Cancer- and Chemotherapy-Induced Anemia

Clinical Practice Guidelines in Oncology

Overview

Anemia is prevalent in 30% to 90% of patients with cancer. Anemia can be corrected through either treating the underlying cause or providing supportive care through either transfusion with packed red blood cells (PRBC) or administration of erythropoiesis-stimulating agents (ESAs), with or without iron supplementation. Recent studies showing 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 Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer- and Chemotherapy-Induced Anemia underwent substantial revisions this year. The purpose of these NCCN Guidelines is twofold: 1) to operationalize the evaluation and treatment of anemia in adult cancer patients, with an emphasis on those who are receiving concomitant chemotherapy, and 2) to enable patients and clinicians to individualize anemia treatment options based on patient condition. (JNCCN 2012;10:628–653)

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.

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

Please Note

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Disclosures for the NCCN Cancer- and Chemotherapy-Induced Anemia Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Cancer- and Chemotherapy-Induced Anemia Panel members can be found on page 653. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
ize the evaluation and treatment of anemia in adult patients with cancer, with an emphasis on those with anemia who are receiving concomitant chemotherapy, and 2) to enable the patient and clinician to assess anemia treatment options based on individual patient conditions.

The pathophysiologic origins of anemia can be grouped into 3 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); available online, in these guidelines, at NCCN.org [MS-13]).

Etiology

Causes of anemia in patients with cancer 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. The malignancy itself can lead to or exacerbate anemia in several ways. 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 survival. Chronic blood loss at tumor sites and organ damage can further exacerbate anemia from cancer. Additional indirect effects may include nutritional deficiencies.
### HEMOGLOBIN CONCENTRATION

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

| Hemoglobin (Hb) | CBC with indices | Blood smear morphology | Evaluate anemia for possible cause as indicated (see Approaches to Evaluation on page 643):
|-----------------|------------------|------------------------|-----------------------------------------------------|
| ≤ 11 g/dL or ≥ 2 g/dL below baseline |                 |                        | First check:
|                 |                  |                        | 1. Reticulocyte count and MCV
|                 |                  |                        | 2. Then consider:
|                 |                  |                        | a. Hemorrhage (stool guaiac, endoscopy)
|                 |                  |                        | b. Hemolysis (Coombs test, DIC panel, haptoglobin)
|                 |                  |                        | c. Nutritional (iron, total iron binding capacity, ferritin, <sup>c</sup>B<sub>12</sub>, folate)
|                 |                  |                        | d. Inherited (prior history, family history)
|                 |                  |                        | e. Renal (GFR < 60 mL/min/1.73 m<sup>2</sup>, low erythropoietin)
|                 |                  |                        | f. Radiation-induced myelosuppression
|                 |                  |                        | Treat as indicated
|                 |                  |                        | 1. If no cause identified, consider:
|                 |                  |                        | a. Anemia of inflammation or myelosuppressive chemotherapy
|                 |                  |                        | b. See facing page

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**Myelodysplastic syndromes**

See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myelodysplastic Syndromes (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org)

**Myeloid malignancies or ALL**

Treat underlying disease per NCCN Guideline (See NCCN Guidelines Table of Contents at NCCN.org) or

Appropriate therapy for acute lymphoblastic leukemia (ALL)

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<sup>a</sup>These guidelines were formulated in reference to adult patients.

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

<sup>c</sup>If 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 wk, then observe with periodic reevaluation for symptoms and risk factors; if hemoglobin does not increase after 4 wk, see functional iron deficiency pathway (see page 634).
RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING

Asymptomatic without significant comorbidities\(^d\)
- Observe
- Periodic reevaluation

Asymptomatic with comorbidities\(^d\) or high risk
- Comorbidities:
  - Cardiac including congestive heart failure and coronary heart disease
  - Chronic pulmonary disease
  - Cerebral vascular disease
- High risk:
  - Progressive decline in hemoglobin with recent intensive chemotherapy or radiation

Consider red blood cell transfusion per guidelines (See Indications for Red Blood Cell Transfusion in Cancer Patients, page 635)

Symptomatic
- Physiological:
  - Sustained tachycardia, tachypnea, chest pain, dyspnea on exertion, lightheadedness, syncope, severe fatigue\(^e\) preventing work and usual activity

Red blood cell transfusion per guidelines (See Indications for Red Blood Cell Transfusion in Cancer Patients, page 635)

See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion (page 632)

See Special Categories in Considering ESA Use (page 633)

\(^d\)Degree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating red blood cell transfusion.

\(^e\)Fatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI) are examples of standardized measures for assessing patient-reported fatigue.
Cancer- and Chemotherapy-Induced Anemia Version 2:2012

COMPARISON OF RISKS AND BENEFITS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION¹

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

<table>
<thead>
<tr>
<th>ESA in the Cancer Setting</th>
<th>Red Blood Cell Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks</strong></td>
<td></td>
</tr>
<tr>
<td>• Increased thrombotic events</td>
<td>• Transfusion reactions (e.g., hemolytic, febrile, nonhemolytic, lung injury)</td>
</tr>
<tr>
<td>• Decreased survival</td>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td>• Time to tumor progression shortened</td>
<td>• Virus transmission (e.g., hepatitis, HIV)</td>
</tr>
<tr>
<td></td>
<td>• Bacterial contamination</td>
</tr>
<tr>
<td></td>
<td>• Iron overload</td>
</tr>
<tr>
<td></td>
<td>• Increased thrombotic events</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>• Transfusion avoidance</td>
<td>• Rapid increase of hemoglobin and hematocrit levels</td>
</tr>
<tr>
<td>• Gradual improvement in fatigue</td>
<td>• Rapid improvement in fatigue</td>
</tr>
</tbody>
</table>

See REMS: Risk Evaluation and Mitigation Strategy for Erythropoiesis-Stimulating Agents (ESAs) (page 639)

¹See the manuscript for detailed information regarding the risks and benefits of ESA use and red blood cell transfusion.
SPECIAL CATEGORIES IN CONSIDERING ESA USE

- **Cancer and chronic kidney disease** (moderate to severe)
  - Consider treatment with ESAs by FDA indications/dosing/dosing adjustments for chronic kidney disease, under REMS guidelines, with informed consent of patient\(^{ij}\)
  - See Management of Functional Iron Deficiency in Patients Receiving ESAs (page 634)

- **Myelosuppressive chemotherapy with curative intent**
  - Examples of cancers for which there is therapy with curative intent include early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin’s lymphoma, testicular cancer, and early-stage non-small cell lung cancer
  - ESAs not recommended

- **Patient undergoing palliative treatment**
  - Consider treatment with ESAs by FDA indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient\(^{ij}\)
  - See Management of Functional Iron Deficiency in Patients Receiving ESAs (page 634)
  - Consider red blood cell transfusion per guidelines (See page 635)

- **Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia**
  - Consider red blood cell transfusion per guidelines (See page 635)
  - Clinical trial
  - Consider treatment with ESAs by FDA indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient\(^{ij}\)
  - See Management of Functional Iron Deficiency in Patients Receiving ESAs (page 634)

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\(^{ij}\)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) (page 639).

\(^{k}\)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, such as history of thromboembolism, heritable mutation, hypercoagulability, elevated prechemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, and hormonal agents. (See NCCN Guidelines for Venous Thromboembolic Disease; to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org).

\(^{l}\)The hemoglobin threshold for treatment and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease.


\(^{b}\)See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion (previous page).

\(^{c}\)See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (pages 636-638).
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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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 (pages 640-641).

Although all combinations of serum ferritin and TSAT could be found in at least 1 of 6 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.

Data are insufficient to consider IV iron as monotherapy for the treatment of functional iron-deficiency anemia.

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

- Functional iron deficiency (ferritin ≤ 800 ng/mL and transferrin saturation < 20%)
  - Consider IV iron supplementation with erythropoietic therapy

- No iron deficiency (ferritin > 800 ng/mL or transferrin saturation ≥ 20%)
  - IV or oral iron supplementation is not needed

See Parenteral Iron Preparations (pages 640 and 641)
INDICATIONS FOR RED BLOOD CELL TRANSFUSION IN CANCER PATIENTS

Goal: Prevent or treat deficit of oxygen-carrying capacity

**Asymptomatic**
- Hemodynamically stable chronic anemia without acute coronary syndrome:
  - Transfusion goal to maintain hemoglobin 7-9 g/dL

**Symptomatic**
- 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 ≥ 10 g/dL
## Erythropoietic Therapy - Dosing and Titration 1-4

### Initial Dosing

<table>
<thead>
<tr>
<th>Package Insert Dosing Schedule</th>
<th>Titration for No Response</th>
<th>Titration for Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa, 150 units/kg 3 times wk by subcutaneous injection</td>
<td>Increase dose of epoetin alfa to 300 units/kg 3 times wk by subcutaneous injection</td>
<td>• The dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.</td>
</tr>
<tr>
<td>Epoetin alfa, 40,000 units every wk by subcutaneous injection</td>
<td>Increase dose of epoetin alfa to 60,000 units every wk by subcutaneous injection</td>
<td>• If Hb reaches a level needed to avoid transfusion or increases &gt; 1 g/dL in any 2-wk period, reduce dose by 25% for epoetin alfa and by 40% for darbepoetin alfa.</td>
</tr>
<tr>
<td>Darbepoetin alfa, 2.25 mcg/kg every wk by subcutaneous injection</td>
<td>Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection</td>
<td></td>
</tr>
<tr>
<td>Darbepoetin alfa, 500 mcg every 3 wk by subcutaneous injection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Alternative Regimens

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

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

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

4 IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See manuscript for detailed discussion.) See Parenteral Iron Preparations (pages 640-641).


ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS

Cancer Patient Survival

- Studies have reported possible decreased survival in patients with cancer receiving erythropoietic drugs for correction of anemia. Analyses of 8 studies in patients with cancer found decreased survival in those 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 FDAWeb site for additional information: http://www.fda.gov/cdrer/drf/infopage/RHE/default.htm. Unless new evidence shows 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 after initiation of therapy and continuing approximately 6 weeks after the completion of treatment.

- Although 3 meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,\(^9\)-\(^12\) 2 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, page 632)

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, such as history of thromboembolism, heritable mutation, hypercoagulability, elevated prechemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, and hormonal agents. (See NCCN Guidelines for Venous Thromboembolic Disease; to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org)

- Four meta-analyses reported an increase in relative risk of thrombotic events ranging from 48% to 69% with ESA use.\(^9\)-\(^12\)-\(^14\)

- The absolute risk of venous thromboembolism was 7.5% in patients treated with ESAs compared with 4.9% in control patients.\(^9\)

- A clinical trial in chronic kidney disease showed a 52% increase in the relative risk of stroke (absolute risk, 5.0% vs. 2.6%) with darbepoetin alfa.\(^19\)

Hypertension/Seizures

- Blood pressure should be controlled in all patients before 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, previous page.)

ESA Neutralizing Antibodies (Pure Red Cell Aplasia [PRCA])

- Between 1998 and 2004, 197 cases of PRCA were reported in patients treated with erythropoietin.\(^20\) More than 90% of these cases occurred with Eprex, an epoetin alfa product used outside of the United States. Patients who develop a loss of response to erythropoietic drugs should be evaluated for possible PRCA, and if present, all erythropoietic drugs should be discontinued.\(^21\)

- 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 through 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 antierythropoietin 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, because antibodies may cross-react.

See References (page 638)
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
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 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.
  - 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
- Patients with cancer using ESAs should:
  - Understand the risks associated with use of ESAs:
    - 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 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 will be asked to sign an acknowledgment form that says they have talked with their health care 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 health care providers:

- 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, and the risk of serious cardiovascular and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- Discontinue ESA therapy after the completion of a chemotherapy course when anemia resolves (usually 6-8 weeks after the last cycle).
- ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy, unless receiving concomitant myelosuppressive chemotherapy.

Selected safety information adapted from: https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp?isi2

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

Selected safety information adapted from: https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp?isi2
### Parenteral Iron Preparations

- Parenteral iron preparations studied in cancer patients:
  - Iron dextran
  - Ferric gluconate
  - Iron sucrose
- Five of six studies have shown parenteral iron products are helpful in treating functional iron deficiency in cancer patients who are receiving ESAs.
- 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 or 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).
- If iron dextran preparation is used, low-molecular-weight iron dextran (INFed) is recommended.

### RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

<table>
<thead>
<tr>
<th>Iron Dextran†</th>
<th>Ferric Gluconate†</th>
<th>Iron Sucrose†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required</td>
<td>MD discretion</td>
<td>MD discretion</td>
</tr>
<tr>
<td>25 mg slow IV push and wait 1 h before giving main dose</td>
<td>25 mg slow IV push or infusion</td>
<td>25 mg slow IV push</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 100 mg IV over 5 min  
  • 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  
  • Repeated dosing given once weekly for 8 doses  
  • Individual doses above 125 mg are not recommended based on published trial results  
  • Maximum total dose = 1000 mg | 200 mg IV over 60 min  
  • Repeated dosing given every 2-3 wk  
  or  
  200 mg IV over 2-5 min  
  • Repeated dosing given every 1-4 wk  
  • Individual doses above 300 mg are not recommended  
  • Maximum total dose = 1000 mg |
| **Routes**    |                  |              |
| IV infusion   | IV injection/infusion | IV injection/infusion |
| IM (INFed) (not recommended) |                      |              |

†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.

*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 wk if inadequate hemoglobin response.

**See References (facing page)**

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**Clinical trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
Test doses are required for iron dextran. Test doses are strongly recommended for ferric patients receiving ESAs. Patients with active infection should not receive IV iron therapy. If iron dextran preparation is used, low-molecular-weight iron dextran (INFed) is recommended. Most adverse events associated with iron dextran occur with high-molecular-weight iron dextran (Dexferrum).

Parenteral iron preparations:

- Iron dextran
- Ferric gluconate
- Iron sucrose

† 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.

**PARENTERAL IRON PREPARATIONS**

**REFERENCES**

caused by loss of appetite in patients with cancer, hemolysis by immune-mediated antibodies, or changes in coagulation capability. For these myriad reasons, anemia is prevalent among patients with cancer at initial presentation. For example, 32% of patients with non–Hodgkin’s lymphoma have anemia at diagnosis, whereas 49% are anemic when diagnosed with gynecologic cancer. In addition, the myelosuppressive effect of chemotherapy is a significant contributing factor to anemia in patients undergoing cytotoxic treatment. 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.

**Anemia Associated With Myelosuppressive Chemotherapy**

Chemotherapeutic agents induce anemia through directly impairing hematopoiesis, including synthesis of RBC precursors, in the bone marrow. In addition, nephrotoxic effects of particular cytotoxic agents (e.g., platinum-containing agents) can also lead to anemia through decreased renal production of erythropoietin.

Studies have identified patients with lung cancer and gynecologic malignancies as having a very high incidence of chemotherapy-induced anemia. Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia caused by combined bone marrow and kidney toxicity. Selected single agents and regimens frequently associated with anemia for different types of cancers are summarized in Table 2 (available online, in these guidelines, at NCCN.org [MS-13]). Importantly, the hematologic toxicities of newer cytotoxic agents, regimens, and schedules are not reflected in this list, and a greater risk for anemia may potentially be associated with some of the more intensive chemotherapy regimens.

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 of anemia with additional chemotherapy cycles. For example, for patients in the European Cancer Anemia Survey (ECAS), the rate of anemia (Hb < 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 and 3 anemia was also associated with a greater number of chemotherapy cycles. Other factors to consider when evaluating risk of chemotherapy-induced anemia include the nadir Hb level, time to the nadir Hb level (roughly estimated at 2 weeks, but can vary), and whether an Hb measurement is considered to be pre- or post-nadir.

**Guideline Overview**

These revised NCCN Guidelines start with an evaluation of anemia to delineate the origin, which is followed by risk assessment to determine the initial intervention plan. Special categories are outlined in considering the use of ESAs for long-term management. Additional guidelines are provided on transfusion, erythropoietic therapy, and iron supplementation.

These NCCN Guidelines focus on patients with solid tumors and chronic lymphoid malignancies. For anemia associated with myelodysplastic syndromes (MDS), myeloid malignancies, and acute lymphoblastic leukemia, clinicians are referred to relevant guidelines in the NCCN Guidelines Table of Contents (available at NCCN.org).

**Screening Evaluation**

Given the wide variation in Hb level among healthy subjects, a universal “normal” value remains elusive. For patients with cancer, the panel agrees that an Hb level of 11 g/dL or below should prompt evaluation for anemia. For patients with a high baseline level, a decrease of 2 g/dL or more is also cause for concern and assessment. A patient with cancer may experience 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 of anemia involves a CBC with indices that will show whether 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 examination must be performed. The history should include the duration and time to 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 Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Related Fatigue as “a distressing persistent subjective sense of tiredness or exhaustion related to cancer or its treatment that is not proportional to recent activity and interferes with normal functioning” (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org). A key characteristic that distinguishes fatigue related to cancer from fatigue in healthy individuals is that it is less likely to be ameliorated by rest.

The clinical manifestations mentioned are neither sensitive nor specific to the type of anemia. Clinicians should be aware of signs of underlying causes, such as jaundice, splenic enlargement, neurologic symptoms, blood in stool, petechiae, and heart murmur.

Approaches to Evaluation

There are 2 common approaches to evaluating anemia: morphologic and kinetic. A complete evaluation often uses both. The morphologic approach is a characterization of anemia based on 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 causes include thalassemia, anemia of chronic disease, and sideroblastic anemia
- **Normocytic** (80–100 fL): may be caused by hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation, or renal insufficiency. The key follow-up test is the reticulocyte count (see following discussion)
- **Macrocytic** (> 100 fL): most is megaloblastic, indicating vitamin 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 diphenytoin, can also cause macrocytosis

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 RBCs) that provides an indication of the RBC production capacity by the bone marrow. A normal RI ranges between 1.0 and 2.0.

- **Low RI**: indicates decreased RBC production, suggesting iron deficiency, vitamin B₁₂/folate deficiency, aplastic anemia, or bone marrow dysfunction caused by cancer or cancer-related therapy (radiation or myelosuppressive chemotherapy)
- **High RI**: indicates normal or increased RBC production, suggesting blood loss or hemolysis in patients with anemia

A comprehensive review of the follow-up and treatment of each subtype of anemia related to causes independent of myelosuppressive cancer therapy is beyond the scope of these guidelines. Following is a summary of additional cues or tests for common underlying ailments:

- **Absolute iron deficiency**: iron and total iron binding capacity (TIBC) resulting in transferrin saturation less than 15% and ferritin less than 30 ng/mL. The reference interval for serum ferritin depends on the specific laboratory. In general, the lower the level, the more probable that true iron deficiency is present, although chronic inflammation may elevate serum ferritin in patients with cancer. Functional iron deficiency is discussed within the context of ESA therapy in a later section
- **Vitamin B₁₂/folate deficiency**: low vitamin B₁₂ or folate levels
- **Hemorrhage**: stool guaiac positive, endoscopy findings
- **Hemolysis**: Coombs test positive, disseminated intravascular coagulation panel positive, low haptoglobin levels, elevated indirect bilirubin
- **Kidney disease**: glomerular filtration rate less than 60 mL/min/1.73 m², 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 origin is identified in a
patient with cancer, the effects of cancer-related inflammation or myelosuppressive chemotherapy (if applicable) should be considered as the cause.

**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 (e.g., if an immediate boost in Hb levels by PRBC transfusion is necessary). Consideration of ESA therapy is generally a long-term management decision given its potential risks.

Importantly, the decision to conduct PRBC transfusion should not be made strictly based on whether the Hb level has reached a certain threshold or “trigger.” The guidelines outline 3 general categories: 1) asymptomatic without significant comorbidities, for which observation and periodic reevaluation 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 onset, severity, and duration of the anemia, and other factors influencing tissue demands for oxygen. When anemia onset is acute, symptoms are likely to be more pronounced, because physiologic adjustments to compensate for a lower oxygen-carrying capacity of the blood can occur with gradual onset. 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 a patient’s ability 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 clinical judgment of the physician. For example, even when a patient with anemia has no physiologic symptoms or significant comorbidity, transfusion may be appropriate if a progressive decline in Hb level occurs after anticancer treatment.

**RBC Transfusion**

PRBCs are the preferred blood product for transfusion to correct anemia, and are concentrated from centrifuged whole blood donations or collected through apheresis. The component is anticoagulated and may contain added preservatives. Further enhancements include leukoreductions, irradiation, freezing, and washing. Certain patients may especially need PRBCs that are cytomegalovirus-negative. One unit of PRBC (300 mL) can have a hematocrit ranging from 50% to 80%, and typically contains 42.5 g to 80 g of Hb (with 147–278 mg of iron) or 128 mL to 240 mL of pure RBCs.

**Benefits of Transfusion**

The major benefit of transfusion with PRBCs, which no other treatment offers, 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 mL) of PRBCs 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.

**Risks of Transfusion**

Risks associated with PRBC transfusion include transfusion-related reactions, congestive heart failure, bacterial contamination and viral infections, and iron overload. Since 1984, the introduction of numerous safety interventions to screen the US blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections. Prestorage leukoreduction has been shown to decrease the incidence of febrile nonhemolytic transfusion reactions, the most common adverse reaction. However, Khorana et al. analyzed data from discharge summaries of patients with cancer admitted to 60 US medical centers between 1995 and 2003 and found increased risks (P < .001).
of venous thromboembolism (VTE; odds ratio [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.

The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anemia (e.g., patients with MDS). However, iron overload is unlikely to occur in patients receiving transfusions restricted to the 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 chemotherapy-induced anemia relates to the limited supply of blood in the United States. 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%.

Transfusion Goals and Basic Principles

Wide variation exists in reported RBC transfusion practice, 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 a deficit of oxygen-carrying capacity in blood to improve oxygen delivery to body tissues. Target Hb ranges for specific conditions recommended by the panel are outlined in the algorithm (see page 635). Transfusion is rarely indicated when the Hb level is greater than 10 g/dL. In the multicenter TRICC (Transfusion Requirements In Critical Care) trial, 838 critically ill patients with no significant in-hospital mortality differences were observed and patients were randomly assigned to receive transfusions to maintain Hb levels of 7 to 9 g/dL (restrictive strategy) versus 10 to 12 g/dL (liberal strategy).

Before transfusion, PRBCs must be crossmatched to confirm compatibility with ABO and other antibodies in the recipient. Premedication (acetaminophen or antihistamine) is seldom required in patients for whom long-term transfusion is not planned. 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.

Erythropoietic Therapy

RBC production is normally controlled by erythropoietin, a cytokine produced in the kidneys. First introduced in 1989, ESAs are a synthetic, recombinant human erythropoietin that can stimulate erythropoiesis in patients with low RBC levels. Currently, 2 ESAs are available in the United States: epoetin alfa and darbepoetin alfa. Unlike transfusion, which almost immediately boosts the Hb level, ESAs can take weeks to initiate an Hb response, but are effective at maintaining a target Hb level with repeated administration. Popularity of ESAs reached a peak in 2003 to 2004, when their use in patients with cancer accounted for 17% of all Medicare Part B spending. However, this paradigm is shifting dramatically as evidence of potential detrimental effects recently began to emerge.

Benefits of ESA Therapy

Avoidance of transfusion is the main benefit of ESAs. Administration of ESA therapy has been shown to decrease PRBC transfusion requirements in patients with cancer undergoing chemotherapy. In a randomized, placebo-controlled study by Littlewood et al., epoetin alfa was shown to reduce transfusion requirements in patients with anemia receiving chemotherapy. 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 vs. 0.5 g/dL; P < .001). A double-blind, placebo-controlled, randomized phase III study enrolled 320 patients (Hb level ≤ 11 g/dL) receiving darbepoetin alfa at 2.25 mcg/kg/wk versus placebo. 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 end point used in a Cochrane review of 42 randomized controlled clinical trials involving use of ESA therapy that enrolled a total of 6510 patients undergoing treatment for cancer. A decreased relative risk (RR) 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: In 2007, the FDA made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa including the addition of a...
“Black Box” label warning and implementation of a risk management program known as Risk Evaluation and Mitigation Strategy (REMS; see page 639). The strengthened FDA restrictions were mainly based on the results of 8 randomized studies that showed a decrease in overall survival and/or locoregional disease control with ESA use for advanced breast, cervical, head and neck, lymphoid, and non–small cell lung cancers. Of the 8 studies, 3 investigated ESA effects in patients who underwent chemotherapy. All 8 trials had an off-label target Hb level of greater than 12 g/dL.

Worsened health outcomes associated with the use of ESAs have been confirmed in 3 recent meta-analyses of 51 to 53 randomized controlled trials. Each reported increased mortality in patients receiving ESAs with RRs/HRs 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 2 other meta-analyses 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. Of these is an update on the PREPARE trial that originally reported increased deaths among patients with breast cancer receiving darbepoetin compared with no darbepoetin. The update found no difference in overall survival; a trend was seen toward decreased disease-free survival that failed to reach statistical significance. Data from randomized studies also showed no increase in mortality with ESA use according to the prescribing label specifically in patients receiving chemotherapy for small cell lung cancer.

Risk of Thromboembolism: Increased thromboembolic risks have been associated with ESA treatment in patients with cancer. The cause of VTE is complex; a heightened baseline risk is related to the malignancy itself and to chemotherapy (see NCCN Guidelines for Venous Thromboembolic Disease; available on the NCCN Web site at NCCN.org). Other risk factors for VTE in patients with cancer include prior history of VTE, heritable mutation, hypercoagulability, elevated prechemotherapy platelet counts, recent surgery, hormonal agents, prolonged inactivity from hospitalization, steroids, and comorbidities such as hypertension.

Overall, results from meta-analyses established a significant association: increased risk of thrombotic events associated with ESA use was reported by Tonelli et al., (RR, 1.69; 95% CI, 1.27–2.24), Bennett et al., (RR, 1.57; 95% CI, 1.31–1.87), Ludwig et al., (HR, 1.57; 95% CI, 1.10–2.26), and Glaspy et al. (OR, 1.48; 95% CI, 1.28–1.72). A combined analysis of 6 trials investigating darbepoetin alfa by Glaspy et al. also found an increased risk of thromboembolism for patients with Hb levels greater than 12 g/dL (RR, 1.66; 95% CI, 0.9–3.04) or those experiencing an increase greater than 1 g/dL in 14 days (RR, 1.67; 95% CI, 0.96–2.88). In addition, an increased risk for stroke was associated with darbepoetin alfa in a clinical trial of patients with chronic kidney disease (CKD; HR, 1.92; 95% CI, 1.38–2.68). The increased risk of thromboembolism in patients with cancer receiving ESA therapy is specified in the black box warnings included in the updated FDA labels. The panel cautions physicians to be alert for the signs and symptoms of thromboembolism in patients with cancer receiving ESAs.

Risk of Hypertension/Seizures: Seizures have been reported in patients with chronic renal failure receiving ESAs. A 2.5% incidence of seizure in patients on dialysis is seen during the first 90 days of therapy. Although whether patients with cancer receiving ESA therapy are at risk for seizures is unclear, 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 anemia syndrome characterized by a low reticulocyte count, 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. Causation was attributed to formulations without human serum albumin, subcutaneous administration, and uncoated rubber stoppers. 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. 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 panel recommends that any patient with cancer who develops a sudden loss of response to ESAs, accompanied by severe anemia and low reticulocyte count, should be evaluated for the cause 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 because 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 page 639).

For patients with cancer, 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. Hence, patients not receiving concomitant myelosuppressive chemotherapy are not eligible. Randomized trial data suggest that ESAs may promote tumor growth in an off-target manner. Therefore, these agents should not be used when the anticipated treatment outcome is cure, including with primary and adjuvant chemotherapy for malignancies such as early-stage breast cancer, non–small cell lung cancer, lymphomas, and testicular cancer. An exception to this may be with small cell lung cancer, for which trials show no negative impact on survival or disease progression (see previous discussion). For patients undergoing palliative treatment, ESA therapy can be considered preferentially over transfusion.

The panel recognized that whether a chemotherapy regimen is considered curative is not always clear. Under these circumstances, given that no other cause of anemia has been identified, the order of priority for anemia management should be consideration of RBC transfusion, clinical trial enrollment if available, followed by consideration of ESAs. When ESA use is decided upon, physicians are advised to use the lowest dose necessary to avoid transfusion.

CKD is an independent indication for ESA therapy. Risks of ESA use in these patients seem to be associated with high doses and/or high target Hb levels, and the FDA label mandates individualized dosing to maintain Hb levels between 10 and 12 g/dL. Because 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.60). For example, patients with CKD not undergoing active therapy for a malignancy should try to avoid ESAs, whereas those receiving palliative chemotherapy may favor ESAs over transfusions to treat severe anemia through carefully dosing for target Hb between 10 and 12 g/dL in keeping with the indication for CKD. In patients with CKD who have 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 transplants require transfusion support. Nonetheless, ESA therapy may be useful in some instances. For example, ESAs may be administered posttransplant to increase the hematocrit to allow phlebotomy in cases of transfusional iron overload. ESA efficacy has been reported in patients who refuse blood transfusions while undergoing autologous stem cell transplantation.61–63 Posttransplant use of ESAs for patients undergoing cancer chemotherapy, those with renal insufficiency, or those with recurrent/secondary MDS should follow NCCN Guidelines for chemotherapy-related anemia, CKD, or MDS, respectively (available at NCCN.org).

Iron studies, such as serum iron, TIBC, and serum ferritin, should accompany ESA therapy to monitor the development of functional iron deficiency (discussed later).

**Dosing Schedules**

Epoetin alfa and darbepoetin alfa are considered equivalent by the panel. Recommended initial dosing schedules for patients receiving chemotherapy are summarized in the algorithm. The most common initial dosing schedules for epoetin alfa evaluated in
clinical trials of patients with cancer are 150 U/kg administered subcutaneously 3 times weekly and 40,000 U subcutaneously once weekly. 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 subcutaneously every 2 weeks and a dose of 120,000 U subcutaneously once every 3 weeks.

Although darbepoetin doses were initially administered at 2.25 mcg/kg subcutaneously every week, interest has been shown 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 3 weeks in 705 patients with nonmyeloid malignancies with an Hb level less than 11 g/dL. The percentage of patients achieving the target Hb level (≥ 11 g/dL) was 77% in the weekly arm and 84% for patients receiving darbepoetin alfa every 3 weeks. Currently the panel recommends both schedules. Several studies have shown the safety and efficacy of alternative dosing schedules for darbepoetin alfa, including a fixed weekly dose of 100 mcg, a fixed dose of 200 mcg biweekly, and 300 mcg every 3 weeks.

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 an increase in the number of RBCs is seen. Hb levels should be measured weekly until they stabilize. Dose reduction 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. Doses of epoetin alfa and darbepoetin alfa should be decreased by 25% to 40%, although individualized dose titrations may be needed.

Conversely, the ESA dose should be increased according to the algorithm (see page 636) in patients receiving chemotherapy who show no response (< 1 g/dL in Hb increase) in Hb level after 4 weeks of epoetin alfa or 6 weeks of darbepoetin alfa. Iron supplementation can be considered to improve response to ESA therapy (see later discussion). 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 described earlier 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 after continued erythropoietin use. As a result, iron supplementation will eventually be required in most patients to maintain optimal erythropoiesis. 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 that blocks the release of iron (bound in macrophages within the RES) to its transporter transferrin. 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 before treatment to rule out absolute iron deficiency (transferrin saturation [TSAT] < 15%, serum ferritin < 30 ng/mL), which may respond to oral or intravenous iron monotherapy without an ESA.

Iron can be administered in oral or parenteral form (low-molecular-weight iron dextran, ferric gluconate, and iron sucrose). Evidence from 5 published studies using iron in conjunction with an ESA suggests that intravenous iron is superior to oral iron. 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 receiving epoetin alfa to either no iron, oral iron, bolus intravenous iron dextran, or iron dextran total dose infusion. Increases in Hb
concentration were greater with intravenous iron (groups 3 and 4) than with oral supplementation or no iron (P < .02), although no difference was seen between the oral and no iron groups (P = .21). In a second open-label study by Henry et al., 187 patients with cancer-related anemia receiving chemotherapy and epoetin alfa were randomized to no iron, oral ferrous sulfate 3 times daily, or weekly intravenous ferric gluconate. Intravenous 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 intravenous arm (73%) compared with oral (45%) or no iron (41%). A third study was conducted in 67 patients with lymphoproliferative malignancies not undergoing chemotherapy. Patients were randomized to weekly epoetin beta with or without intravenous iron sucrose. Although an oral iron arm was not included, intravenous iron resulted both in higher mean change in Hb level from baseline (2.76 vs. 1.56 g/dL; P = .0002) and a higher Hb level response rate (≥ 2 g/dL increase; 87% vs. 53%; P = .0014) compared with the no-iron group.

Two additional studies were published in 2008. Bastit et al. reported their open-label trial of 396 patients with nonmyeloid malignancies undergoing chemotherapy (Hb < 11 g/dL). These were treated with darbepoetin alfa with or without intravenous iron (iron sucrose or ferric gluconate, proportion of patients receiving each preparation has not been reported), 200 mg every 3 weeks for 16 weeks. Again, hematopoietic responses and time to reach target Hb level were improved in the intravenous iron arm. Most significantly, this is the first and only study to associate intravenous iron with fewer RBC transfusions in patients with cancer (9% vs. 20%; P = .005). In a study by Pedrazzoli et al., 149 patients with solid tumors and chemotherapy-induced anemia 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 greater than 100 ng/mL and TSATs greater than 20%. The ESA/intravenous iron group showed a higher hematopoietic response rate (93% vs. 70%; P = .0033) compared with the control group. These studies showed that concurrent intravenous iron enhanced hematologic response to ESAs, although evidence is insufficient to determine whether iron supplementation can allow an ESA dose decrease. Long-term effects of intravenous iron supplementation in patients with cancer were not assessed in any of these 5 trials.

In 2011, Steensma et al. published findings from the largest trial to date that challenged results from the studies mentioned earlier. Roughly 500 patients with cancer-induced anemia were randomized 1:1:1 to intravenous ferric gluconate, oral ferrous sulfate, or oral placebo. Intravenous 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 intravenous iron group was 22.5%, a value greater than 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. This includes 7 randomized controlled trials involving 1777 patients with chemotherapy-induced anemia. Oral or intravenous iron supplementation with ESAs reduced transfusion rates compared with no iron. Intravenous iron but not oral iron was associated with improved hematopoietic response rates compared with ESA alone. No difference in adverse events was found.

**NCCN Recommendations**

In these NCCN Guidelines, intravenous iron products alone (without an ESA) are recommended for iron repletion in patients with cancer with absolute iron deficiency (ferritin < 30 ng/mL, transferrin saturation < 15%). Intravenous iron monotherapy has not been studied in patients with chemotherapy-induced anemia and functional iron deficiency (ferritin ≤ 800 ng/mL, transferrin saturation < 20%). Therefore, the currently recommendation is that ESAs be used in addition to intravenous iron for patients with chemotherapy-induced anemia and functional iron deficiency. Common adverse events after FDA-approved doses of parenteral iron include hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness. Most adverse events associated with iron dextran occur with high-molecular-weight iron dextran (Dexferrum). The recommended iron dextran product is low-molecular-weight iron dextran (IN-Fed). 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 have other drug allergies. Dosage details for administering parenteral iron therapy are listed in the algorithm (see page 640). Although data are conflicting in the literature, concerns exist regarding intravenous iron possibly promoting inflammation and bacterial growth. Hence, iron supplementation is not recommended for patients with active infection.

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 intravenous iron in reducing transfusion needs, the optimal dose and frequency of intravenous 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 chemotherapy-induced anemia, such as iron isomaltoside and ferric carboxymaltose. More information about these agents can be found at ClinicalTrials.gov.

References

Cancer- and Chemotherapy-Induced Anemia

## Individual Disclosures for the NCCN Cancer- and Chemotherapy-Induced Anemia Panel

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<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
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<td>Michael M. Millenson, MD, FACP</td>
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<td>Denise Reinke, MS, NP</td>
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The NCCN guidelines staff have no conflicts to disclose.