NCCN Cancer- and Treatment-Related Anemia Panel Members

* George M. Rodgers, III, MD, PhD/Chair ‡
  Huntsman Cancer Institute at the University of Utah

David Cella, PhD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Asher Chanan-Khan, MD †
Roswell Park Cancer Institute

Carolyn Chesney, MD
St. Jude Children’s Research Hospital/University of Tennessee Cancer Institute

Charles Cleeland, PhD †
The University of Texas M. D. Anderson Cancer Center

Peter F. Coccia, MD ‡ €
UNMC Eppley Cancer Center at The Nebraska Medical Center

George D. Demetri, MD †
Dana-Farber/Brigham and Women’s Cancer Center | Massachusetts General Hospital Cancer Center

Benjamin Djulbegovic, MD, PhD † ‡ ₦
H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida

Jennifer L. Garst, MD † ₪
Duke Comprehensive Cancer Center

Eric H. Kraut, MD ‡
Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

Weei-Chin Lin, MD, PhD † ‡
University of Alabama at Birmingham Comprehensive Cancer Center

Michael Millenson, MD ‡ ₪
Fox Chase Cancer Center

Victoria Mock, DNSc #
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Denise Reinke, APRN, BC, AOCN #
University of Michigan Comprehensive Cancer Center

Joseph Rosenthal, MD ‡ €
City of Hope Cancer Center

Paul Sabbatini, MD † ₪
Memorial Sloan-Kettering Cancer Center

Ravi Vij, MD ‡
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

‡ Hematology/Hematology oncology
θ Psychiatry/Psychology
† Medical oncology
€ Pediatric oncology
₦ Bone marrow transplantation
₽ Internal medicine
# Nursing
* Writing Committee Member

Continue
Table of Contents

NCCN Anemia Panel Members
Screening Evaluation and Risk Assessment (ANEM-1)
Evaluation for Symptomatic Anemia Risk (ANEM-2)
Treatment and Evaluation (ANEM-3)
Response Assessment (ANEM-4)
Follow-up Therapy and Symptom Response (ANEM-5)
Erythropoietic Therapy - Dosing and Titration (ANEM-A)
Parenteral Iron Preparations (ANEM-B)

Guidelines Index
Print the Anemia Guideline
Order the Patient Version of the Cancer and Treatment-Related Anemia Guidelines

For help using these documents, please click here

Manuscript
References

Clinical Trials: The 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 Consensus: All recommendations are Category 2A unless otherwise specified.
See NCCN Categories of Consensus

Summary of Guidelines Updates

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.
Summary of the Guidelines updates

Changes in the 3.2007 version of the Cancer- and Treatment-Related Anemia Guidelines from the 2.2007 version include:

- In the "ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY" attachment (ANEM-A 3 of 4), bullet 4 under Cancer Patient Survival was updated to reflect the FDA alert regarding the safety of erythropoiesis stimulating agents (ESAs):
  Analyses of four new studies in patients with cancer found a higher chance of serious and life-threatening side effects and/or death with the use of ESAs. Please refer to the FDA website for additional information: [link]
  Until new research evidence changes current benefit: risk estimates, physicians should be advised not to administer ESAs (darbepoetin, epoetin alfa) to patients outside of the treatment period of cancer-related therapy (radiation therapy, chemotherapy). A treatment period is defined as 6 weeks after the completion of treatment.
- Footnote "d" is new throughout the Guidelines.
- The target hemoglobin was changed from 12 g/dL to 11-12 g/dL throughout the Guidelines. The recommendation threshold for holding therapy was changed from 13 g/dL to 12 g/dL. (ANEM-A 1 of 4).

Change in the 2.2007 version of the Cancer- and Treatment-Related Anemia Guidelines from the 2.007 version:

- The following statement was added to the "ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY" attachment (ANEM-A 3 of 4):
  The results of a large, multicenter, randomized, placebo-controlled study showed that darbepoetin was ineffective in reducing red blood cell transfusions or fatigue in patients with cancer who have anemia that is not due to concurrent chemotherapy. The study also showed higher mortality in patients receiving darbepoetin.

Summary of changes in the 1.2007 version of the Cancer- and Treatment-Related Anemia Guidelines from the 2.2006 version include:

- A footnote was added that the "NCCN Cancer and Treatment-Related Anemia Guidelines were formulated in reference to adult patients" (ANEM-1).
- Footnote j was modified to indicate that IV iron appears to have superior efficacy over oral iron and remains under investigation and a new reference was added (ANEM-3, ANEM-4).
- The alternative regimen dose of darbepoetin 3 mcg/kg every 2 wks by subcutaneous injection with an increase of darbepoetin to 5 mcg/kg every 2 wks by subcutaneous injection was removed (ANEM-A 1 of 4).
- Two additional dosing schedules of darbepoetin were added to the alternative regimens (ANEM-A 1 of 4):
  - Darbepoetin 100 mcg fixed dose every wk by subcutaneous injection with an increase of darbepoetin to up to 150-200 mcg fixed dose every wk by subcutaneous injection
  - Darbepoetin 300 mcg fixed dose every 3 wks by subcutaneous injection with an increase of darbepoetin to up to 500 mcg fixed dose every 3 wks by subcutaneous injection
- Two additional dosing schedules of epoetin alfa were added to the alternative regimens (ANEM-A 1 of 4):
  - Epoetin alfa 80,000 units every 2 wks by subcutaneous injection
  - Epoetin alfa 120,000 units every 3 wks by subcutaneous injection
- In titration for response, the reason for holding therapy with hemoglobin values over 13 g/dL was added (ANEM-A 1 of 4).
**Cancer- and Treatment-Related Anemia**

### PRESENTATION\(^a,b\)

- Hemoglobin (Hb) < 11 g/dL (See MS-1 for definition of anemia)

### SCREENING EVALUATION\(^c\)

- CBC with indices
- Review of peripheral smear, as clinically indicated
- Cancer or treatment-related anemia\(^d\)
  - Non-cancer or non-treatment-related anemia-specific cause:
    - Bleeding
    - Hemolysis
    - Nutritional deficiency
    - Hereditary
    - Renal dysfunction
    - Iron deficiency

### RISK ASSESSMENT

- Disease-specific anemia\(^e\)
- Acuity
- Severity
  - Mild (Hb 10-11 g/dL)
  - Moderate (Hb 8-10 g/dL)
  - Severe (Hb < 8 g/dL)
- Symptoms-physiological
  - Cardiac symptoms\(^f\)
  - Fatigue\(^g\)
- Comorbidities
  - Cardiac history/decompensation
  - Chronic pulmonary disease
  - Cerebral vascular disease

\(\text{See Symptom Assessment and Evaluation of Anemia Risk (ANEM-2)}\)

---

\(^a\)The NCCN Cancer and Treatment-Related Anemia Guidelines were formulated in reference to adult patients.

\(^b\)Transplant-related anemia is not included.

\(^c\)The following studies should have been completed if clinically indicated: reticulocyte count, iron studies, B12/folate, stool guaiac, LDH, fractionated bilirubin, bone marrow examination, direct Coombs, Hb electrophoresis, creatinine and/or creatinine clearance. There is no clear evidence that erythropoietin levels are predictive of response.

\(^d\)Erythropoiesis-stimulating agents (ESAs) have been mainly tested in the setting of chemotherapy or radiation-related anemia. Several small trials indicate that ESAs may be useful in the treatment of anemia due to cancer, but recent studies (see FDA warning [http://www.fda.gov/cder/drug/infopage/RHE/default.htm] and page ANEM-A 3 of 4) indicate that the use of ESAs in this setting may be ineffective and harmful.


\(^f\)Symptoms include chest pain, dyspnea on exertion, peripheral edema, sustained tachycardia, orthostatic lightheadedness/near syncope or syncope.

\(^g\)See also [NCCN Cancer-Related Fatigue Guidelines](http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf).

---

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.
**Cancer- and Treatment-Related Anemia**

**SYMPTOM ASSESSMENT**

Immediate correction required

- Transfuse as indicated based on institutional guidelines

Immediate correction not required

- Complete symptom assessment:
  - Symptoms-functional
  - Quantitative scales\(^g\)
  - Activity level
  - Performance status
  - Patient-reported fatigue\(^h\)

**EVALUATION FOR SYMPTOMATIC ANEMIA RISK**

Asymptomatic

Evaluate risk factors for developing symptomatic anemia:
- Transfusion in past 6 mo
- History of prior myelosuppressive therapy (eg, BMT)
- History of radiotherapy > 20% of skeleton
- Myelosuppression potential of current therapy
  - Duration
  - Schedule
  - Agents
  - Age
  - Hemoglobin level

Symptomatic\(^f\)

Risk factors not present

- See Treatment (ANEM-3)

Risk factors present

- See Treatment (ANEM-3)

---

\(^g\) See also NCCN Cancer-Related Fatigue guideline.

\(^h\) Examples include the Fatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI).

**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.
### Cancer- and Treatment-Related Anemia

**TREATMENT**

<table>
<thead>
<tr>
<th>Asymptomatic; Risk factors not present</th>
<th>Observation or Consider erythropoietic therapy&lt;sup&gt;d,i&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic; Risk factors present</td>
<td>Observation or Transfuse as indicated based upon symptoms and institutional guidelines and/or Consider erythropoietic therapy&lt;sup&gt;d,i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Symptomatic&lt;sup&gt;g&lt;/sup&gt;</td>
<td>• Hb 10-11 g/dL: Consider erythropoietic therapy&lt;sup&gt;d,i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Hb &lt; 10 g/dL: Strongly consider erythropoietic therapy (category 1)&lt;sup&gt;d,i,j&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**ADDITIONAL EVALUATION**

<table>
<thead>
<tr>
<th></th>
<th>Iron studies: Iron panel (serum iron, total iron binding capacity, serum ferritin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic re-evaluation for symptoms and risk factors</td>
<td></td>
</tr>
<tr>
<td>Transfuse as indicated based upon symptoms and institutional guidelines</td>
<td></td>
</tr>
</tbody>
</table>

**TREATMENT REGIMEN**

<table>
<thead>
<tr>
<th>See Erythropoietic Therapy - Dosing and Titration (ANEM-A) ± iron supplementation&lt;sup&gt;k&lt;/sup&gt; as indicated (ferritin &lt; 100, transferrin saturation &lt; 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>See Response Assessment (ANEM-4)</td>
</tr>
</tbody>
</table>

<sup>d</sup>Erythropoiesis-stimulating agents (ESAs) have been mainly tested in the setting of chemotherapy or radiation-related anemia. Several small trials indicate that ESAs may be useful in the treatment of anemia due to cancer, but recent studies (see FDA warning [http://www.fda.gov/cder/drug/infopage/RHE/default.htm](http://www.fda.gov/cder/drug/infopage/RHE/default.htm) and page [ANEM-A 3 of 4](#)) indicate that the use of ESAs in this setting may be ineffective and harmful.

<sup>g</sup>See also NCCN Cancer-Related Fatigue guideline.

See Adverse Effects of Erythropoietic Therapy (ANEM-A 3 of 4).


**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.
INITIAL RESPONSE ASSESSMENT

Response (hemoglobin increase by 1 g/dL) → Titrate dosage to maintain optimal hemoglobin (11-12 g/dL)¹

No response at 4 weeks for epoetin alfa and 6 weeks for darbepoetin → Increase dose of erythropoietic agentᵐ (See Erythropoietic Therapy - Dosing and Titration ANEM-A) ± iron supplementation⁰ as indicated

SUBSEQUENT RESPONSE ASSESSMENT

Response (hemoglobin increase by 1 g/dL) at 8-12 wks → Titrate dosage to maintain optimal hemoglobin (11-12 g/dL)¹

Stable hemoglobin level (within 1-2 g/dL of baseline) while receiving chemotherapy → Continue erythropoietic therapy

No hemoglobin response at 8-12 wks → • Discontinue erythropoietic therapy • Transfuse as indicated based upon symptoms and institutional guidelines


ᵐThis is only applicable to regimens with a dosing schedule of 3x weekly, weekly, or every 2 weeks.

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.
**Anemia Table of Contents**

**Cancer- and Treatment-Related Anemia**

**FOLLOW-UP THERAPY**

- Re-evaluate symptoms at each visit.
- If hemoglobin level decreases, check iron stores and evaluate for development of other anemia specific causes.

**SYMPTOM RESPONSE**

- Hemoglobin 11-12 g/dL or > 2 g/dL from initial level

  - No improvement in symptoms
  - Improvement in symptoms

- Consider erythropoietic therapy to maintain optimal hemoglobin

  - See NCCN Cancer-Related Fatigue guideline
  - See NCCN Distress Management guideline

- Titrate dosage to maintain optimal hemoglobin (11-12 g/dL)

---

**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.

---

*See Erythropoietic Therapy - Dosing and Titration (ANEM-A).*

*Indications include future transfusion needs.*
# Erythropoietic Therapy - Dosing and Titration (1 of 4)

<table>
<thead>
<tr>
<th>Package Insert Dosing Schedule</th>
<th>Titration for No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dosing</strong></td>
<td><strong>Titration for No Response</strong></td>
</tr>
<tr>
<td>Epoetin alfa 150 units/kg 3 times weekly by subcutaneous injection</td>
<td>Increase dose of epoetin alfa to 300 units/kg 3 times weekly by subcutaneous injection</td>
</tr>
<tr>
<td>or 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>
</tr>
<tr>
<td>or Darbepoetin 2.25 mcg/kg every wk by subcutaneous injection</td>
<td>Increase darbepoetin to up to 4.5 mcg/kg every wk by subcutaneous injection</td>
</tr>
<tr>
<td>or Darbepoetin 500 mcg every 3 wks by subcutaneous injection</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative Regimens</strong></td>
<td><strong>Titration for Response</strong></td>
</tr>
<tr>
<td>Darbepoetin 100 mcg fixed dose every wk by subcutaneous injection</td>
<td>If hemoglobin increases by more than 1 g/dL in a 2 week period, dose should be reduced by 25%.</td>
</tr>
<tr>
<td>or Darbepoetin 200 mcg fixed dose every 2 wks by subcutaneous injection</td>
<td>If hemoglobin exceeds 12 g/dL, hold therapy. Reinitiate therapy if hemoglobin falls below 12 g/dL at 25% dose reduction of the prior dose.</td>
</tr>
<tr>
<td>or Darbepoetin 300 mcg fixed dose every 3 wks by subcutaneous injection</td>
<td></td>
</tr>
<tr>
<td>or Epoetin alfa 80,000 units every 2 wks by subcutaneous injection</td>
<td></td>
</tr>
<tr>
<td>or Epoetin alfa 120,000 units every 3 wks by subcutaneous injection</td>
<td></td>
</tr>
</tbody>
</table>

See Adverse Effects of Erythropoietic Therapy (ANEM-A 3 of 4)

See Footnotes and References (ANEM-A 2 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 OF 4)

FOOTNOTES AND REFERENCES

2 Studies evaluating loading dose regimens and less frequent administration schedules are currently being investigated. Optimal dosing regimens have not yet been determined.
3 Less frequent dosing regimens are under investigation, and could be considered as an alternative to dose reduction.
4 The dosages and regimens included in this table have been evaluated in cancer patients receiving chemotherapy.
5 Oral iron is more commonly used but IV iron appears to have superior efficacy and remains under investigation. (Auerbach M, Ballard H, Trout JR et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004;22(7):1301-1307. See Parenteral Iron Preparations (ANEM-B).
ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY

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-A 1 of 4)

Thrombosis
- Early trials of recombinant human erythropoietin reported that a high target hematocrit (42 ± 3%) was associated with increased mortality and an increased number of vascular events (arterial and venous).
- The hemoglobin level should be targeted to 12 g/dL to decrease risk of thrombotic complications. Erythropoietin may have a thrombogenic potential independent of hemoglobin levels. In patients receiving erythropoietic drugs, physicians should be suspicious of signs and symptoms of thrombosis.
- A recent analysis update on thrombotic complications confirms an increased thrombosis risk with use of erythropoietic agents. This same study demonstrated a non-significant trend toward worse survival.

Pure red cell aplasia (PRCA)
- Between 1998-2004, almost 200 cases of PRCA were reported in patients treated with erythropoietin. 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.

Cancer Patient Survival
- Two studies have reported decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia.
- A recent meta-analysis of nine trials of epoetin-β in anemic patients with cancer receiving chemotherapy or undergoing cancer surgery found no effect of erythropoietic therapy on survival, tumor progression, or thrombosis mortality.
- 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.
- Analyses of four new studies in patients with cancer found a higher chance of serious and life-threatening side effects and/or death with the use of ESAs. Please refer to the FDA website for additional information: http://www.fda.gov/cder/drug/infopage/RHE/default.htm

Until new research evidence changes current benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin, epoetin alfa) to patients outside of the treatment period of cancer-related therapy (radiation therapy, chemotherapy). A treatment period is defined as 6 weeks after the completion of treatment.

See Footnotes and References (ANEM-A 4 of 4)
ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (4 OF 4)

ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY

FOOTNOTES AND REFERENCES


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.
PARENTERAL IRON PREPARATIONS

- Parenteral Iron Preparations
  - Iron dextran
  - Ferric gluconate
  - Iron sucrose
- These products are helpful in treating iron deficiency in patients intolerant or unresponsive to oral iron therapy, and in treating functional iron deficiency as seen in chronic renal failure patients, and cancer patients who are receiving erythropoietic drugs.
- 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.
- Patients receiving these drugs should also receive pretreatment with diphenhydramine and acetaminophen to minimize adverse events.

---

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Anemia may be a sign of disease and often has multiple causes. This algorithm recognizes the multiple etiologies of cancer- and treatment-related anemia but specifically addresses the treatment of anemia caused by the myelosuppressive effects of chemotherapy and the anemia associated with chronic disease. It provides guidelines for the use of erythropoietic agents in patients with cancer receiving chemotherapy.

Before 1980, improvements in blood banking technology had allowed liberal transfusion practices, with many patients transfused at thresholds as high as 10 g/dL. The 1980s brought recognition of infection risks, as well as limits on supply. Consequently, stringent transfusion guidelines were developed, lowering the threshold for transfusion to 7 to 8 g/dL with the goal of preventing “physiological” complications. Two erythropoietic agents, epoetin alfa and darbepoetin (collectively known as erythropoiesis stimulating agents, i.e. ESA), are now available, providing an alternative to transfusion. In addition, the development of newer agents for cancer treatment shifted the management of malignancy in many cases to that of a more chronic disease. As a result a wider interest in QOL and validated tools for its assessment emerged. Anemia may be associated with fatigue and thus decreased QOL. The traditional definitions of “clinically significant anemia” are being reconsidered, and this focus has prompted a complete recording of all grades of anemia in clinical trials, with the idea that anemia of lesser grades may be more important than previously suspected.

Definition and Incidence of Cancer- and Treatment-related Anemia

The National Cancer Institute (NCI) considers normal hemoglobin levels as 12 to 16 g/dL for women and 14 to 18 g/dL for men. Both the World Health Organization (WHO) and NCI have provided scales for characterizing levels of hemoglobin with slight variations in the definitions of “mild anemia”.

<table>
<thead>
<tr>
<th>Grade</th>
<th>(Severity)</th>
<th>NCI Scale</th>
<th>WHO Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(none)</td>
<td>Normal Limits *</td>
<td>&gt; 11</td>
</tr>
<tr>
<td>1</td>
<td>(mild)</td>
<td>10 - normal</td>
<td>9.5 - 10</td>
</tr>
<tr>
<td>2</td>
<td>(moderate)</td>
<td>8 - 10</td>
<td>8 - 9.4</td>
</tr>
<tr>
<td>3</td>
<td>(severe)</td>
<td>6.5 - 7.9</td>
<td>6.5 - 7.9</td>
</tr>
<tr>
<td>4</td>
<td>(life-threatening)</td>
<td>&lt; 6.5</td>
<td>&lt; 6.5</td>
</tr>
</tbody>
</table>

\* 14-18 g/dL for men, 12-16 g/dL for women.

Using a definition of hemoglobin level less than 12 g/dL, a retrospective review showed that patients receiving radiotherapy for colorectal, lung, and cervix cancer had anemia by the end of treatment in 67%, 63%, and 82% of patients, respectively. The incidence of anemia, taking into account all grades, is also frequent for patients receiving chemotherapy.

### Incidence of Anemia in Patients with Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumor Type</th>
<th>Grade 1 or 2 (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAF</td>
<td>Breast (n = 165)</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Ovary (n = 111)</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>CHOP</td>
<td>NHL (n = 212)</td>
<td>49</td>
<td>17 - 79</td>
</tr>
<tr>
<td>Paclitaxel/Carboplatin</td>
<td>NSCLC (n = 81)</td>
<td>10 - 59</td>
<td>5 - 34</td>
</tr>
</tbody>
</table>

*WHO or NCI scales


### Cancer- and Treatment-Related Anemia: Etiology

Cancer- and treatment-related anemia is multifactorial, adding to the complexity of the problem in evaluating patients. Etiologies may include bleeding, hemolysis, bone marrow infiltration, renal insufficiency, nutritional deficiencies and the anemia of chronic disease, or a combination of these. In addition, the myelosuppressive effects of chemotherapy must be considered.

The contribution of anemia of chronic disease (ACD) has been underappreciated. This form of anemia is mediated by inflammatory cytokines that directly suppress erythropoiesis and also inhibit erythropoietin production. Patients with ACD have low serum iron levels, but the bone marrow is replete with iron, suggesting an iron utilization defect rather than a deficiency. This has been termed “functional iron deficiency.” Serum ferritin levels may sometimes be elevated in patients with cancer as a result of inflammation and may not always be reflective of iron stores. Despite the limitations of measuring serum iron parameters, a functional iron deficiency has been generally characterized by a serum ferritin level less than 100 ng/mL or a transferrin saturation (TSAT) level less than 20%. The blunted erythropoietin response in patients with ACD is illustrated by a comparison between erythropoietin levels in patients with cancer-associated anemia and iron deficiency as reported by Miller et al.

![Erythropoietin Response to Anemia](image)

Defining the Target Hemoglobin

The human homeostatic mechanism results in an increase in erythropoietin production as hemoglobin levels fall below 12 g/dL, suggesting an importance for maintaining normal hemoglobin levels as observed in the review by Finch et al. 5 It is intriguing that the threshold hemoglobin value of 12 g/dL also appears important when the anemia and quality-of-life data is analyzed for the hemoglobin value at which the maximum gain in QOL is seen.

In determining the target hemoglobin value for the initiation of treatment and the goal of continued therapy, it is essential to define the endpoint of the intervention. Goals for the intervention of mild to moderate anemia can range from the prevention of transfusion (a lower set-point near 10 g/dL, and extensive randomized data to support the benefit) to the optimization of QOL (normal hemoglobin as the endpoint, and large patient numbers suggesting a benefit but less definitive randomized data).

The QOL data support that optimal improvement occurs by moving hemoglobin into the 11 g/dL to 12 g/dL range. 6 If an improvement in patient function is the goal, the panel has selected 11 g/dL as the level to consider intervention based on the eligibility criteria of the majority of the large community based studies, the lag time for erythropoietin to improve hemoglobin, and the desire to maintain the hemoglobin in the 11 to 12 g/dL range for the longest duration during therapy.

Quality of Life Assessment

The relationship between anemia and fatigue has been suggested as one factor responsible for decreased QOL in patients with cancer. A variety of tools have been used in clinical trials to assess anemia related QOL, including LASA (linear analog scale assessment), FACT-An (Functional Assessment of Cancer Therapy-anemia subscale), and the SF-36 (Short Form-36). The LASA is a self-reporting, 100-mm scale that measures energy level, ability to perform usual activities, and overall QOL. The FACT-An is a 55-item cancer-specific questionnaire with the anemia subscale (An) which has questions specifically related to fatigue. The SF-36 is an 11-item scale measuring mental and physical components of QOL but it is not cancer-specific Using anchor-based and distribution-based methods (linking QOL score changes to the clinical indicators: hemoglobin level, performance status, and response to treatment), minimum changes of 3.0 on the fatigue subscale, and 4.0 on the FACT instrument, have been estimated as conservative “minimum” estimates. Using subjective global estimates, rather than nonpatient-reported anchors, a minimal clinically meaningful change of 5.5 has been suggested for the FACT instrument. 7 These or similar figures also are expected to be useful in planning future clinical trials in terms of determining sample sizes necessary to detect these differences, and in defining clinically meaningful QOL changes.

Treatment of Chemotherapy Induced Anemia

Impact on Transfusion Incidence

In a randomized, placebo-controlled study by Littlewood et al, epoetin alfa was shown to reduce transfusion requirements in patients with anemia receiving chemotherapy. 8 Three hundred seventy-five patients with solid or nonmyeloid hematologic malignancies and hemoglobin levels 10.5 g/dL or less; or greater than 10.5 g/dL, but 12.0 g/dL or less after a hemoglobin decrease of 1.5 g/dL or less since starting chemotherapy; were randomized 2:1 to epoetin alfa 150 to 300 IU/kg (n = 251) or placebo (n = 124) TIW for 12 to 24 weeks. Transfusion requirements were statistically significantly decreased in the epoetin alfa arm compared with placebo (24.7% vs. 39.5%, respectively, \( P = .0057 \)), and hemoglobin level was increased (2.2 g/dL vs. 0.5 g/dL, respectively, \( P < .001 \)). 8

The ability of epoetin alfa to reduce transfusion requirements was one endpoint of a systematic review and meta-analysis of controlled clinical
Clinical trials with similar endpoints using darbepoetin alfa have also resulted in its approval for use in cancer patients. A pivotal, double blind, placebo-controlled, randomized phase III study of darbepoetin alfa enrolled 320 patients receiving darbepoetin alfa at 2.25 mcg/kg/week versus placebo. Patents receiving darbepoetin alfa required fewer transfusions (27% vs. 52%, mean difference 25%, 95% CI 14%-36%, P < .001) than patients receiving placebo. “Hematopoietic response” was defined as a 2 g/dl rise in hemoglobin, or reaching a hemoglobin of 12 g/dl. Hematopoietic responses occurred in favor of the treated patients (66% versus 24%, mean difference = 42%; 95% CI 31% to 53%, P < .001).10

Impact on Quality of Life
Quality of life has been addressed in one randomized study of epoetin by Littlefield, as cited above. In this study the group treated with epoetin alfa had a mean improvement in QOL scores using LASA (energy, P < .001; daily activities, P < .01; and overall QOL, P < .01) and FACT-An (P < .001) when compared with the placebo group, which had a worsening in scores. An improvement of similar magnitude was seen in the SF-36 scale, but results did not quite reach statistical significance. Studies evaluating the clinical significance, or “meaningfulness,” of changes in scores on the target subscales of FACT-anemia suggest that the differences noted are clinically meaningful.

The remainder of the data supporting the relationship between anemia and fatigue is derived from nonrandomized trials and includes three open-label community-based studies providing approximately 7,000 additional patients for analysis. Two of these studies used epoetin alfa at 10,000 units 3 times weekly, and the third evaluated 40,000 units subcutaneously weekly. The results of these studies in terms of hemoglobin improvement, transfusion reduction, and improvement in QOL appear similar. In each of the three studies, hemoglobin was statistically significantly improved over baseline, and transfusion requirements were statistically significantly reduced. Using patient-reported survey instruments to measure QOL, including the FACT-An (or anemia subscale only in the latter two studies), a statistically significant improvement in QOL was seen in association with an improvement in hemoglobin. One study prospectively demonstrated a correlation between a change in hemoglobin level and a change in overall QOL independent of response to chemotherapy.
Correlations were seen in patients who had a complete response (r = 0.242, P < .001), partial response (r = 0.275, P < .001), or stable disease (r = 0.253, P < .001) but not in those who had progressive disease (r = 0.084, P = .072). With regards to darbepoetin alfa and QOL, the randomized placebo-controlled study in 320 lung cancer patients by Vansteenkiste et al. using darbepoetin alfa weekly, used the Functional Assessment of Cancer Therapy-Fatigue scale (FACT-F). Fifty six percent (95% CI = 47% to 65%) of the patients in the darbepoetin alfa group and 44% (95% CI = 35% to 52%) of patients in the placebo group had an improvement in the FACT-F score (P = .052). Thirty two percent (95% CI = 23% to 40%) of patients in the treatment group versus 19% (95% CI = 12% to 26%) of patients in the placebo group had at least a 25% improvement in scores (mean difference = 13%; 95% CI 2% to 23%; P = .019).

The BCBS TEC study reported by Seidenfeld et al. did not find sufficient randomized evidence to perform a meta-analysis with regards to the effect of epoetin alfa on QOL. Clinical trials suitable for inclusion in the study were screened prior to the final publication of the randomized study by Littlewood et al. In addition, the randomized study with darbepoetin alfa also supports QOL improvements with erythropoietin use.

Systematic reviews have also reported that erythropoietin or darbepoetin are associated with improvements in QOL. For example, in a 2006 Cochrane review of controlled trials, Bohlius and colleagues reviewed 57 trials enrolling 9,353 patients who were treated for cancer-related anemia with either darbepoetin or epoetin. The authors reported that there was suggestive evidence that either drug was associated with an improvement in quality of life. Another 2006 review included both controlled trials and prospective uncontrolled studies. A total of 40 studies including 21,378 patients were analyzed. The authors reported that patients receiving either darbepoetin or epoetin experienced a significant improvement in QOL. Specifically, the mean difference in Functional Assessment of Cancer Therapy-Fatigue score for treated patients versus controls was 0.23 (95% CI, 0.10-0.36; P=0.001).

Using the data from 4,382 patients in two of the community-based studies receiving epoetin alfa, a study reported by Crawford et al. applied an incremental analysis technique to determine the hemoglobin range associated with the greatest incremental increase in QOL using the LASA and FACT scores. Quality of life improvements were seen across hemoglobin levels ranging from 8.0 to 14.0 g/dL. The largest QOL improvements for each 1 g/dL increment in hemoglobin increase occurred when the hemoglobin level increased from 11.0 to 12.0 g/dL.

Recommendations in the algorithm to consider treatment of mildly anemic patients (10-11 g/dL) who are symptomatic from a functional point of view are derived from a panel review of currently available data recognizing the limitations associated with the lack of randomized information. The algorithm recommendation for this treatment group is termed “consider erythropoietin.” Those patients having hemoglobin values 10 g/dL or less with functional symptoms have the added support of the data in the meta-analysis supporting a transfusion reduction benefit, and the recommendation for this group is termed “strongly consider erythropoietin” (category 1).

**Dose Schedules**

The most common epoetin alfa dose and schedule evaluated in clinical trials was 150 IU/kg TIW or 10,000 units TIW SC. In general, patients were escalated to 300 IU/kg or 20,000 units TIW if response was not 1 g/dL or greater at 4 weeks (called “nonresponders”). Treatment was discontinued in patients who were nonresponders despite iron supplementation after 4 additional weeks at the higher dose. The study by Gabrilove et al. used a 40,000 units SC weekly dose and showed similarities in hemoglobin increase, transfusion reduction, and increase in QOL scores. Doses were increased to 60,000 U SC weekly in...
nonresponders and likewise discontinued at 8 weeks if no response despite adequate iron supplementation. While the bulk of the data evaluated dosing thrice weekly, and recognizing the study by Garbrilove et al. is the only published study evaluating weekly dosing to date, the available data suggests that either the weekly or TIW schedule appears effective. The weekly schedule is more convenient for patients and is frequently used in clinical practice. Other dosing ranges and schedules of epoetin alfa are under evaluation. Initial studies with darbepoetin alfa used a starting dose of 2.25 mcg/kg administered weekly SC with increases up to 4.5 mcg/kg weekly if hemoglobin increase was <1.0 g/dl after 6 weeks.

There has been interest in using higher doses of epoetin at more prolonged intervals. For example, while the package insert indicates that 40,000 units of epoetin can be used at weekly intervals, maintenance doses of 80,000 units at 2 week intervals or 120,000 units at three week intervals are considered acceptable alternative regimens. In one trial, 365 patients initially received 3 weekly doses of 40,000 U of epoetin and then were randomized to receive either maintenance with ongoing weekly doses of 40,000 U or 120,000 every three weeks. There was no difference in transfusion rates between the two groups, although increases in Hb were higher in those receiving weekly maintenance. Epoetin at a dose of 80,000 U every 2 weeks has also been investigated in 310 patients with a baseline Hb <or= 11 g/dL randomized to weekly vs. biweekly doses. The mean change in Hb and transfusion rate was comparable between the two groups. The authors concluded that extended dosing (80,000 U Q2W) and once-weekly dosing (40,000 U QW) of epoetin provided comparable safety and efficacy for chemotherapy-induced anemia. Biweekly dosing is frequently used in clinical practice. Finally, Patton et al. are exploring a dosing schedule loading with epoetin alfa at 60,000 units weekly for 8 weeks followed by maintenance therapy at 120,000 units every three weeks. Longer follow-up will be required to determine if this schedule should be further pursued.

While recommended darbepoetin doses were initially 2.25 mcg/kg every week, there has been interest in using either fixed doses or higher doses at decreased frequency. A fixed weekly dose of 100 mcg of darbepoetin has been studied as an alternative in a phase III trial of 320 patients with lung cancer and a Hb <= 11 g/dl. In this placebo controlled trial, patients receiving darbepoetin required fewer transfusions, had more hematopoietic responses and had better improvement in FACT-Fatigue scores.

Two small studies have explored lengthening the dosing interval from weekly to biweekly. Glaspy et al. reported a phase I/II study of 128 patients receiving either 3.0, 5.0, 7.0, or 9.0 mcg/kg of darbepoetin every two weeks or epoetin alfa 40,000 units weekly. Clinically effective doses of darbepoetin in this study were 3.0 and 5.0 mcg/kg given every two weeks with hematopoietic response rates (equal to or greater than 2 g/dl rise or 12 g/dl reached) of 66% and 84% respectively. The conclusion was that responses were seen using a biweekly dosing regimen with darbepoetin alfa. These responses appeared similar to those seen with epoetin alfa on a weekly or TIW dosing schedule. Thames and colleagues conducted a chart review of usage of darbepoetin in patients with a Hb <= 11 g/dl or a hematocrit of < 33% who were either switched from epoetin or were erythropoietic agent (naïve) to receive a fixed dose of 200 mcg Q2W of darbepoetin. Doses and schedule could be adjusted after 4 weeks of treatment depending on Hgb values. During darbepoetin alfa treatment, 77% of the 296 patients required 200 mcg Q2W or less. The mean change in Hgb after 4 weeks of treatment was similar in naïve and switched patients, indicating that even patients who were previously receiving EPO benefited from the switch to darbepoetin alfa.
A 500 mcg fixed dose on an every three week schedule (Q3W) allows synchronization with many chemotherapy treatments, providing a convenience to patients. Boccia and colleagues conducted a multicenter open-label 16 week trial of 500 mcg darbepoetin Q3W in 1493 patients receiving multicycle chemotherapy and reported results based on the baseline Hb of greater or less than 10 g/dl.23 While patients with higher baseline Hb levels responded more quickly than those with lower levels, similar proportions of patients in both groups maintained hemoglobin levels within the target range (73% vs. 71%). The authors concluded that darbepoetin alfa Q3W is well tolerated and effective for treating chemotherapy induced anemia. Canon and colleagues came to similar conclusions based on a randomized trial comparing Q2W and Q3W dosing in a noninferiority study enrolling 705 patients with a Hb <=11 g/dl. The percentages of patients achieving the target hemoglobin level (> or = 11) were similar in the two treatment arms.24 Every three week darbepoetin is now an FDA labeled dose.

Recommended dosing schedules for epoetin and darbepoetin are summarized on ANEM-A, which also provides guidelines for dose titration based on response. For example, if the hemoglobin exceeds 12 g/dl, therapy should be held and reinitiated at a 25% dose reduction if the hemoglobin falls below 12 g/dl. The target level of 11-12 g/dl is based in part on the increased mortality at hemoglobin levels above 12 g/dl. This increase in mortality was noted in the preliminary results of 4 trials of patients with cancer related anemia treated with ESAs. These trial results prompted the FDA to revise prescribing information for ESAs. While this issue is discussed further below under Treatment of Cancer Related Anemia, the revised labeling includes the following specific recommendations for patients with cancer:25

- Use the lowest dose possible to gradually increase the hemoglobin concentration to avoid the need for transfusion.
- Measure hemoglobin twice a week for 2 to 6 weeks after any dosage adjustment to ensure that hemoglobin has stabilized in response to the dose change.
- Withhold the dose of the ESA if the hemoglobin increase exceeds 12 g/dl or rises by 1 g/dl in any 2 week period.

**Comparative Studies**
Several randomized studies have provided a head to head comparison of darbepoetin and epoetin alfa. In a noninferiority study, 1,220 patients with Hb <= 11 g/dl were randomly assigned to receive either darbepoetin every two weeks or epoetin every week.26 There was no significant difference in the primary outcome of transfusion. Other outcomes such as hemoglobin, quality of life, and safety end points were similar in both groups. The authors concluded that the two drugs were similar in efficacy but that the less frequent dosing of darbepoetin offered potential benefits for patients, caregivers and health care providers. Schwartzberg and colleagues compared once weekly darbepoetin vs. twice weekly epoetin in a series of three identical trials in 312 patients with chemotherapy induced anemia and breast, gynecologic or lung cancer, respectively.27 In general, no difference between treatment groups was observed for hemoglobin- and transfusion-based outcomes. Waltzman and colleagues presented data from the preliminary results of 123 patients with solid tumors and a Hb <= 11 g/dl participating in a randomized trial comparing epoetin and darbepoetin.28 End points included proportion of patients with ≥1-g/dL Hb increase after 4 wks, Hb change over time and transfusion rates for all pts. While epoetin was associated with a greater increase in Hb at each time point, there was no difference between the two groups in the transfusion rate.

A pooled analysis of three clinical trials reported by Mirtching et al. reviewed 260 patients receiving darbepoetin alfa at 3.0 mcg/kg every 2 weeks and 115 patients receiving epoetin alfa TIW or QW.
Hematopoietic responses were seen in similar numbers of patients in the two groups: darbepoetin alfa 71% (95% CI = 65-78%), epoetin alfa 71% (95% CI = 61-81%).

Ross and colleagues reported a systematic review of the literature of both epoetin and darbepoetin in patients with chemotherapy induced anemia. A total of 40 studies with 21,378 patients were reviewed. The authors reported that there were no clinically relevant differences in transfusion rates between these drugs.

Treatment of Cancer Associated Anemia

The above discussion focuses on treatment of chemotherapy induced anemia. However, patients with cancer may have anemia due to a variety of etiologies. For example, etiologies may include bleeding, hemolysis, bone marrow infiltration, nutritional deficiencies, which may be corrected with successful treatment of these underlying diseases. However, after ruling out other etiologies, anemia of chronic disease may be diagnosed, and there has been interest in the role of erythropoietin therapy for this indication. While clearly the etiologies of anemia can overlap in the individual patient, one method of investigating this indication is to study erythropoietic drugs in patients with cancer who are not receiving therapy. Recently, data has become available from 4 trials of erythropoiesis stimulating agents (ESA) that have investigated their use for patients not receiving chemotherapy. For example, as summarized by the FDA, one trial studied darbepoetin in 989 patients with Hb <=11 g/d, randomized to receive placebo or darbepoetin for a total of 16 weeks, with an additional 16 week extension study. The target Hb in the treatment group was 12 g/dl and the primary outcome was the incidence of transfusions. Final data from the initial 16 week study period are now available. There was no statistically significant difference between the two groups in the incidence of transfusion, which was 24% in the placebo arm and 18% in the darbepoetin arm. However, more deaths were reported in the darbepoetin arm (26%, 136/515) compared to the control arm (20%; 94/470). A second placebo controlled trial investigated whether the use of epoetin was associated with an improvement in the quality of life in anemic patients with non-small cell lung cancer. While the targeted accrual for this trial was 300 patients the trial was terminated after enrollment of 70 patients because the data monitoring identified higher mortality in those treated with epoetin. The full manuscripts of these trials are not available, and while there is no obvious explanation, these findings prompted the FDA to issue a “Dear Doctor” letter in January 2007 alerting health care professionals to the apparent increase in mortality. Additionally, the FDA has changed the prescribing information for Aranesp, Epogen and Procrit to include the following black-boxed warning:

- Avoid serious cardiovascular and arterial and venous thromboembolic events by using the lowest dose of [ESA] that will gradually raise the hemoglobin concentration to the lowest level sufficient to avoid the need for blood transfusion.
- [ESAs] increased the risk for death and for serious cardiovascular events when doses to achieve a target hemoglobin of greater than 12 g/dl.
- Use of ESAs to achieve a target hemoglobin of 12g/dl or greater in cancer patients:
  - Shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy;
  - Shortened overall survival and increased deaths attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy;
  - Increased the risk of death in patient with active malignant disease not under treatment with chemotherapy or radiation therapy. ESAs are not indicated for this patient population.
• Patients treated before surgery with epoetin alfa to reduce allogenic red blood cell transfusions had a higher incidence of deep venous thrombosis. Aransep is not approved for this indication.

Meta-analyses have not demonstrated a survival advantage or disadvantage with ESA therapy. Physicians should carefully consider the risks and benefits of using ESAs in anemic cancer patients not receiving chemotherapy, and these issues should be discussed with patients. The NCCN guidelines indicate that until new evidence changes the current benefit:risks estimates, physicians should be advised not to administer ESAs outside of the treatment period of cancer-related therapy. It can be difficult to distinguish chemotherapy-associated anemia from cancer-related chemotherapy, but a consensus of the NCCN panelists agreed that a treatment period is defined as 6 weeks after the completion of either chemotherapy or radiation therapy.

Anemia: Impact on Treatment Outcome

The potential impact of anemia correction on treatment outcome is an area of research interest. For example, anemia may be associated with hypoxic areas within tumors that may decrease the sensitivity to radiation therapy and oxygen-dependent chemotherapeutic agents. Correction of anemia could increase the sensitivity of tumors to standard cancer treatment and improve patient outcomes.\(^{30-32}\) The issue of whether anemia correction and erythropoietin use impacts cancer treatment outcome for various modalities can only be determined in large, adequately stratified, and powered prospective trials. Separate trials will need to be conducted for those patients receiving radiation therapy, chemotherapy, or both. In the absence of such prospective data, no recommendations can currently be proposed in this area. The panel has confined the evidence based consensus recommendations in these guidelines regarding erythropoietin use in patients receiving chemotherapy to two endpoints: 1) its ability to reduce transfusion, and 2) its supportive role in quality of life improvement. Sufficient data is not currently available to address this issue with regards to patients receiving chemotherapy for whom these NCCN anemia guidelines are applicable. Therefore, no recommendations can be made regarding this endpoint at this time.

The bulk of available data concerning anemia and treatment outcome is retrospective in patients receiving radiation therapy and is hypothesis generating only. It is unknown whether this data likewise applies to patients receiving chemotherapy, or in those receiving both modalities. A retrospective review of patients with cervical cancer treated in Canada from 1989-1992, for example, showed the average weekly nadir hemoglobin levels (AWNH) as highly predictive of treatment outcome in patients receiving radiotherapy.\(^{33}\) The 5-year survivals were shown to be 74% for patients with AWNH levels 12 g/dL or greater, 52% for patients with AWNH levels 10 g/dL to 12 g/dL, and 45% for patients with AWNH levels less than 10 g/dL (\(P < .0001\)).\(^{33}\) Blood transfusion providing correction of anemia was shown to overcome the effects of low presenting hemoglobin levels and AWNH levels in this study.\(^{33}\) Preliminary data suggest a similar association in a retrospective analysis between average nadir hemoglobin during treatment and survival with concurrent chemoradiation in patients with stage IB to IVA cervical cancer. In univariate analysis, nadir hemoglobin was the most predictive factor for treatment failure (RR 1.92, \(P = .015\)) followed by disease stage (RR = 0.51, \(P = .074\)).\(^{33}\) In a multivariate model, nadir hemoglobin remained the only prognostically relevant factor predicting response to chemoradiation.\(^{34}\) Multiple other retrospective studies have shown that anemia serves as a pretreatment prognostic factor for patients with head and neck cancer and support the idea that anemia may impact negatively on locoregional control, and possibly overall survival, in patients treated with radiation therapy.\(^{35,36}\)
Recently, one of the only currently available randomized placebo-controlled studies using epoetin β as anemia correction therapy by Henke et al. in 351 patients with head and neck cancer showed that epoetin β corrected anemia, but did not improve cancer control or survival.\(^{37}\) In this study, 148 patients (82%) given epoetin β achieved hemoglobin levels > 14.0 g/L (women) or 15.0 g/L (men) compared with 26 (15%) given placebo. The relative risks favored placebo for locoregional progression RR 1.69 (1.16-2.47, \(P = 0.007\)), and survival RR 1.39 (1.05-1.84, \(P = 0.02\)) suggesting that the erythropoietin treated patients fared worse. The authors addressed the issues associated with these results, and put the study into the context of other existing data. With regards to head and neck cancers, it is recognized that the study evaluated a heterogeneous group of patients, and, for example patients with hypopharynx cancers fared worse than other patients, which could be more related to baseline characteristics than intervention. In addition, patients receiving epoetin β who had measurable cancer (strata 2 and 3) did worse relative to those without. Chemotherapy was not employed in these patients and results cannot be extrapolated to those patients receiving chemosensitization with radiotherapy, or chemotherapy alone, nor can they be compared to patients receiving radiation therapy and having anemia correction with transfusion. Finally, it is not possible to determine if the level of hemoglobin correction is important or would make a difference in outcome (i.e., the mean corrected hemoglobin in this study was elevated at 15.4 g/L in erythropoietin treated patients).\(^{22}\) Several large randomized trials with darbepoetin alfa are underway that have been specifically designed to focus on survival as a primary outcome.\(^{38}\)

Aapro and colleagues conducted a meta-analysis of nine randomized clinical trials comparing epoetin beta with placebo or standard care focusing on treatment outcome.\(^{39}\) Epoetin beta provided a slight beneficial effect on tumour progression but did not impact early survival or thromboembolic-related mortality. Another study suggested that epoetin-β has no significant effect on long-term survival compared to placebo in anemic patients with lymphoproliferative malignancies.\(^{40}\)

Additional studies need to also address issues such as the relationship between anemia and tumor/tissue hypoxia as well as other potential roles for the erythropoietin receptor in determining outcome.

**Future Directions**

Other potential roles of the erythropoietin receptor in addition to erythropoiesis are being explored. As with other cytokines and their receptors, EPO receptors are found on multiple tissues, including those of the central nervous system. Animal studies reported by Brines et al. have supported a neuroprotective function of EPO when intracerebral ventricular injection is performed, offering protection of neuronal tissues during periods of ischemic and hypoxic stress.\(^{41}\) In addition, early data supports that epoetin alfa crosses the blood-brain barrier, and clinical trials have just begun evaluating systemically administered epoetin alfa in situations in which the neuroprotective benefit could potentially be useful. It is unknown whether this effect will be of benefit in humans at this time.\(^{41}\)

**Algorithms**

**Screening and Evaluation (ANEM-1)**

Initial screening for anemia includes a complete blood cell count with indices and a review of the peripheral smear. Other studies that may be performed to further characterize the anemia and rule out other etiologies include: reticulocyte count, iron studies, serum B12 and folate levels, stool for guaiac, lactate dehydrogenase (LDH), fractionated bilirubin, creatinine and/or creatinine clearance, bone marrow examination, direct Coombs and Hb electrophoresis. Erythropoietin levels are generally uniformly low in patients with cancer in whom erythropoietin use is being considered, and no correlation was seen between erythropoietin levels and the efficacy of erythropoietin therapy in this patient population in the community trials.\(^{11,12}\) Measurement of
serum erythropoietin levels in patients with cancer is therefore not recommended.

The algorithm distinguishes cancer- or treatment-related anemia from non-cancer- or non-treatment-related anemia-specific causes (bleeding, hemolysis, nutritional deficiency, hereditary, iron deficiency, and renal dysfunction). Anemia-specific causes identified during this evaluation should be treated as appropriate. The NCCN Non-Hodgkin’s Lymphoma Guidelines or the NCCN Myelodysplastic Syndromes Guidelines can also be consulted if these cancer-specific anemias are present.

Following the identification of anemia (defined for the purpose of considering intervention as hemoglobin levels equal to or less than 11 g/dL) and the evaluation for anemia specific causes, an initial risk assessment should be completed. Anemia can be characterized as acute versus nonacute. The severity can be described as mild (Hb 10-11 g/dL), moderate (Hb 8-10 g/dL) or severe (Hb <8 g/dL). The history should assess whether accompanying symptoms are present, such as chest pain or dyspnea. Comorbidities such as cardiac disease or underlying pulmonary disease must be considered. Ultimately, the assessment of risk is a clinical decision. If in the judgment of the treating physician immediate correction is required, the patient should be transfused according to institutional guidelines.

**Functional Symptom Assessment (ANEM-2)**

Following transfusion for appropriate patients, and in those patients in whom immediate correction is not required, a functional symptom assessment is the next step. Varieties of components are included in symptom assessment and involve the patient’s activity level, quantitative scales, performance status, and patient-reported fatigue. This symptom assessment attempts to quantify functional impairment as a result of anemia not requiring immediate correction (ie, transfusion). A symptom assessment is best conducted using reproducible measures to the extent possible, and research to provide simple and reproducible tools is underway. A physician-determined Karnofsky performance status (KPS) may be helpful but is not adequate, and patient self-assessed reports have shown more reliability. The NCCN Cancer-Related Fatigue Guideline has specific suggestions for patient self-reporting. In the simplest form, a quantitative or semiquantitative assessment can be performed. For example, on a 0 to 10 numeric rating scale, mild fatigue may be indicated as 0 to 3, moderate to severe fatigue as 4 to 6, and severe fatigue as 7 to 10. Preliminary data suggests that scores of 7 or greater indicate markedly impaired function. An alternative is to ask patients simply to categorize fatigue as mild, moderate, or severe. Serial assessments can be performed at subsequent visits. If the patient is asymptomatic, he/she should be further evaluated for risk factors for developing symptomatic anemia. These risk factors are: transfusion in past 6 months, history of prior myelosuppressive therapy or radiotherapy to >20% of the skeleton, myelosuppressive potential of current therapy (duration, schedule, and agents), advanced age, and low hemoglobin level.

In the algorithm, candidates for intervention include patients who have functional symptoms related to anemia or those patients deemed at high risk for developing symptomatic anemia. Patients who are at “high risk” represent a poorly characterized group with little prospective data to validate the categories, and this listing represents an amalgam of observations from available studies and clinical practice.

Prospective trials would ideally be needed for these patient groups. A variety of retrospective studies have variously identified clinical characteristics predictive for moderate anemia. For example, in one study 50% of patients with pre-chemotherapy hemoglobin levels less than 10 g/dL who received carboplatin- and paclitaxel-based
chemotherapy required transfusion (in the pre-erythropoietin era from 1993 to 1996) as compared with 7.7% of patients with hemoglobin levels greater than 10 g/dL who received cisplatin with paclitaxel, suggesting that pretreatment hemoglobin and choice of agents can be predictive. The review by Groopman and Itri lists observed anemia of all grades for a variety of chemotherapy regimens. The use of erythropoietin in these patients “at risk” for symptomatic anemia is currently at the discretion of the physician, and specific recommendations cannot be proposed.

Treatement with Erythropoietin (ANEM-3)
Observation or erythropoietic therapy should be considered for asymptomatic patients with risk factors for developing anemia. The decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. For symptomatic patients, transfusion and/or erythropoietic therapy are recommended. If the patient’s hemoglobin level is between 10-11 g/dL, the panel recommends the consideration of erythropoietic therapy with or without transfusion. If the patient’s hemoglobin level is <10 g/dL, the panel strongly recommends erythropoietic therapy (category 1). One randomized trial has compared the strategy of early vs. late erythropoietin treatment, for example, either proactively when the patient has mild anemia between a Hb of 10 and 12 g/dl, or reactively when the Hb has dropped to 9 g/dl. This issue was explored by Straus and colleagues who reported a trial of 269 patients with hematologic malignancies who were randomized to receive early or late erythropoietin therapy. The primary outcome was the mean change in the FACT-An. The mean score in the early treatment group increased 3.84 compared to a decrease of 4.37 in the late treatment group. The authors concluded that treating mild anemia immediately in patients with hematologic malignancies significantly improved quality of life.

Periodic re-evaluation for symptoms and risk factors is recommended after transfusion. If the patient is to receive erythropoietic therapy, additional iron studies, including serum iron, total iron binding capacity (TIBC), and serum ferritin should be performed prior to treatment.

The results of recent clinical trials and the accumulation of clinical experience have prompted a variety of dosing schedules for erythropoietin, which are summarized on ANEM-A and discussed in detail above. It is noted that a “functional” iron deficiency often arises after continued erythropoietin use, and iron supplementation will eventually be required in most patients to maintain erythropoiesis. In general, serum ferritin levels less than 100 ng/mL or TSAT levels less than 20% are taken as evidence of functional iron deficiency, and oral supplementation may be warranted. Oral iron is more commonly used but recent data suggest that IV iron may be superior to oral iron. For example, a prospective, multicenter, open-label trial randomized 157 patients with chemotherapy-related anemia to a placebo group, an oral iron supplementation group or IV supplementation. Mean Hb increases were greater with IV iron compared to oral supplementation. Patients receiving IV iron showed increases in energy, activity, and overall QOL from baseline, compared with a decrease in energy and activity for no-iron group and no change in activity or overall QOL for oral iron group. Three parenteral iron products are available: iron dextran (INFed®, DexFerrum®), ferric gluconate (Ferrlecit®), and iron sucrose (Venofer®). These products are particularly indicated for treating patients intolerant or unresponsive to oral iron therapy. 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. Patients receiving these drugs should also receive pretreatment with diphenhydramine and acetaminophen to minimize adverse events. Of the two iron dextran products, INFed® has a better safety profile than DexFerrum®.
Adverse event data indicates that ferric gluconate and iron sucrose are safer than iron dextran.

Table 1 summarizes the recommendations for administering parenteral iron therapy.

<table>
<thead>
<tr>
<th>Table 1. Recommendations for Administering Parenteral Iron Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Dextran</td>
</tr>
<tr>
<td>Test dose</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Dosage</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Routes</td>
</tr>
</tbody>
</table>

A new oral iron product - heme iron polypeptide (HIP) has been studied as an alternative to IV iron in treating functional iron deficiency in hemodialysis patients. Heme iron polypeptide is derived from bovine hemoglobin, and heme iron is absorbed from the intestine by a different mechanism than non-heme iron. Nissenson et al. reported that HIP successfully replaced intravenous iron therapy and maintained iron stores in a majority of anemic hemodialysis patients receiving erythropoietic drugs.

Response Assessment and Follow Up (ANEM-4, ANEM-5)

An initial response assessment distinguishes patients with a response (Hb increase by 1 g/dL) from those with no response to erythropoietic therapy. In patients with a response, erythropoietin should be continued to maintain an optimal hemoglobin (11-12 g/dL). Assessment of patients with no response to therapy should be performed at 4 weeks for epoetin alfa and 6 weeks for darbepoetin. If no response is detected, a dose increase of the erythropoietic agent is recommended with or without iron supplementation as indicated. If the hemoglobin level increases by 1 g/dL at 8-12 weeks of erythropoietic therapy then a dosage titration should be performed to maintain an optimal hemoglobin level at 11-12 g/dL. Erythropoietic therapy should be discontinued and transfusion initiated as indicated if there is no hemoglobin response at 8-12 weeks of therapy. (ANEM-4)

If the Hb increases by more than 1 g/dL in a 2 week period, the dose should be reduced by 25%. If hemoglobin exceeds 12 g/dL, therapy should be held due to safety concerns regarding a Hb greater than 12 g/dL. Therapy can be reinitiated at a 25% dose reduction if the hemoglobin falls below 12 g/dL. Dosage and titration for erythropoietic agents are shown on page ANEM-A, 1 of 4.

Follow-up therapy includes re-evaluation of symptoms at each visit. Iron level as well as other anemia-specific causes should be checked if hemoglobin level decreases. The NCCN Cancer-Related Fatigue Guidelines and the NCCN Distress Management Guidelines should also be consulted if there is no improvement in symptoms despite improvement in the anemia.

There are many factors that need to be evaluated prior to and during erythropoietic therapy. Hypertension/seizures, thrombosis, and pure red cell aplasia (PRCA) are among the adverse effects that might complicate erythropoietic therapy (ANEM-A, 3 of 4). The hemoglobin
level should be targeted between 11-12 g/dL to decrease risk of thrombotic complications. For example in a meta-analysis of epoetin and darbepoetin including 35 trials and 6769 patients, the relative risk of thromboembolic events was 1.67. Blood pressure should be controlled in all patients prior to initiating therapy with erythropoietic drugs and must be monitored regularly in treated patients. The incidence of hypertension was reported by a few studies in patients with cancer but the results were not statistically significant. Bohlius and colleagues’ study showed insufficient evidence for the role of erythropoietin in increasing the risk of hypertension and thrombotic complications. Almost 200 cases of pure red cell aplasia (PRCA) were reported during 1998-2004 in patients treated with erythropoietin. 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.

Disclosures for the NCCN Cancer- and Treatment-Related Anemia Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Amgen, Celgene, Johnson & Johnson, and Ortho Biotech.

Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
References


