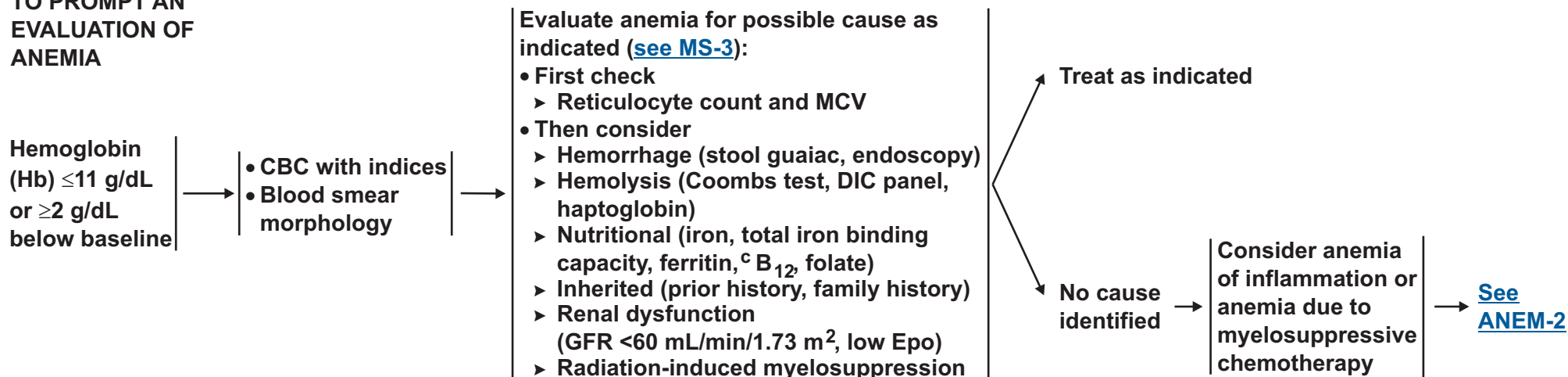


NCCN Guidelines Version 1.2013

Cancer- and Chemotherapy-Induced Anemia

HEMOGLOBIN CONCENTRATION TO PROMPT AN EVALUATION OF ANEMIA

EVALUATION OF ANEMIA ^{a,b}



Myelodysplastic syndromes → [See NCCN Myelodysplastic Syndromes Guidelines](#)

Myeloid malignancies or Acute lymphoblastic leukemia → [Treat underlying disease per NCCN guideline](#)
[See NCCN Guidelines Table of Contents](#)

^aThe NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines were formulated in reference to adult patients.

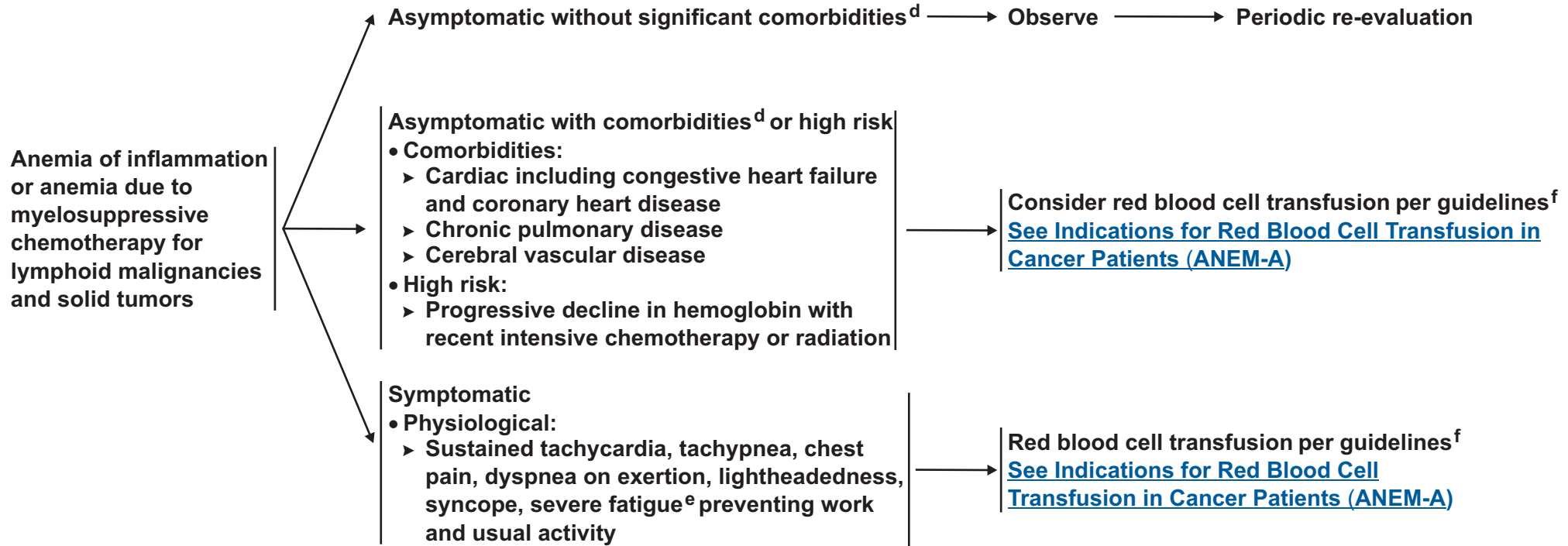
^bThis is a basic evaluation for possible causes of anemia.

^cIf absolute iron deficiency is present (ferritin <30 ng/mL and transferrin saturation <15%), consider IV or oral iron supplementation. Note, 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. If hemoglobin increases after 4 wks then observe with periodic re-evaluation for symptoms and risk factors, if hemoglobin does not increase after 4 wks, see functional iron deficiency pathway ([See ANEM-5](#)).

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RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING



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

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

^dDegree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating red blood cell transfusion.

^eFatigue (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.

^fSee Discussion for further details on treating patients who may refuse blood transfusion (eg, Jehovah's Witnesses).

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Cancer- and Chemotherapy-Induced Anemia

COMPARISON OF RISKS AND BENEFITS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION⁹

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

| ESA in the Cancer Setting | | Red Blood Cell Transfusion |
|---------------------------|--|--|
| Risks | <ul style="list-style-type: none"> • Increased thrombotic events • Decreased survival • Time to tumor progression shortened | <ul style="list-style-type: none"> • Transfusion reactions (hemolytic, febrile, non-hemolytic, lung injury, etc.) • Congestive heart failure • Virus transmission (hepatitis, HIV, etc.) • Bacterial contamination • Iron overload • Increased thrombotic events • Decreased survival |
| Benefits | <ul style="list-style-type: none"> • Transfusion avoidance • Gradual improvement in fatigue | <ul style="list-style-type: none"> • Rapid increase of hemoglobin and hematocrit levels • Rapid improvement in fatigue |

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

⁹See Discussion for detailed information regarding the risks and benefits of ESA use and red blood cell transfusion.

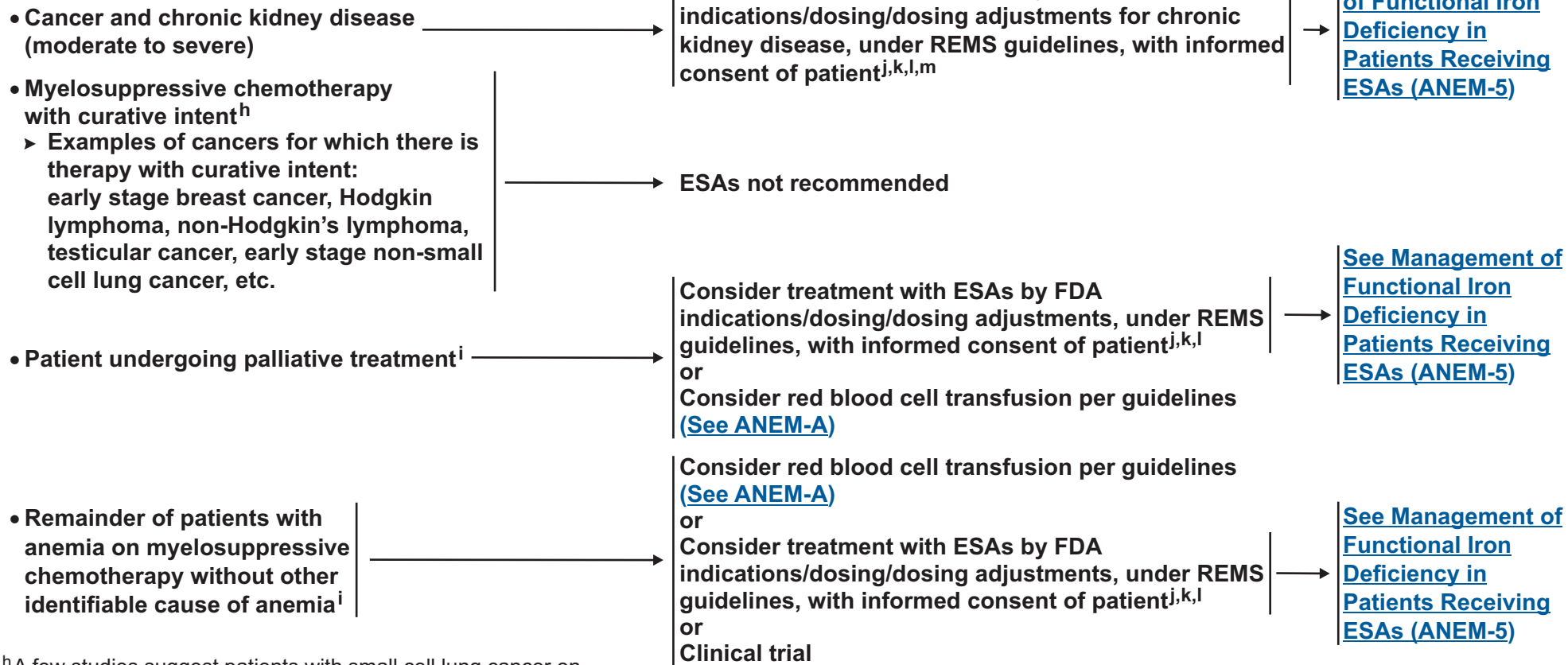
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SPECIAL CATEGORIES IN CONSIDERING ESA USE



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

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

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

^kHealthcare providers prescribing ESAs need to enroll in the ESA APPRISE program. [See REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis Stimulating Agents \(ESAs\) \(ANEM-C\).](#)

^lPatients 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 Venous Thromboembolic Disease Guidelines](#)).

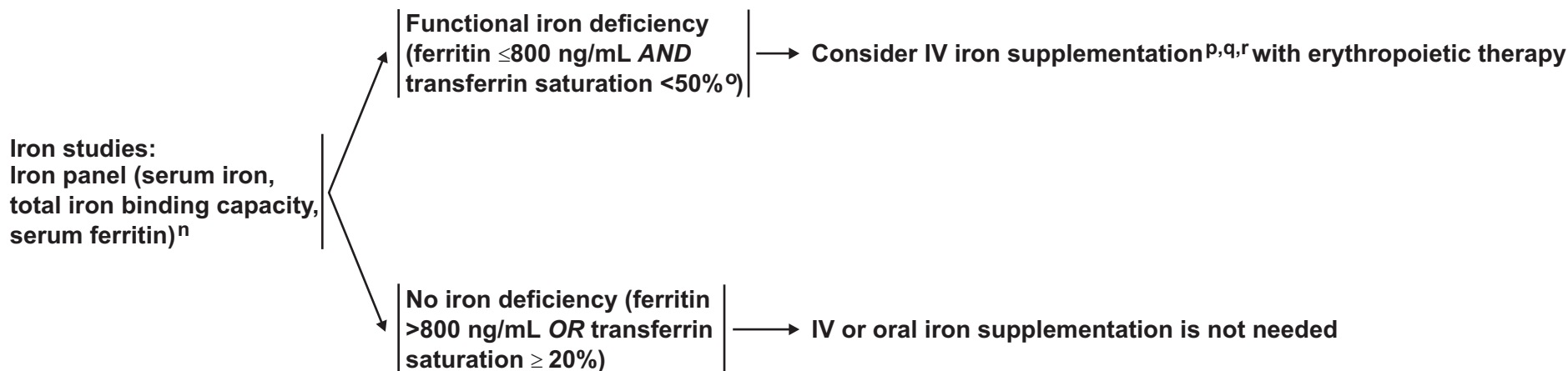
^mThe hemoglobin threshold for treatment and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease.

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MANAGEMENT OF FUNCTIONAL IRON DEFICIENCY IN PATIENTS RECEIVING ESAs



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

ⁿIf absolute iron deficiency is present (ferritin <30 ng/mL and transferrin saturation <15%), consider IV or oral iron supplementation. Note, 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.

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

^pIV 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 \(ANEM-D\)](#).

^qAlthough 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.

^rThere is insufficient data to recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency anemia.

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Cancer- and Chemotherapy-Induced Anemia

INDICATIONS FOR RED BLOOD CELL TRANSFUSION IN CANCER PATIENTS^a

Goal: Prevent or treat deficit of oxygen-carrying capacity

Asymptomatic Anemia

- **Hemodynamically stable chronic anemia without acute coronary syndrome:**
 - ▶ **Transfusion goal to maintain hemoglobin 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 (hemoglobin < 10 g/dL):**
 - ▶ **Transfusion goal to maintain hemoglobin 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 hemoglobin \geq 10 g/dL**

^aThe 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 Mar 26. [Epub ahead of print]

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

INITIAL DOSING

TITRATION FOR NO RESPONSE

TITRATION FOR RESPONSE

PACKAGE INSERT DOSING SCHEDULE

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

- The dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.
- If Hb reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-week period, reduce dose by 25% for epoetin alfa and by 40% for darbepoetin alfa.

ALTERNATIVE REGIMENS

| | | |
|--|---|---|
| Darbepoetin alfa 100 mcg fixed dose every wk by subcutaneous injection or Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection ⁷ or Darbepoetin alfa 300 mcg fixed dose every 3 wks by subcutaneous injection or Epoetin alfa 80,000 units every 2 wks by subcutaneous injection ⁸ or Epoetin alfa 120,000 units every 3 wks by subcutaneous injection ⁹ | → | Increase darbepoetin alfa to up to 150-200 mcg fixed dose every wk by subcutaneous injection ⁵ Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection ⁶ Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection ⁷ |
|--|---|---|

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

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

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 OF 5)

FOOTNOTES AND REFERENCES FOR 1 of 5

Footnotes

- ¹The 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. *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.
- ²Less frequent dosing regimens could be considered as an alternative to dose reduction.
- ³The dosages and regimens included in this table have been evaluated in cancer patients receiving chemotherapy.
- ⁴IV 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

- ⁵ Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 2002;94:1211-1220.
- ⁶ Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naïve patients and patients switched from epoetin alfa. *Pharmacotherapy* 2004;24:313-323.
- ⁷ Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every 3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. *J Natl Cancer Inst* 2006;98:273-284.
- ⁸ Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80 000 U Q2W) vs weekly dosing (40 000 U QW) in patients with chemotherapy-induced anemia. *Curr Med Res Opin* 2006;22:1403-1413.
- ⁹ Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol* 2006;24:1079-1089.

[See Erythropoietic Therapy -
Dosing and Titration \(ANEM-B 1 of 5\)](#)

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

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**ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 OF 5)****Cancer Patient Survival**

- **Studies have reported possible decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels of >12 g/dL.¹⁻⁸ One analysis in patients with cancer not receiving active therapy found decreased survival in ESA treated patients.⁶ Please refer to the FDA website for additional information: <http://www.fda.gov/cder/drug/infopage/RHE/default.htm>. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.**
- **While three meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,^{9,10,11,12} two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.^{13,14}**
- **Recent pharmacovigilance trials have reported no adverse effects on survival in cancer patients with chemotherapy-induced anemia receiving ESAs.¹⁵⁻¹⁷**
- **The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target hemoglobin of < 12 g/dL.**
- **Additional prospective clinical trials designed and powered to measure cancer patient survival 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 hemoglobin levels.¹⁸ Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. ([See NCCN Venous Thromboembolic Disease Guidelines](#))**
- **Four meta-analyses reported an increase in relative risk of thrombotic events ranging from 48% to 69% with ESA use.^{9,12,13,14} The absolute risk of venous thromboembolism was 7.5% in patients treated with ESAs compared to 4.9% in control patients.⁹**
- **A clinical trial in chronic kidney disease demonstrated a 92% increase in the relative risk of stroke (absolute risk 5.0% vs 2.6%) with darbepoetin alfa.¹⁹**

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

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 OF 5)

Hypertension/seizures

- Blood pressure should be controlled in all patients prior to initiating therapy with erythropoietic drugs and must be monitored regularly in treated patients.
- Seizures have been reported in chronic renal failure patients receiving erythropoietic drugs.
- Hemoglobin 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.²⁰ 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.²¹
- In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia.²² Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa.²³ This interpretation resulted in a class label change for all ESAs. The toxicity has been reported predominantly in patients with chronic renal failure receiving ESAs by subcutaneous administration. Any patient who develops a sudden loss of response to an ESA, accompanied by a severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, ESAs should be withheld and plasma should be sent for evaluation of assays for binding and neutralizing antibodies. ESAs should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESA products as antibodies may cross-react.

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

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

- ¹Leyland-Jones B, BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 2003;4:459-460.
- ²Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet* 2003;362:1255-1260.
- ³Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007;25:1027-1032.
- ⁴Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. *Br J Haematol* 2003;122:394-403.
- ⁵Overgaard J, Hoff C, Sand Hansen, H, et al. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of head and neck (HNCSS): The Danish Head and Neck Cancer Group DAHANCA 10 rand [abstract] *Eur J Cancer Suppl* 2007;5:7.
- ⁶Smith R, Apro MS, Ludwig H, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Oncol* 2008;26:1040-1050.
- ⁷Thomas G, Ali S, Hoebbers FJ, Darcy KM, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* 2008;108:317-325.
- ⁸Untch M, Fasching PA, Bauerfeind I, et al. PREPARE trial. A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF with a standard dosed epirubicin/ cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer: A preplanned interim analysis of efficacy at surgery. *J Clin Oncol* 26:2008 (May 20 suppl; abstr 517).
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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.**



REMS: RISK EVALUATION AND MITIGATION STRATEGY FOR ERYTHROPOIESIS STIMULATING AGENTS (ESAs)¹

- The FDA requires that Erythropoiesis-Stimulating Agents (ESAs) be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure the safe use of these drugs.
- As part of REMS for ESAs:
 - ▶ A Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving ESAs.
[See Epoetin Alfa Medication Guide](#) and [See Darbepoetin Alfa Medication Guide](#).
 - ▶ Healthcare 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.
- Patients with cancer using ESAs should:
 - ▶ 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 healthcare professional has received special training about the use of ESAs in patients with cancer.
 - ▶ Read the Medication Guide to understand the benefits and risks of using an ESA.
 - ▶ Talk with their healthcare professional about any questions they may have about using ESAs.
 - ▶ Be aware that they will be asked to sign an acknowledgment form that says they have talked with their healthcare professional about the risks of ESAs. This form must be signed before patients begin a course of treatment with an ESA.

Selected safety information for healthcare providers:²

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid red blood cell transfusion.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue ESA therapy following the completion of a chemotherapy course.
- ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy, unless receiving concomitant myelosuppressive chemotherapy.

¹Adapted from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm>

²Selected safety information adapted from: <https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp#isi>

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PARENTERAL IRON PREPARATIONS¹⁻⁶ (1 of 3)

- Parenteral iron preparations studied in cancer patients:
 - ▶ Iron dextran
 - ▶ Ferric gluconate
 - ▶ Iron sucrose
- Five²⁻⁶ of six⁷ studies have shown parenteral iron products are helpful in treating absolute or functional iron deficiency in cancer patients 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 3-4 weeks of administration. Clinicians may consider repeating iron studies if/when the mean corpuscular volume (MCV) <80 fL, or evidence of hypochromic red blood cells are seen in the peripheral blood.
 - ▶ If the patient fails to respond to iron after 4-6 weeks and after the total intended dose has been administered, repeat iron studies may be considered.^{5,7} If evidence exists of iron overload, do not administer IV iron. Subsequent doses of iron should be withheld if the serum ferritin exceeds 1000 ng/mL^{5,6} or TSAT exceeds 50%.²
- Test doses are required for iron dextran, but not for ferric gluconate or iron sucrose. Test doses are strongly recommended for ferric gluconate and iron sucrose if patients have exhibited sensitivities to iron dextran, other IV iron preparations, or who have multiple drug allergies.
- Most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferrum[®]).⁸
- If iron dextran preparation is used, IV low molecular weight iron dextran (INFeD[®]) is recommended.⁹
- Patients with active infection should not receive IV iron therapy.

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

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

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PARENTERAL IRON PREPARATIONS¹⁻⁶ (2 of 3)

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

| | Iron Dextran ^{11†} | Ferric gluconate ^{12†} | Iron sucrose ^{13†} |
|-----------------------|---|--|--|
| Test dose | Required | MD discretion | MD discretion |
| | 25 mg slow IV push and wait 1 hr before giving remainder of dose | 25 mg slow IV push or infusion | 25 mg slow IV push |
| Dosage ^{10‡} | 100 mg IV over 5 min ³ • Repeated dosing once weekly for 10 doses to achieve total dose of 1 g or • Total dose infusion given over several hours* | 125 mg IV over 60 min ^{2,4,5,7} • Repeated dosing given once weekly for 8 doses <hr/> • Individual doses above 125 mg are not recommended based on published trial results ⁷ • Total treatment course = 1000 mg | 200 mg IV over 60 min ⁶ • Repeated dosing given every 2-3 weeks or 200 mg IV over 2-5 min • Repeated dosing given every 1- 4 weeks <hr/> • Individual doses above 300 mg are not recommended ¹⁴ • Total treatment course = 1000 mg |
| Routes | IV infusion <hr/> IM (not recommended) | IV injection/infusion | IV injection/infusion |

† 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.

‡ For additional details about iron dosing, see prescribing information.

*Dose = 0.0442 (Desired Hgb - Observed Hgb) X LBW + (0.26 X LBW). LBW = Lean Body Weight
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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PARENTERAL IRON PREPARATIONS¹⁻⁶ (3 of 3)

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Anemia is prevalent in 30% to 90% of cancer patients.¹ 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. Recent studies demonstrating detrimental health effects of ESAs sparked a series of FDA label revisions and a sea change in the perception of these once commonly used agents. In light of this, the NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines underwent substantial revisions this year. 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 (RBC), 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 National Cancer Institute (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.^{2, 3} The malignancy itself can lead to or exacerbate anemia in a number of ways.⁴ 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 these 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,⁵ while 49% of patients are anemic when diagnosed with gynecological cancer.⁶ In addition, the myelosuppressive effect of chemotherapy is a significant contributing factor to anemia for patients undergoing cytotoxic treatment.⁷ 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.⁸

Anemia associated with myelosuppressive chemotherapy

Chemotherapeutic agents induce anemia by directly impairing hematopoiesis, including synthesis of RBC precursors, in the bone marrow.⁴ 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.⁴

Studies have identified patients with lung cancer and gynecologic malignancies as having a very high incidence of chemotherapy-induced anemia.^{6,7} 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.⁷ Selected single agents and regimens frequently associated with anemia for different types of cancers taken from the 1999 review by Groopman and Itri are summarized in Table 2. It is important to note that the hematologic toxicities of newer cytotoxic agents, regimens and schedules are not reflected in this list, and a greater risk of anemia may potentially be associated with some of the more intensive chemotherapy regimens.⁷

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)⁶, 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 2-3 anemia was also associated with a greater number of chemotherapy cycles. Other factors for consideration when evaluating risk of chemotherapy-induced anemia 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.⁴

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 guidelines are provided on transfusion, erythropoietic therapy, as well as iron supplementation.

This guidelines algorithm is mainly focused on patients with solid tumors and lymphoid malignancies. For anemia associated with myelodysplastic syndromes, 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 Panelists are in agreement that a 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, as well as 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 Cancer-Related Fatigue Guidelines](#)). A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that it is less likely to be ameliorated by rest.⁹ 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, 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. Myelodysplastic syndrome and certain drugs such as hydroxyurea or diphenytoin 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



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therapy is beyond the scope of this guideline. Below is a summary of additional cues or tests for common underlying ailments:

- Absolute iron deficiency = An iron and total iron binding capacity (TIBC) resulting in transferrin saturation < 15%, ferritin < 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, although chronic inflammation may elevate serum ferritin in cancer patients. Functional iron deficiency is discussed within the context of ESA therapy in a later section
- B12/folate deficiency – low vitamin B12 or folate levels
- Hemorrhage – stool guaiac positive, endoscopy findings
- Hemolysis – Coombs test positive, disseminated intravascular coagulation (DIC) panel positive, low haptoglobin levels, elevated indirect bilirubin
- Chronic kidney disease (CKD) – glomerular filtration rate (GFR) < 60 mL/min/1.73 m² for three or more consecutive months, low erythropoietin level
- Inherited anemia – personal and family history
- Sideroblastic anemia – sideroblasts present in bone marrow biopsy

Any 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.

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 physiological 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 leukoreductions, 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 50-80%, and typically contains 42.5-80 g of Hb (with 147-278 mg of iron) or 128-240 mL of pure RBCs.¹⁰

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 receiving myelosuppressive chemotherapy 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.^{10, 11} Additionally, patients receiving concomitant fluid resuscitation may not realize a hemoglobin 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 (hazard ratio=0.26; 95% CI, 0.09-0.75, P=0.01).¹²

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 Ludwig¹³). 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.^{14, 15} Pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse reaction.^{16, 17} However, Khorana et al analyzed data from discharge summaries of cancer patients admitted to 60 US medical centers between 1995 and 2003 and found increased risks (P < 0.001) of venous thromboembolism (OR=1.60; 95% CI, 1.53-1.67), arterial thromboembolism (OR=1.53; 95% CI, 1.46-1.61) and mortality (OR=1.34; 95% CI, 1.29-1.38) associated with PRBC transfusions.¹⁸

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).¹⁹ 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). Another factor for possible consideration in the context of full reliance on PRBC transfusion as a treatment for



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chemotherapy-induced anemia relates to the limited supply of blood in the U.S. A recent analysis which 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%.²⁰

Transfusion goals and basic principles

There is wide variation in reported RBC transfusion practice,^{14, 21, 22} 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 (“Indications for Red Blood Cell Transfusion in Cancer Patients” section). Transfusion is rarely indicated when the Hb level is above 10 g/dL.²³ 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.²² AABB recommendations include: 1) using a hemoglobin level of 7 to 8 g/dL as a threshold for hospitalized patients who are stable; 2) considering transfusions for hospitalized patients with preexisting cardiovascular disease who have symptoms and a hemoglobin level of 8 g/dL or less; 3) making transfusion decisions for all patients based on symptoms as well as hemoglobin 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 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, co-morbidities, 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.^{24, 25} If repeated transfusions are required, leukocyte-reducing blood and use of premedication can minimize adverse transfusion reactions. In most instances, PRBCs should be transfused by the unit and reassessment should be conducted after each transfusion.

Patients Who Refuse Blood Transfusions

Patients who refuse blood transfusions (e.g. Jehovah's Witnesses) are occasionally seen in clinical practice. Their religious beliefs or personal preference 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.²⁶⁻²⁸ 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 if functional iron deficiency is present, intravenous iron should be used. ESAs can be offered before and after chemotherapy, however prior approval from third party payers may be necessary to prevent increasing the financial



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burden of the patient. Patients should also be made aware of the potential increased risks of thrombosis and tumor progression, and that under these circumstances the drugs are being used off-label. Lastly, in extreme cases with severe, life-threatening anemia, pure oxygen (400 mmHg, $S_AO_2 = 1.0$) has been used to increase dissolved oxygen in patient's blood; the patient had a hemoglobin level of 1.8 g/dL.²⁷

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 U.S.: 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. 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.²⁹ However, this paradigm is shifting dramatically as evidence of potential detrimental effects started to emerge 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.³⁰ Transfusion requirements were significantly decreased in the epoetin arm compared with placebo (24.7% versus 39.5%, $P = 0.0057$), and rise in Hb level was increased (2.2 g/dL versus 0.5 g/dL; $P < 0.001$).³⁰ A double blind, placebo-

controlled, randomized phase III study of darbepoetin alfa enrolled 320 patients (Hb level ≤ 11 g/dL) receiving darbepoetin alfa at 2.25 mcg/kg/week versus placebo.³¹ Patients receiving darbepoetin alfa required fewer transfusions (27% vs. 52%; 95% CI, 14%-36%, $P < 0.001$) than patients receiving placebo. The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review of 42 randomized, controlled clinical trials involving use of ESA therapy which enrolled a total of 6,510 patients undergoing treatment for cancer.³² A decreased relative risk for transfusion was observed in the patients receiving erythropoietin (RR=0.64; 95% CI, 0.60-0.68).

Risks of ESA therapy

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,^{33, 34} 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 eight randomized studies that individually showed a decrease in overall survival and/or decreased loco-regional disease control with ESA usage for advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers.³⁵⁻⁴² Of the eight studies, three investigated ESA effects in patients who underwent chemotherapy. All eight 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 three recent meta-analyses of 51-53 randomized controlled trials.⁴³⁻⁴⁶ Bohlius et al⁴⁴, Tonelli et al⁴⁵, and Bennett et al⁴³ each reported increased mortality in patients receiving ESAs with relative risks/hazard ratios of 1.17 (95% CI, 1.06-1.30), 1.15 (95% CI, 1.03-1.29), and 1.10 (95% CI, 1.01-1.20), respectively. However, this

association has been refuted by two other meta-analyses by Ludwig et al⁴⁷ (HR = 0.97; 95% CI, 0.85-1.1) and Glaspy et al⁴⁸ (OR = 1.06; 95% CI, 0.97-1.15) reporting no 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.⁴⁹⁻⁵¹ 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.³⁵ The update found no difference in overall survival; there was a trend towards decreased disease-free survival that failed to reach statistical significance.⁵¹ 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).^{52, 53}

Risk of thromboembolism

Increased thromboembolic risks have been associated with ESA treatment of cancer patients. The cause of venous thromboembolism (VTE) is complex; a heightened baseline risk is related to the malignancy itself as well as chemotherapy (see [NCCN Venous Thromboembolic Disease Guidelines](#)).⁵⁴⁻⁵⁷ 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, as well as comorbidities such as hypertension.⁵⁸

Overall, results from meta-analyses established significant association: increased risk of thrombotic events with ESA usage was reported by Tonelli et al⁴⁵ (RR=1.69; 95% CI, 1.27-2.24), Bennett et al⁴³ (RR=1.57; 95% CI, 1.31-1.87), Ludwig et al⁴⁷ (HR = 1.57; 95% CI, 1.10-2.26), and Glaspy et al⁴⁸ (OR = 1.48; 95% CI, 1.28-1.72). A combined analysis of

six trials on darbepoetin alfa by Glaspy and colleagues⁵⁹ also found an increased risk of thromboembolism for patients with Hb > 12 g/dL (RR=1.66; 95% CI, 0.9-3.04) or patients achieving over 1 g/dL increase in 14 days (RR= 1.67; 95% CI, 0.96 -2.88). As well, an increased risk of stroke was associated with darbepoetin alfa in a clinical trial of patients with chronic kidney disease (HR = 1.92; 95% CI, 1.38-2.68).⁶⁰ 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.⁶¹ 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.

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.^{62, 63} Causation was attributed to formulations without human serum albumin, subcutaneous administration, and uncoated rubber stoppers.⁶⁴ 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



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without other cytopenias, associated with neutralizing antibodies.⁶⁵ PRCA resulted in a class label change for all ESAs. Toxicity has been reported predominantly in patients with chronic renal failure receiving subcutaneous 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 that 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).

For cancer patients, the black-box warning on the revised FDA label states that ESAs should only be used to treat chemotherapy-induced anemia and should be discontinued once the chemotherapy course is complete.³³ 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, 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, 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). For patients undergoing palliative treatment, ESA therapy can be considered preferentially over transfusion. 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.^{60, 66-68} Since almost one-third of patients with end-stage renal disease are also afflicted with cancer, these represent a unique group that require personalized use of ESAs based on very careful weighing of risks and benefits (reviewed by Bennett et al⁶⁹). 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 carefully dosing for target Hb between 10 g/dL and 12 g/dL in keeping with the indication for CKD. 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.⁷⁰⁻⁷² 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, chronic kidney disease, 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 subcutaneously^{30, 73} and 40,000 units once weekly SC.^{38, 41, 42, 74} 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 U SC every 2 weeks⁷⁵ and a dose of 120,000 U SC once every 3 weeks.⁷⁶

Although darbepoetin doses were initially administered at 2.25 mcg/kg SC every week,^{31, 36, 77} 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 vs. fixed dosing at 500 mcg every three weeks in 705 patients with non-myeloid malignancies with a Hb level <11 g/dL. The percentage of patients achieving the target Hb level (≥11 g/dL) was 77% in the weekly arm and 84% for patients receiving darbepoetin alfa every three weeks.⁷⁷ 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,³¹ a fixed dose of 200 mcg biweekly,⁷⁸ and 300 mcg every 3 weeks.⁷⁹

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 (less than 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

“Functional” iron deficiency often arises following continued erythropoietin use. As a result iron supplementation will eventually be required in most patients in order to maintain optimal erythropoiesis.^{80, 81} This is because rapid ESA-stimulated RBC production increases the rate of iron mobilization from the usable iron pool in the reticuloendothelial system (RES) to the bone marrow. Release of iron from the RES can be further delayed by inflammatory cytokine release from tumors or chemotherapy used to treat cancer. These inflammatory cytokines lead to the upregulation of hepcidin, a molecule which inhibits the release of iron (bound in macrophages within the RES) to its transporter-transferrin.⁸¹ The overall result is a blunted erythropoietic response to anemia. If the patient is to receive exogenous erythropoietic therapy to overcome the aforementioned response, iron studies, including serum iron, TIBC, and serum ferritin should be performed prior to treatment, in order to rule out absolute iron deficiency which may respond to oral or intravenous iron monotherapy without an ESA.

Iron can be administered in oral form or parenteral form (low-molecular weight iron dextran, ferric gluconate, and iron sucrose).⁸² Evidence

from five published studies utilizing iron in conjunction with an ESA suggests that IV iron is superior to oral iron.⁸³⁻⁸⁷ Patients participating in these trials had serum ferritin levels ranging from ≥ 100 ng/mL to ≤ 900 ng/mL. A prospective, multicenter, open-label trial randomized 157 patients with chemotherapy-induced anemia (CIA) receiving epoetin alfa to (1) no iron, (2) oral iron, (3) iron dextran IV bolus, (4) iron dextran total dose infusion.⁸³ Increases in Hb concentration were greater with IV iron (groups 3 and 4) compared to oral supplementation or no iron ($P < 0.02$) while there was no difference between the oral and no iron groups ($P = 0.21$). Additionally, there was no statistically significant difference between groups 3 and 4 ($P = 0.53$), suggesting that lower, intermittent doses of IV iron are as equally efficacious as TDI. In a second open-label study by Henry and colleagues,⁸⁶ 187 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 (≥ 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.⁸⁵ Patients were randomized to weekly epoetin beta with or without IV iron sucrose. Although an oral iron arm was not included, IV iron resulted both in higher mean change in Hb level from baseline (2.76 g/dL versus 1.56 g/dL, $P = 0.0002$) and in a higher Hb level response rate (≥ 2 g/dL increase) (87% versus 53%, $P = 0.0014$) 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).⁸⁴ 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% versus 20%, $P = 0.005$). In a study by Pedrazzoli et al,⁸⁷ 149 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% versus 70%, $P = 0.0033$) 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 published findings from the largest trial to date that challenged results from the above studies.⁸⁸ 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 additional benefit in terms of Hb response, transfusion rates, or quality of life. 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.⁸⁹ This includes seven randomized controlled trials involving 1,777 patients with CIA. Oral or IV iron supplementation with ESAs reduced transfusion rates compared to no iron. Intravenous 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 NCCN guidelines, IV iron products alone (without an ESA) are recommended for iron repletion in cancer patients with absolute iron deficiency (ferritin < 30 ng/mL and transferrin saturation $< 15\%$). Intravenous iron monotherapy has not been studied in patients with CIA and functional iron deficiency (ferritin ≤ 800 ng/mL and transferrin saturation $< 50\%$). Therefore, it is currently recommended that ESAs be used in addition to IV iron for patients with CIA and functional iron deficiency. Common adverse events following FDA approved doses of parenteral iron include hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness.⁹⁰⁻⁹² Most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferrum®).⁹³ The recommended iron dextran product is low molecular weight iron dextran (INFed®).⁹⁴ Test doses are required for iron dextran, and 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.⁹⁵ Hence iron supplementation is not recommended for patients with 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.^{85, 88} 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 TSAT exceeds 50%.⁸⁴⁻⁸⁶

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 intravenous iron agents are currently being studied as monotherapy (without an ESA) in CIA such as iron isomaltoside and ferric carboxymaltose. More information about these agents can be found at www.clinicaltrials.gov. In addition, soluble transferrin receptor level has been suggested as a marker of iron deficiency that can aid in differential diagnosis.⁹⁶



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Table 1. NCI Anemia Scale (Hb Level in g/dL)

| Grade | Scale |
|----------------------|----------------------------|
| 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>.

Table 2. Incidence of anemia associated with chemotherapeutic agents and regimens.

| Agent | Grade 1/2 (%) * | Grade 3/4 (%) * | Cancer |
|------------------------------|-----------------|-----------------|------------|
| Cisplatin | NR | 11 | H & N |
| Docetaxel | 73 - 85 | 2 - 10 | NSCLC |
| | 58 - 60 | 27 - 42 | Ovarian |
| 5-FU | NR | 11 | H & N |
| | 50 - 54 | 5 - 8 | Colorectal |
| Paclitaxel | 93 | 7 | Breast |
| Topotecan | NR | 32 | SCLC |
| | 67 | 32 | Ovarian |
| Vinorelbine | 67 - 71 | 5 - 14 | Breast |
| Regimen | | | |
| Cisplatin - cyclophosphamide | 43 | 9 | Ovarian |
| Cisplatin - etoposide | 59 | 16 - 55 | SCLC |
| VIP | NR | 52 | SCLC |
| 5-FU - carboplatin | 42 | 14 | H & N |
| CHOP | 49 | 17 | NHL |
| Paclitaxel - doxorubicin | 78 - 84 | 8 - 11 | Breast |
| Paclitaxel - carboplatin | 10 - 59 | 5 - 34 | NSCLC |

NR = not reported; H&N = head and neck cancer; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; NHL = non Hodgkin's lymphoma; 5-FU = 5-fluorouracil; VIP = etoposide – ifosfamide – cisplatin; CHOP = cyclophosphamide – doxorubicin – vincristine – prednisone.
* WHO or NCI scales.
Source: Adapted from Groopman JE, Itri LM, JNCI 1999;91:1616-1634.

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