National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Cancer- and Chemotherapy-Induced Anemia

V.2.2010

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NCCN Guidelines Panel Disclosures

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

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines Updates

Changes in the 2.2010 version of the Cancer- and Chemotherapy-Induced Anemia Guidelines from the 1.2010 version include:

ANEM-3

- **Footnote 'g' was revised as follows: "For patients receiving chemotherapy for breast, advanced head and neck, lymphoid, non-small cell lung, and cervical cancers with non-curative intent, ESAs should *be used with caution. Some studies have demonstrated an increase in mortality for patients with these tumor types who are treated with ESAs. See manuscript (MS-6) for detailed discussion and references.*"**

Changes in the 1.2010 version of the Cancer- and Chemotherapy-Induced Anemia Guidelines from the 3.2009 version include:

ANEM-3

- **For cancer treatment goals, "curative" was clarified as "chemotherapy with curative intent" and "non-curative" was clarified as "chemotherapy with non-curative intent".**
- **The following footnotes were added to the page.**
  - **Footnote 'f': An example of therapy with curative intent includes adjuvant chemotherapy.**
  - **Footnote 'j': 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.**

ANEM-5

- **For asymptomatic, risk factors present for development of symptomatic anemia: treatment recommendation for "no iron deficiency" was added.**
- **For absolute iron deficiency, "after 4 weeks" was added to "hemoglobin increases" and "hemoglobin does not increase".**
- **For functional iron deficiency, ferritin level was changed from "< 300 ng/mL" to "≤ *800 ng/mL*" and "*Consider* IV iron supplementation" was added to the "erythropoietic therapy" option.**

ANEM-6

- **Symptomatic, a statement "Ensure iron studies (iron panel- serum iron, total iron binding capacity, serum ferritin) do not indicate absolute iron deficiency" was added to "consider erythropoietic therapy" treatment option for clarification.**

ANEM-A 3 of 5

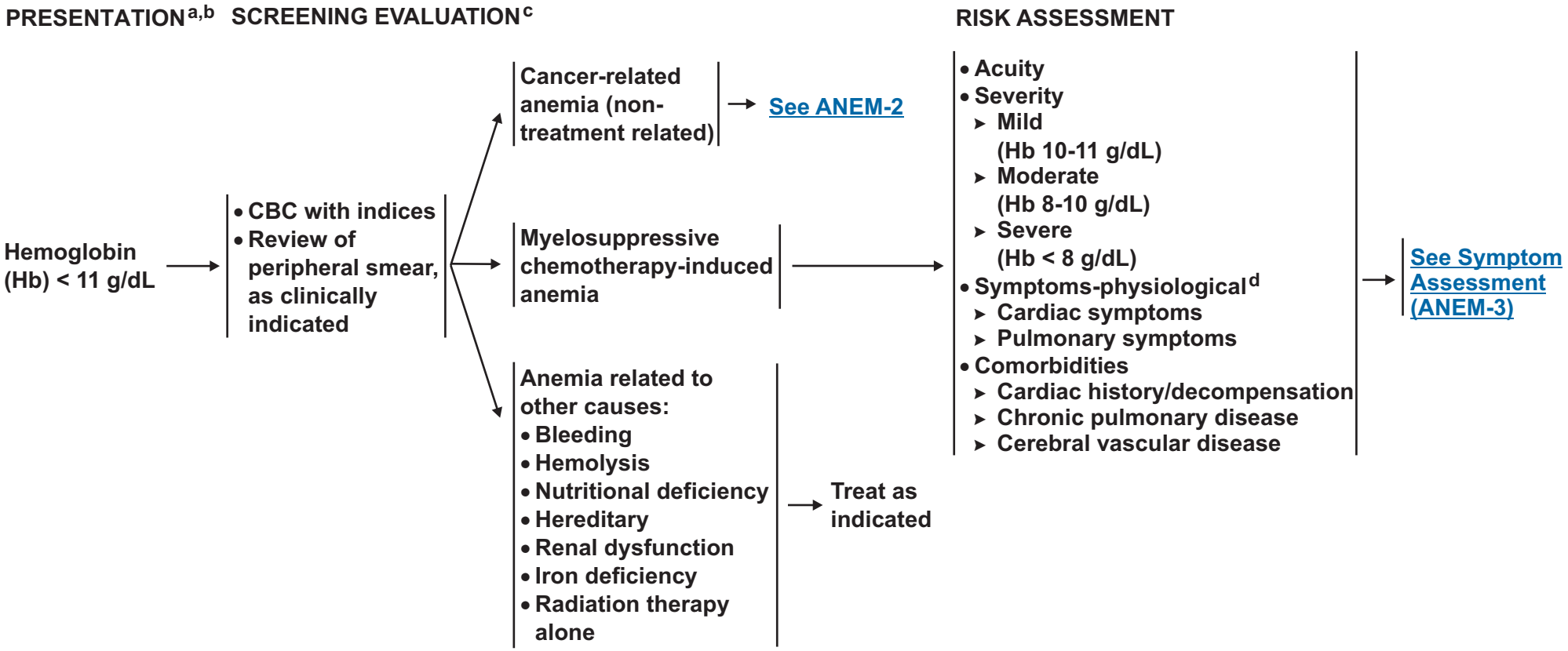
- **Cancer Patient Survival**
  - **Bullet 1 was modified by adding, "One analysis in patients with cancer not receiving active therapy found decreased survival in ESA treated patients."**
  - **Bullet 2, two new references of meta-analysis on survival confirming an increased mortality risk with the use of ESAs were added.**

ANEM-B 1 of 2

- **Risks of the use of ESA in the cancer setting: "increased" was added to "thrombotic events".**
- **Benefits of the use of ESA in the cancer setting: "avoidance of red blood cell transfusion" was modified as "transfusion avoidance"**
- **Risks of the use of red blood cell transfusion: "febrile and non-hemolytic" were added as examples of transfusion reactions.**

ANEM-C 2 of 3

- **"Recommendations for administering parenteral iron products" table was revised:**
  - **For all preparations, the following statement was added, "Examples of adverse events associated with FDA approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritis, headaches, and dizziness."**
  - **Iron dextran, dosage was clarified as "Total dose infusion given over several hours" and a corresponding statement "Dose = 0.0442 (Desired Hgb - Observed Hgb) X LBW + (0.26X LBW) LBW = Lean Body Weight. If dose exceeds 1000 mg, remaining dose may be given after 4 wks if inadequate hemoglobin response" was added.**
  - **Ferric gluconate, dose was clarified as "Maximum dose = 250 mg per infusion"**
  - **Iron sucrose, dose was clarified as "Maximum dose = 300-400 mg per infusion"**



[a] The NCCN Cancer- and Chemotherapy-Induced 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 test, Hb electrophoresis, creatinine and/or creatinine clearance. There is no clear evidence that erythropoietin levels are predictive of response.

[d] Objective physical symptoms may include peripheral edema, sustained tachycardia, and tachypnea and other subjective physical symptoms may include chest pain, dyspnea on exertion, orthostatic lightheadedness/near syncope or syncope, and fatigue.

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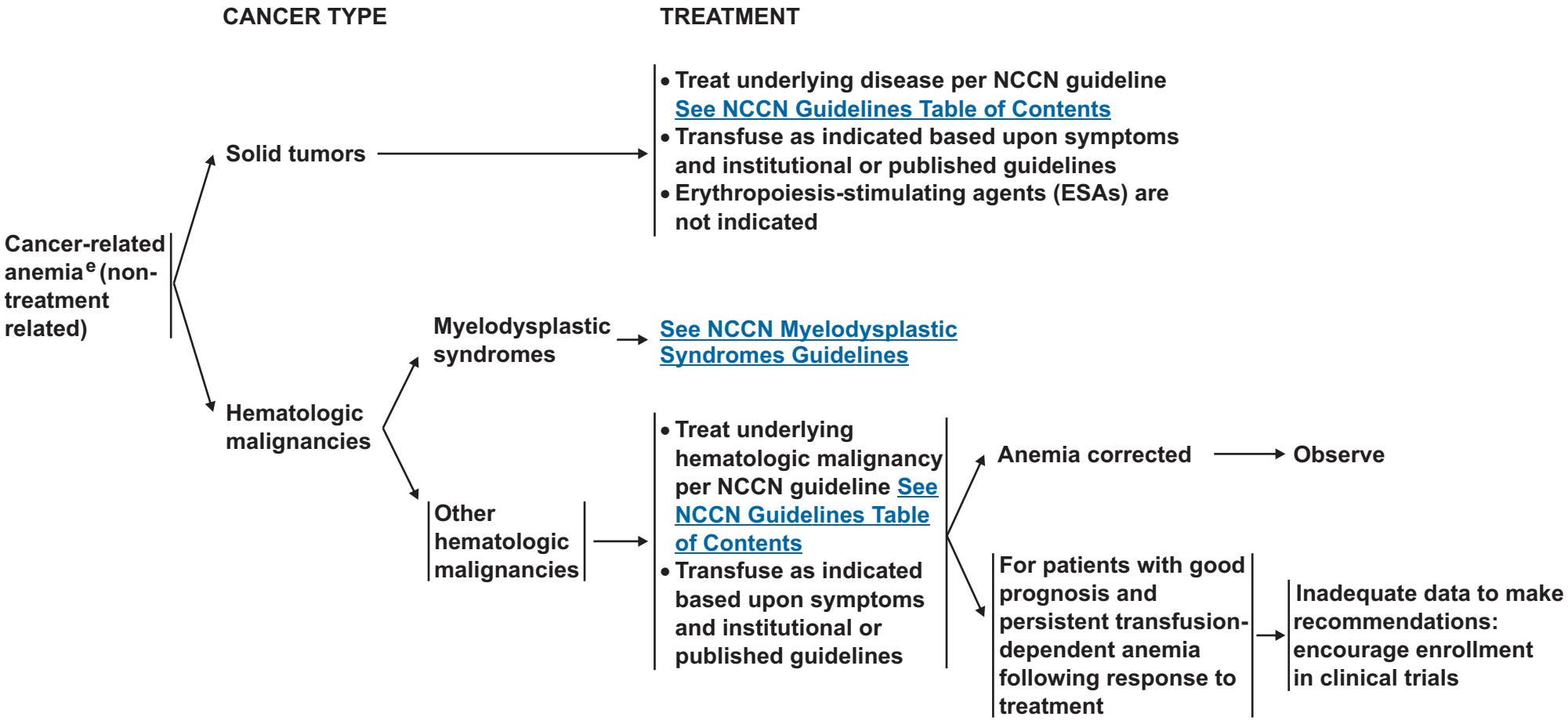
CANCER-RELATED ANEMIA (NON-TREATMENT RELATED)



[e]Patients with terminal cancer who are not receiving chemotherapy should not be treated with ESAs. (See manuscript for detailed discussion and references.)

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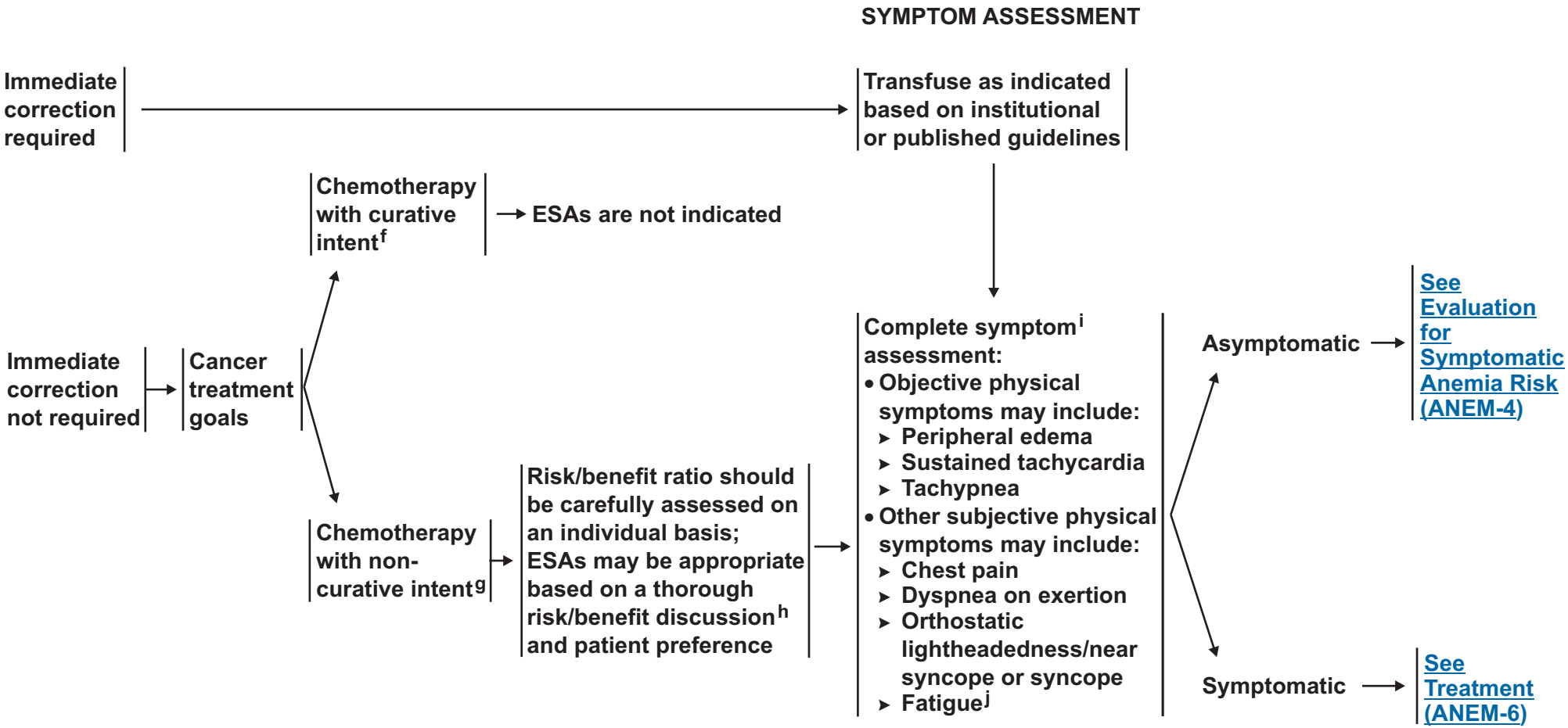
MYELOSUPPRESSIVE CHEMOTHERAPY-INDUCED ANEMIA



[f] An example of therapy with curative intent includes adjuvant chemotherapy.

[g] For patients receiving chemotherapy for breast, advanced head and neck, lymphoid, non-small cell lung, and cervical cancers with non-curative intent, ESAs should be used with caution. Some studies have demonstrated an increase in mortality for patients with these tumor types who are treated with ESAs. See manuscript (MS-6) for detailed discussion and references.

[h] See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion (ANEM-B).

[i] Other anemia-related symptoms include: decreased activity level, and decreased performance status.

[j] 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.

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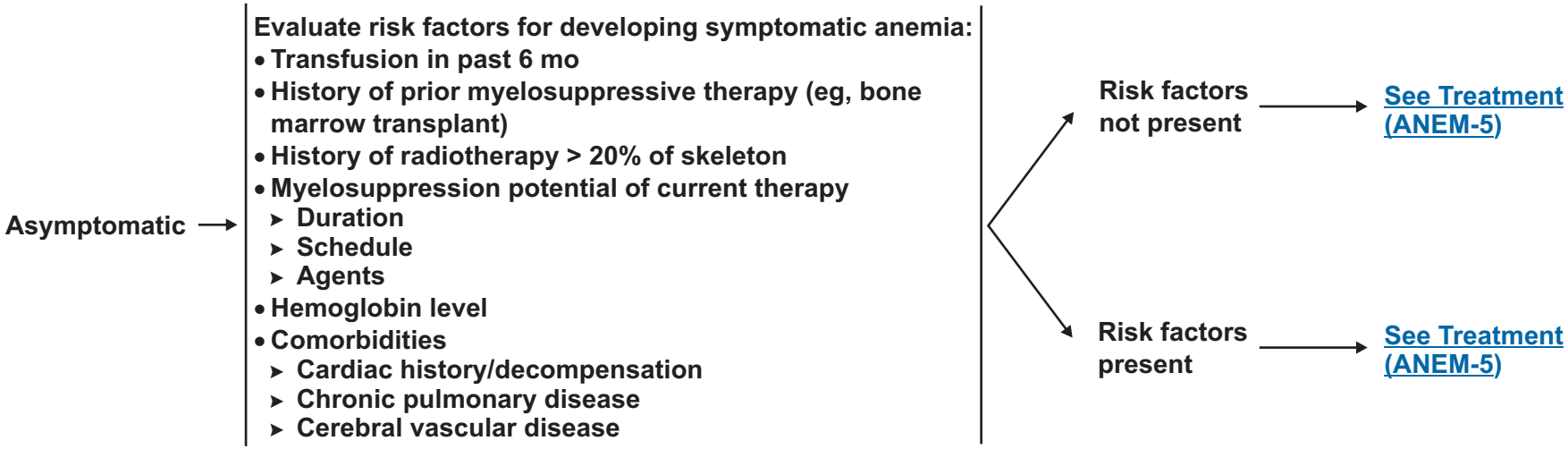
EVALUATION FOR SYMPTOMATIC ANEMIA RISK AMONG CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY WITHOUT CURATIVE INTENT



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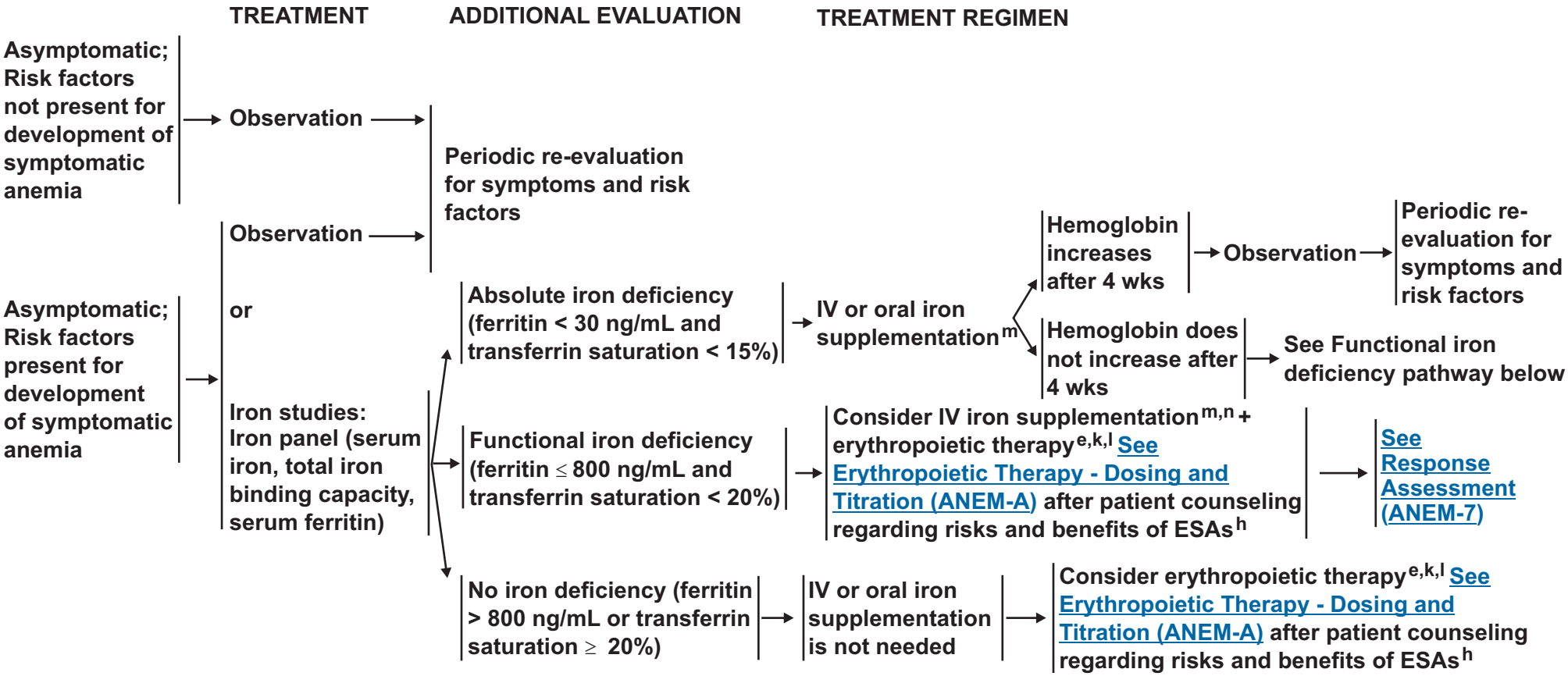
CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY WITHOUT CURATIVE INTENT



[e] Patients with terminal cancer who are not receiving chemotherapy should not be treated with ESAs. (See manuscript for detailed discussion and references.)

[h] See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion (ANEM-B).

[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: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. (See NCCN Venous Thromboembolic Disease Guidelines)

[l] See Adverse Effects of Erythropoietic Therapy (ANEM-A 3 of 5).

[m] IV iron appears to have superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See manuscript for detailed discussion and references.) See Parenteral Iron Preparations (ANEM-C).

[n] Five randomized trials which evaluated IV iron with the use of ESA included patients with serum ferritin values ranging from ≥ 100 ng/mL to ≤ 900 ng/mL. (See manuscript for references.)

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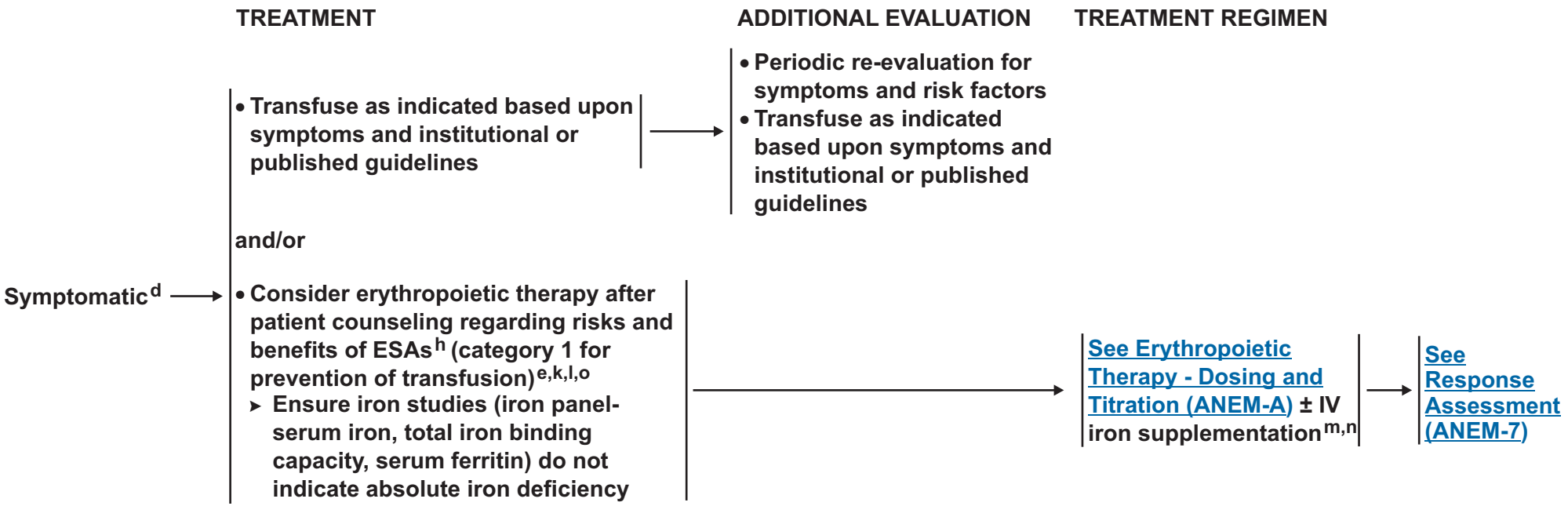

[d] Objective physical symptoms may include peripheral edema, sustained tachycardia, and tachypnea and other subjective physical symptoms may include chest pain, dyspnea on exertion, orthostatic lightheadedness/near syncope or syncope, and fatigue.

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[o] Seidenfeld J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative effectiveness review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. May 2006. Available at: http://effectivehealthcare.ahrq.gov/repFiles/EPO%20Final.pdf.
Rizzo JD, Somerfield MR, Hagerty KL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J of Clin Oncol. 2008;26:132-149.

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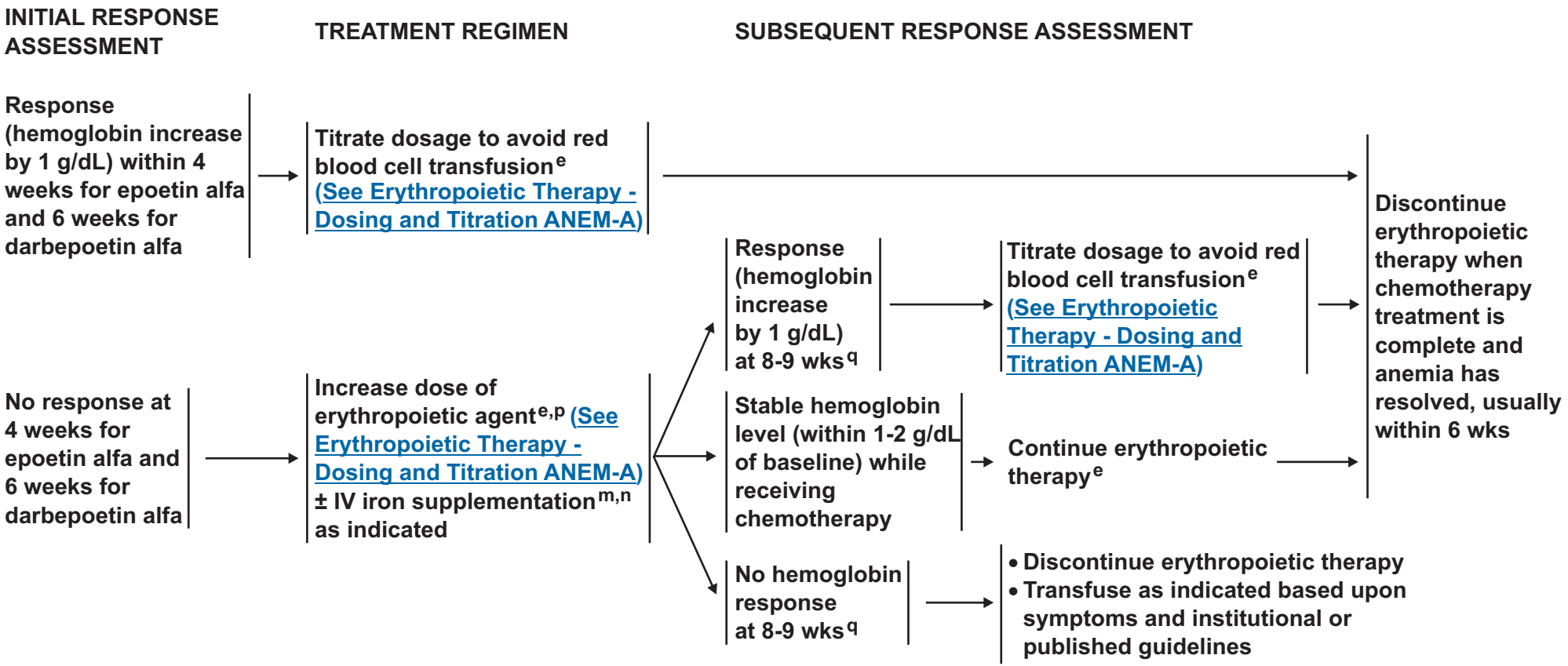

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[n] Five randomized trials which evaluated IV iron with the use of ESA included patients with serum ferritin values ranging from ≥ 100 ng/mL to ≤ 900 ng/mL. (See manuscript for references.)

[p] This is only applicable to regimens with a dosing schedule of 3x weekly, weekly, or every 2 weeks.

[q] For every 3 week dosing schedule, use 9 weeks for subsequent response assessment.

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

INITIAL DOSING

PACKAGE INSERT DOSING SCHEDULE

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

or

Epoetin alfa 40,000 units every wk by subcutaneous injection → Increase dose of epoetin alfa to 60,000 units every wk by subcutaneous injection

or

Darbepoetin alfa 2.25 mcg/kg every wk by subcutaneous injection → Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection

or

Darbepoetin alfa 500 mcg every 3 wks by subcutaneous injection

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[6]

or

Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection[7] → Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection[7]

or

Darbepoetin alfa 300 mcg fixed dose every 3 wks by subcutaneous injection → Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection[8]

or

Epoetin alfa 80,000 units every 2 wks by subcutaneous injection[9]

or

Epoetin alfa 120,000 units every 3 wks by subcutaneous injection[10]

TITRATION FOR NO RESPONSE

TITRATION FOR RESPONSE

- The dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.
- If hemoglobin increases by more than 1 g/dL in a 2 week period, dose should be reduced by 25-50% of the prior dose.

See Footnotes and References (ANEM- A 2 of 5)

See Adverse Effects of Erythropoietic Therapy (ANEM-A 3 of 5)

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 OF 5)

FOOTNOTES AND REFERENCES

[1]The head to head comparison of regimens are inconclusive with regard to superiority of one drug over another. Schwartzberg LS, Yee LK, Senecal, FM, et al. A randomized comparison of every-2 week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic. The Oncologist 2004;9:696-707. Waltzman R, Croot C, Justice G, et al. Randomized comparison of epoetin alfa (40 000 U weekly) and darbepoetin alfa (200 mcg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist 2005;10:642-650.

[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]IV iron appears to have superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See manuscript for detailed discussion.) See Parenteral Iron Preparations (ANEM-C).

[6] Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002;94:1211-1220.

[7]Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naïve patients and patients switched from epoetin alfa. Pharmacotherapy 2004;24:313-323.

[8]Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every 3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006;98:273-284.

[9]Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80 000 U Q2W) vs weekly dosing (40 000 U QW) in patients with chemotherapy-induced anemia. Curr Med Res Opin 2006;22:1403-1413.

[10]Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. J Clin Oncol 2006;24:1079-1089.

See Erythropoietic Therapy - Dosing and Titration (ANEM-A 1 of 5)

See Adverse Effects of Erythropoietic Therapy (ANEM-A 3 of 5)

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (3 OF 5)
ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY

Cancer Patient Survival

- Recent studies have reported decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels of >12 g/dL.[1-8] One analysis in patients with cancer not receiving active therapy found decreased survival in ESA treated patients.[6] Please refer to the FDA website for additional information: http://www.fda.gov/cder/drug/infopage/RHE/default.htm. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.
- Three recent meta-analysis updates on survival confirms an increased mortality risk with the use of ESAs.[9,10,11,12]
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target hemoglobin of < 12 g/dL.
- Additional prospective clinical trials designed and powered to measure cancer patient survival are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus red blood cell transfusion. (See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion (ANEM-B)).

Thrombosis

- Early trials of recombinant human erythropoietin reported that a high target hematocrit (42 ± 3%) was found to have an increased mortality and an increased number of vascular events (arterial and venous).
- Erythropoietin has a thrombogenic potential independent of hemoglobin levels.[13] Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. (See NCCN Venous Thromboembolic Disease Guidelines)
- A recent analysis update on thrombotic complications confirms an increased thrombosis risk with use of erythropoietic agents.[9]

Adverse Effects of Erythropoietic Therapy continued (ANEM-A 4 of 5)
See References (ANEM- A 5 of 5)

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (4 OF 5)
ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY CONTINUED

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 5)

ESA Neutralizing Antibodies (Pure red cell aplasia-PRCA)

- Between 1998-2004, 197 cases of PRCA were reported in patients treated with erythropoietin.[14] 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.[15]
- In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia.[16] 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.[17] This interpretation resulted in a class label change for all ESAs. The toxicity has been reported predominantly in patients with chronic renal failure receiving ESAs by subcutaneous administration. Any patient who develops a sudden loss of response to an ESA, accompanied by a severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, ESAs should be withheld and plasma should be sent for evaluation of assays for binding and neutralizing antibodies. ESAs should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESA products as antibodies may cross-react.

See References (ANEM- A 5 of 5)

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (5 OF 5)
ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY

REFERENCES

[1]Leyland-Jones B, BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol 2003;4:459-460.
[2]Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255-1260.
[3]Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007;25:1027-1032.
[4]Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol 2003;122:394-403.
[5]Overgaard J, Hoff C, Sand Hansen, H, et al. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of head and neck (HNCSS): the Danish Head and Neck Cancer Group DAHANCA 10 rand [abstract] Eur J Cancer Suppl 2007;5:7.
[6]Smith R, Aapro MS, Ludwig H, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. J Clin Oncol 2008;26:1040-1050.
[7]Thomas G, Ali S, Hoebers FJ, Darcy KM, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2008;108:317-325.
[8]US Food and Drug Administration. Press release: FDA receives new data on risks of anemia drugs consistent with previous data on tumor growth and death. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116830.htm Accessed July 27, 2009.
[9]Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299(8):914-924.
[10]Bennett CL, Henke M, Lai SY. Erythropoiesis- Stimulating Agents in the Treatment of Cancer-Associated Anemia Reply. JAMA. 2008;300(24):2855-2857.
[11]Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. The Lancet 2009;373:1532-1542.
[12]Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ 2009;180(11):E62-71.
[13]Singh A, Szczech L, Tang K, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-2098.
[14]Bennett CL, Luminari S, Nissenson, AR et al. Pure red-cell aplasia and epoetin therapy. N Eng J Med 2004;351:1403-1408.
[15]Bennett CL, Cournoyer D, Carson KR, et al. Long-term outcome of individuals with pure red cell aplasia and aniterythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood 2005;106:3343-3347.
[16]FDA Patient Safety News. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=430
[17]McKoy J, Stonecash R, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008;48:1754-1762.

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COMPARISON OF RISKS AND BENEFITS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION[1]

Risks and Benefits of the Use of ESA in the Cancer Setting		Risks and Benefits of the Use of Red Blood Cell Transfusion	
Risks	• Increased thrombotic events • Decreased survival • Time to tumor progression shortened	Risks	• Transfusion reactions (hemolytic, febrile, non-hemolytic, lung injury, etc.) • Congestive heart failure • Virus transmission (Hepatitis, HIV, etc.) • Bacterial contamination • Iron overload
Benefits	• Transfusion avoidance • Gradual improvement in fatigue	Benefits	• Rapid increase of hemoglobin and hematocrit levels • Rapid improvement in fatigue

See Patient Counseling Information Regarding the Use of ESAs (ANEM-B 2 of 2)

[1] See the manuscript for detailed information regarding the risks and benefits of ESA use and red blood cell transfusion.

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PATIENT COUNSELING INFORMATION REGARDING THE USE OF ESAs

A Medication Guide for epoetin alfa or darbepoetin alfa must be provided to all patients who are dispensed/administered this drug. See Epoetin Alfa Medication Guide.

Physicians and other healthcare professionals should discuss the following with their patients:

- **Discuss goals of therapy and risks and benefits of ESA use.**
- **ESAs have been found to shorten overall survival and/or the time to progression in patients with breast cancer, non-small cell lung cancer, head and neck cancer, lymphoid, and cervical cancer when dosed to target a hemoglobin of ≥ 12 g/dl. These risks have not been excluded when ESAs are dosed to target a hemoglobin < 12 g/dl.**
- **ESAs have been associated with an increased risk of death in patients with cancer receiving radiotherapy or not receiving treatment with chemotherapy. ESAs are not indicated for this population.**
- **The FDA has indicated that ESAs should not be used for cancer patients receiving potentially curative therapy.**
- **Data indicate that ESAs may improve fatigue in a small percentage of patients, however more research is needed.[1-4]**
- **The primary goal of treatment with ESAs is to increase the number of red blood cells in order to avoid receiving blood transfusions.**

[1] Minton O, Stone P, Richardson A, et al. Drug therapy for the management of cancer related fatigue. Cochrane Database Syst Rev. 2008:CD006704.
[2] Cella D, Eton DT, Lai J-S, et al. Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. J Pain Symptom Manage 2002; 24:547-561.
[3] Cella D, Dobrez D, Glaspy J. Control of cancer-related anemia with erythropoietic agents: A review of evidence for improved quality of life and clinical outcomes. Ann Oncol 2003;14:511-519.
[4] Fallowfield L, Gagnon D, Cella D, et al. Multivariate regression analyses of data from a randomized, double-blind, placebo-controlled study confirmed quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. Br J Cancer 2002;87:1341-1353.

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

- 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 ESAs.
- 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.
- Most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferrum®).[7]
- The recommended iron dextran product is low molecular weight iron dextran (INFed®).[8]
- Clinicians should exclude the possibility of infection before giving IV iron therapy.

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

See References (ANEM- C 3 of 3)

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RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS[1-6] (2 of 3)

	Iron Dextran†	Ferric gluconate†	Iron sucrose†
Test dose	Required	MD discretion	MD discretion
	25 mg slow IV push and wait 1 hr before giving main dose	25 mg slow IV push or infusion	25 mg slow IV push
Dosage[9]	100 mg over 5 min	125 mg over 60 min	200 mg over 60 min
	Total dose infusion given over several hours*	Repeated dosing given once weekly for 8 doses	Repeated dosing given every 2-3 weeks
		Maximum dose = 250 mg per infusion	Maximum dose = 300-400 mg per infusion
Routes	IM (INFed®) (not recommended)	IV injection/infusion	IV injection/infusion
	IV infusion		

†Examples of adverse events associated with FDA approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritis, 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 wks if inadequate hemoglobin response.

See References (ANEM- C 3 of 3)

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RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS[1-6] (3 of 3)

REFERENCES

[1] Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004;76:74-78.
[2] Henry DH. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231-242.
[3] 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;22:1301-1307.
[4] Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. J Clin Oncol 2008;26:1619-1625.
[5] Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia 2007;21:627-632.
[6] Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611-1618.
[7] Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378-382.
[8] Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet 2007;369:1502-1504.
[9] Gilreath JA, Sageser DS, Jorgenson JA, Rodgers GM. Establishing an anemia clinic for optimal erythropoietic-stimulating agent use in hematology-oncology patients. J Natl Compr Canc Netw 2008;6:577-584.

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

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Anemia is prevalent in 30% to 90% of cancer patients.[1] Correction of anemia by either transfusion with packed red blood cells (PRBC) or the administration of erythropoiesis-stimulating agents (ESAs) is a supportive care measure. The purpose of these NCCN Cancer- and Chemotherapy-induced Anemia Guidelines is two-fold: 1) to operationalize the evaluation and treatment of anemia in cancer patients, with an emphasis on those patients with anemia who are receiving concomitant chemotherapy, and 2) to enable the patient and clinician to evaluate anemia treatment options based upon their risks and benefits.

Diagnosis and Evaluation of Anemia in the Cancer Patient

The pathophysiologic origins of anemia can be grouped into 3 categories: 1) decreased production of functional red blood cells, 2) increased destruction of red blood cells, and 3) blood loss. Hence, anemia is characterized by a decrease in hemoglobin concentration, red blood cell (RBC) count or packed cell volume to subnormal levels. 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. The same anemia scale by grade is provided by the World Health Organization (WHO) and NCI (see Table 1).

Table 1. Anemia Toxicity Scales (Hemoglobin Level in g/dL)

Grade	(Severity)	NCI / WHO Scale
0	(none)	normal*
1	(mild)	10 – normal
2	(moderate)	8 – <10
3	(severe)	6.5 – <8
4	(life-threatening)	< 6.5 (life-threatening)

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

Source: Adapted from the Common Toxicity Criteria for adverse events. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf.

Screening evaluation

Causes of anemia in cancer patients are often multifactorial, adding to the complexity of the problem in evaluation. Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, hereditary disease, renal insufficiency, nutritional deficiencies, anemia of chronic disease, or a combination of these. [2,3] The malignancy itself can lead to or exacerbate anemia in a number of ways. [4] Cancer cells may directly suppress hematopoiesis through bone marrow infiltration. They may produce cytokines that lead to iron sequestration which decreases red blood cell 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 caused by loss of appetite in the cancer patient, hemolysis by immune-mediated antibodies, or changes in coagulation capability. For these myriad reasons, anemia is prevalent among cancer patients at initial presentation. For example, 32% of non-Hodgkin's lymphoma patients have anemia at diagnosis, [5] while 49% of patients are anemic when diagnosed with gynecological cancer. [6] In addition, the myelosuppressive effect of chemotherapy is a significant contributing factor to anemia for patients undergoing cytotoxic treatment.[7]

Initial screening for anemia in patients (see ANEM-1) with hemoglobin levels < 11 g/dL includes a complete blood cell count with indices and a review of the peripheral blood 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 test and hemoglobin electrophoresis. Erythropoietin levels are generally uniformly low in patients with cancer in whom erythropoietin use is being considered; however, no correlation was seen between erythropoietin levels and the efficacy of erythropoietin therapy in this patient population in community trials. [8,9] Measurement of serum erythropoietin levels in patients with cancer is therefore not recommended.

The Guidelines algorithm distinguishes 3 distinct types of anemia: cancer-related anemia (non-treatment-related), anemia related to myelosuppressive chemotherapy, and anemia due to other causes (eg, bleeding, hemolysis, iron deficiency, hereditary, nutritional deficiency, renal dysfunction, or radiotherapy alone). Blood and marrow stem cell transplant-related anemia is not addressed in these guidelines.

Initial risk assessment for cancer patients receiving myelosuppressive chemotherapy

There is a paucity of evidence on which to base decisions regarding when to transfuse either oncology patients with anemia who are receiving chemotherapy or patients with anemia in other clinical settings. Although institutional and clinical practice guidelines regarding transfusion practices are often "restrictive" in that they are based on limiting exposure to allogeneic blood, [10] there is wide variation in reported RBC transfusion practice. [4,10,11]

It is also important to note that identification of those patients receiving myelosuppressive chemotherapy who require PRBC transfusion for rapid correction of anemia cannot be made strictly on the basis of whether the hemoglobin level of the patient has reached a certain threshold or "trigger". The clinical manifestations of anemia are associated with the onset, severity, and duration of the anemia, as well as other factors influencing tissue demands for oxygen. For example, when anemia onset is acute, symptoms are likely to be more pronounced, since physiologic adjustments to compensate for lower oxygen-carrying capacity of the blood can occur with gradual onset of anemia. The presence of preexisting cardiovascular or pulmonary disease may also limit the ability of a patient to tolerate anemia. Hence, decisions related to whether immediate correction of anemia is needed must be based on an assessment of individual patient characteristics, comorbidities, and the clinical judgment of the physician. (See section on Treatment of Anemia.)

Evaluating risks and benefits of PRBC transfusion versus ESA therapy based on cancer treatment goals

Due to emerging evidence regarding the potential harm of ESA treatment when used for cancer patients (see section on Risks of ESA therapy), it is important to identify the goals of cancer treatment for each individual patient at an early time point. In the latest FDA labeling

decision,[12] ESAs are not indicated for anemic patients undergoing potentially curative cancer therapy. Transfusion is an option to correct anemia.

For patients undergoing chemotherapy with non-curative intent, ESAs can be used with caution. Individualized counseling must include a thorough discussion on the risks and benefits of ESAs (see ANEM-B). Decreased survival has been associated with ESA use in patients with lymphomas and breast, head and neck, non-small cell lung, and cervical cancers (see Risks of ESA Therapy). All patients taking ESAs must also be given a medication guide approved by the FDA. See Epoetin Alfa Medication Guide.

Complete symptom assessment for cancer patients receiving myelosuppressive chemotherapy

The next step in the evaluation process of the patient undergoing myelosuppressive chemotherapy is a complete symptom assessment performed independently of whether the patient received PRBC transfusion. The purpose of the complete symptom assessment is to identify those patients for whom an initial or additional intervention is needed to correct anemia. The complete symptom assessment consists of a thorough evaluation of both objective physical symptoms associated with anemia, such as sustained tachycardia or tachypnea, as well as subjective physical symptoms associated with anemia, such as dyspnea on exertion, orthostatic lightheadedness, and fatigue (see ANEM-3). Cancer-related fatigue is defined in the NCCN Guidelines as "a distressing persistent subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with normal functioning" (see NCCN Cancer-Related Fatigue Guidelines). A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that it is less likely to be ameliorated by rest. [13]

Other anemia-related symptoms which should be part of the evaluation include decreased activity level and decreased performance status. It is important to note, however, that the etiologies of both the objective and subjective symptoms can be multifactorial and difficult to identify. For an individual patient, a particular symptom may or may not be attributable to anemia, or anemia may be only a partial contributor to the symptom. For example, although there is a known association between cancer-related fatigue and low hemoglobin levels, [14] the overall level of fatigue reported by cancer patients without anemia has been reported to be greater than for the general population. [15] Furthermore, it is unlikely that a single subjective symptom (eg, fatigue) would place a patient in the "symptomatic" category so as to warrant an intervention in the absence of objective symptoms of anemia.

An evaluation of symptoms should also be performed in the context of hemoglobin level. If it is determined that the patient has symptomatic anemia and an intervention is necessary, treatment options are PRBC transfusion and/or ESA therapy (ANEM-6). Following treatment, periodic re-evaluation for symptoms and risk factors for anemia is recommended.

Evaluation for symptomatic anemia risk in the asymptomatic patient with anemia receiving myelosuppressive chemotherapy (non-curative intent)

Chemotherapeutic agents induce anemia by directly impairing hematopoiesis, including synthesis of RBC precursors, in the bone marrow. [4] Neutropenia and thrombocytopenia frequently occur before the decline in RBC count because white blood cells and platelets have a shorter lifespan; however, loss of these cells can indirectly contribute to anemia.[4] In addition, nephrotoxic effects of particular cytotoxic agents (eg, platinum-containing agents) can also lead to anemia through decreased production of erythropoietin by the kidney. [4]

Studies have identified patients with lung cancer and gynecologic malignancies as having a very high incidence of chemotherapy-induced anemia. [6,7] Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity.[7] Selected single agents and regimens frequently associated with anemia for different types of cancers taken from the 1999 review by Groopman and Itri are summarized in Table 2. It is important to note that the hematologic toxicities of newer cytotoxic agents, regimens and schedules are not reflected in this list, and a greater risk of anemia may potentially be associated with some of the more intensive chemotherapy regimens.[7]

The myelosuppressive effects of particular cytotoxic agents are likely to accumulate over the course of repeated cycles of therapy, resulting in a steady increase in the rate of anemia with additional chemotherapy cycles. For example, for patients in the European Cancer Anemia Survey (ECAS)[6], the rate of anemia (hemoglobin level < 12 g/dL) was found to increase from 19.5% in cycle 1 to 46.7% by cycle 5. An increase in the fraction of grades 2-3 anemia was also associated with a greater number of chemotherapy cycles. Other factors for consideration when evaluating risk of chemotherapy-induced anemia include the nadir hemoglobin level, the time to the nadir hemoglobin level (roughly estimated at 2 weeks, but time can vary), and whether a hemoglobin measurement is considered to be pre- or post-nadir. [4]

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. [16]

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

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

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

Patients determined to be asymptomatic following a complete symptom assessment should be further evaluated for risk factors for the development of symptomatic anemia, which may potentially require immediate correction by PRBC transfusion in the future. These risk factors include: low hemoglobin level, transfusion in the past 6 months, prior radiotherapy to >20% of the skeleton, and history of prior

myelosuppressive chemotherapy along with the myelosuppressive potential of the current therapy (agents, duration, and schedule) (see ANEM-4). Again, comorbidities including cardiac history, chronic pulmonary disease, diabetes mellitus, hypertension, and cerebral vascular disease should also be taken into consideration.

Options for asymptomatic patients with risk factors for the development of symptomatic anemia include either observation or ESA therapy, whereas asymptomatic patients without these risk factors may simply be observed (see ANEM-5). Patients undergoing observation should be periodically re-evaluated for symptoms and risk factors.

Treatment of Anemia: Benefits and Risks

The clinical consequences of the development of anemia in cancer patients undergoing cancer treatment can be severe, necessitating rapid correction by transfusion. Treatment decisions for an individual patient should be made following careful patient counseling regarding the risks and benefits of interventions (see ANEM-B).

Since the relationship between risks and benefits of ESA therapy varies with the clinical scenario, one tool that has been proposed to assist patients and physicians in making a choice utilizes a preference-based approach (see Appendix). The decision to use ESA support versus transfusion will depend on the patient's values and preferences. These tables are available to further assist patients and physicians in making decisions; they are not intended to replace physician judgment or the standard discussion between the physician and patient.

Benefits of transfusion with PRBC

The major benefit of transfusion with PRBC, offered by no other treatment of anemia, is a rapid increase in hemoglobin and hematocrit levels. Hence, PRBC transfusion is the only intervention option for patients receiving myelosuppressive chemotherapy who require immediate correction of anemia. Transfusion of 1 unit (300 cc) of PBRC has been estimated to result in an average increase in hemoglobin level of 1 g/dL (within 1 hour [4]) in a normal-size adult who is not experiencing a simultaneous loss of blood. [17,18]

Results of a number of studies evaluating the impact of transfusion on mortality in critically-ill patients have been conflicting, with some studies showing a survival benefit for patients receiving transfusion. For example, in a study of 56 consecutive patients with unresectable esophageal cancer receiving chemoradiation therapy, blood transfusion was associated with an increase in overall survival (hazard ratio=0.26; 95% CI, 0.09-0.75, P=0.01). [19] No significant in-hospital mortality differences were observed for critically-ill patients randomly assigned to receive transfusions to maintain hemoglobin levels of 7-9 g/dL (restrictive) versus 10-12 g/dL (liberal). [20,21]

Risks of transfusion with PRBC

Risks associated with PRBC transfusion include transfusion-related reactions, congestive heart failure, bacterial contamination and viral infections, and iron overload. [10,21-36] Since 1984, the introduction of numerous safety interventions to screen the U.S. blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections.[10,22] Pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions.[31,36] However, Khorana et al recently analyzed data from discharge summaries of cancer patients admitted to 60 US medical centers between 1995 and 2003 and found increased risks ($P < 0.001$) of venous thromboembolism (OR=1.60; 95% CI, 1.53-1.67), arterial thromboembolism (OR=1.53; 95% CI, 1.46-1.61) and mortality (OR=1.34; 95% CI, 1.29-1.38) associated with PRBC transfusions.[37]

The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anemia (ie, patients with MDS). [38] However, iron overload is unlikely to occur in patients receiving transfusions that are restricted to

the limited time period corresponding to chemotherapy treatment (usually < 1 year). Another factor for possible consideration in the context of full reliance on PRBC transfusion as a treatment for chemotherapy-induced anemia relates to the limited supply of blood in the U.S. A recent analysis which modeled the impact of reducing ESA use in this population indicated that approximately 202,000 additional units of PRBC would be required to treat anemia in patients undergoing chemotherapy if ESA use was reduced by 75%.[39]

Benefits of ESA therapy

Avoidance of transfusion is the main benefit of ESAs. Administration of ESA therapy has been demonstrated to decrease transfusion requirements in cancer patients undergoing chemotherapy. In a randomized, placebo-controlled study by Littlewood and colleagues, epoetin alfa was shown to reduce transfusion requirements in patients with anemia receiving chemotherapy. [40] Transfusion requirements were significantly decreased in the epoetin arm compared with placebo (24.7% versus 39.5%, P = 0.0057), and rise in hemoglobin level was increased (2.2 g/dL versus 0.5 g/dL; P < 0.001). [40] A double blind, placebo-controlled, randomized phase III study of darbepoetin alfa enrolled 320 patients (hemoglobin level ≤ 11 g/dL) receiving darbepoetin alfa at 2.25 mcg/kg/week versus placebo. [41] Patients receiving darbepoetin alfa required fewer transfusions (27% vs. 52%; 95% CI, 14%-36%, *P* < 0.001) than patients receiving placebo. The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review of 42 randomized, controlled clinical trials involving use of ESA therapy which enrolled a total of 6,510 patients undergoing treatment for cancer. [42] A decreased relative risk for transfusion was observed in the patients receiving erythropoietin (RR=0.64; 95% CI, 0.60-0.68).

Risks of ESA therapy

Increased mortality and tumor progression. The FDA labeled indications for ESAs underwent multiple revisions.[43,44] On July 30, 2008, the FDA issued a letter ordering additional warnings for epoetin alfa and darbepoetin alfa. The “Black Box” warnings alert physicians of increased risk of tumor progression and shortened survival in patients with advanced breast, cervical, head and neck, lymphoid and non-small cell lung cancers.[12] Physicians were advised to use the lowest dose necessary to avoid transfusion. In addition, use of ESAs is restricted to the treatment of anemia specifically related to myelosuppressive chemotherapy without curative intent. ESAs should be discontinued once the course of chemotherapy has been completed and the anemia has resolved. ESAs are not indicated for the treatment of cancer-related fatigue.

The strengthened FDA warnings were mainly based on the results of 8 randomized studies (Table 3) that individually showed a decrease in overall survival and/or decreased locoregional disease control with ESA usage. Of the 8 studies, only three investigated ESA effects in patients who underwent chemotherapy.

The Breast Cancer Erythropoietin Survival Trial (BEST) [45] randomly assigned 939 women with metastatic breast cancer to receive weekly epoetin alfa or placebo for 1 year. These patients received first-line chemotherapy; in addition, concurrent radiotherapy and hormonal therapy were also allowed. Epoetin alpha was initiated if the baseline hemoglobin level was ≤ 13 g/dL or when hemoglobin level decreased below that level during the study. Of note, this study aimed at maintaining normal hemoglobin levels (12-14 g/dL) in mainly nonanemic patients (the median baseline hemoglobin level was 12.8 g/dL). The primary endpoint was 12-month overall survival, with objective tumor response rates and time to disease progression as secondary endpoints. In accordance with a recommendation from the

data monitoring committee, the study was terminated early after completion of patient enrollment due to higher mortality in the ESA arm. Final analysis showed reduced one-year survival of patients who received ESA versus those who received placebo (70% versus 76%, respectively, P = 0.01). HR was significant after adjusting for demographic and prognostic factors (HR = 1.36; 95% CI, 1.053 to 1.753; P = 0.02). The two groups were similar with respect to the secondary endpoints. The increased number of thrombovascular events explained some, but not all, of the increased mortality.

Another phase 3, randomized, double-blind placebo-controlled trial (Study 20000161) was conducted in patients with lymphoma or myeloma receiving chemotherapy. [46] In this study, 344 anemic patients (hemoglobin level ≤ 11 g/dL) were randomly assigned to either darbepoetin alfa or placebo arms, with the proportion of patients achieving a hemoglobin level increase of ≥ 2 g/dL as the primary endpoint (target hemoglobin level: 13-15 g/dL in men; 13-14 g/dL in women). The duration of ESA treatment was 12 weeks. No significant difference in progression-free survival was observed when the two arms were compared, but overall survival was statistically significantly lower in the ESA arm versus control (HR=1.37; 95% CI, 1.02 -1.82; P = 0.037).

The PREPARE study[43] was a Phase 3, open-label trial of darbepoetin alfa that randomized 733 breast cancer patients receiving preoperative chemotherapy. Patients were non-anemic at enrollment (mean hemoglobin level 13.6 g/dL), and the goal was to prevent anemia by maintaining hemoglobin levels between 12.5 and 13 g/dL. The interim analysis showed no difference in tumor response to neoadjuvant chemotherapy at the time of surgery between the two groups, but a higher mortality rate (14% versus 9.8%) and an increased rate of tumor progression events (25% versus 19%) were recorded for the ESA arm.

Two other trials measured ESA effects on patients receiving radiotherapy. The ENHANCE study [47] randomly assigned 351 patients with head and neck cancers to epoetin beta versus placebo in a double blind fashion. All patients received definitive or postoperative radiation, without chemotherapy. The primary end point for the study was locoregional progression-free survival, and secondary end points included overall survival and time to tumor progression. Eligible patients had baseline hemoglobin levels <12 g/dL (women) or <13 g/dL (men), and the target hemoglobin level was ≥14 g/dL women or ≥15 g/dL (men), and the duration of ESA treatment was 7-9 weeks. Compared to the control group, ESA-treated patients showed significantly shorter locoregional progression-free survival (HR=1.62; 95% CI 1.22 -2.14; P = 0.0008), as well as shorter time to locoregional progression (HR=1.69; 95% CI, 1.16- 2.47; P = 0.007) and shorter overall survival (HR=1.39; 95% CI, 1.05-1.84; P = 0.02).

The DAHANCA 10 study, [48] a randomized, open-label, multicenter trial by the Danish Head and Neck Cancer Group, was conducted in 522 patients with primary squamous cell carcinoma in the head and neck region. Patients undergoing radiotherapy were assigned to darbepoetin alfa plus radiotherapy or radiotherapy alone. The target hemoglobin was 14-15.5 g/dL. The primary outcome was locoregional disease control. This trial was stopped in 2006 because of unexpected adverse events. An interim analysis on 484 patients reported significantly poorer locoregional control at 5 years (RR=1.44; 95% CI, 1.06-1.96; P = 0.02). Overall survival was also shorter in the ESA arm but did not reach statistical significance (RR=1.28; 95% CI, 0.98-1.68; P = 0.08).

Two trials evaluated ESA use in cancer-associated anemia. EPO-CAN-20 [49] was a randomized (epoetin alfa versus placebo), double-blind trial of metastatic non-small cell lung cancer patients investigating cancer-related anemia, with quality of life as the primary end point. Inclusion criteria included hemoglobin level < 12.1 g/dL and no concurrent

systemic therapy. The target hemoglobin level was 12-14 g/d, and the duration of ESA treatment was 12 weeks. However, as the routine use of palliative therapy affected accrual, these restrictions were later relaxed to exclude only platinum-based chemotherapy. An interim analysis of 70 of 300 patients planned showed a marked decrease in survival in the ESA arm (median survival 63 vs. 129 days, HR=1.84; P = 0.04) and the trial was terminated.

The Amgen 103 Anemia of Cancer study (Study 20010103) [50], a Phase 3, double-blind trial, enrolled 989 anemic cancer patients neither receiving nor planning to receive chemotherapy or myelosuppressive radiotherapy. Most cancers were solid tumors, with non-small cell lung, breast and prostate being the most common. Patients were randomly assigned to darbepoetin alfa or placebo every four weeks for up to 16 weeks, and the primary end point was transfusion incidence from weeks 5 though 17. Patients eligible for the study had hemoglobin levels ≤ 11 g/dL and the target hemoglobin was 12-13 g/dL. Darbepoetin alfa was not associated with transfusion reductions, but was instead found to be associated with shorter overall survival (8 versus 10.8 months, HR=1.30; P = 0.008).

GOG-191, [51] a Phase 3 study by the National Cancer Institute's Gynecologic Oncology Group, accrued 114 patients with advanced cervical cancer undergoing chemoradiotherapy. Patients were randomly assigned to cisplatin and radiation with or without darbepoetin alfa to maintain hemoglobin levels above 12 g/dL, with transfusions conducted as needed in the control arm (target hemoglobin level of 12-14 g/dL). Both progression-free survival (58% versus 65%) and overall survival (61% versus 75%) was found to be lower in the ESA group, and the study was prematurely terminated.

Worsened health outcomes associated with the use of ESAs have been confirmed in three recent meta-analyses of 51-53 randomized controlled trials.[52-54] Bohlius et al[53], Tonelli et al[54], and Bennet et al[52] each reported increased mortality in patients receiving ESAs with relative risks/hazard ratios of 1.17 (95% CI, 1.06-1.30), 1.15 (95% CI, 1.03-1.29), and 1.10 (95% CI, 1.01-1.20), respectively.

Risk of thromboembolism. Increased thromboembolic risks have been associated with ESA treatment of cancer patients. The cause of venous thromboembolism (VTE) is complex; a heightened baseline risk is related to the malignancy itself as well as chemotherapy (see NCCN Venous Thromboembolic Disease Guidelines). [55-58] Other risk factors for VTE in cancer patients include prior history of VTE, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, prolonged inactivity by hospitalization, steroids, as well as comorbidities such as hypertension.[59]

Overall, results from meta-analyses established significant association: increased risk of thrombolic events with ESA usage was reported by Tonelli et al[54] (RR=1.69; 95% CI, 1.27-2.24) and Bennett et al[52] (RR=1.57; 95% CI, 1.31-1.87). A combined analysis of six trials on darbepoetin alfa by Glaspy and colleagues [60] also found an increased risk of thromboembolism for patients with hemoglobin > 12 g/dL (RR=1.66; 95% CI, 0.9-3.04) or patients achieving over 1 g/dL increase in 14 days (RR= 1.67; 95% CI, 0.96 -2.88). The increased risk of thromboembolism in cancer patients receiving ESA therapy is specified in the black-box warnings included in the updated FDA labels. The NCCN panel cautions physicians to be alert of the signs and symptoms of thromboembolism in cancer patients receiving ESAs (ANEM-A 3 of 5)

Table 3. Summary of randomized trials that showed adverse health effects with ESA.

Study/Tumor/(n)	ESA treatment, duration	Hb start value (g/dL)	Hb target value (g/dL)	Adverse Outcome
Chemotherapy				
PREPARE,[43] breast cancer, n=733	Darbepoetin alfa (4.5 µg/kg/2 wk), Not reported	Mean 13.6	≥13	Decreased OS, 14% vs 10% death; faster tumor growth
BEST,[45] metastatic breast cancer, n=939	Epoetin alfa (40 000 U/wk), 12 months	≤ 13	>14	Decreased 12-month survival, 70% vs 76%, P = 0.01
20000161,[46] lymphoid malignancy, n=344	Darbepoetin alfa (2.25 µg/kg/wk), 12 wk	≤11	≥14 (women) ≥15 (men)	Decreased OS, HR for death = 1.37, P = 0.04
Radiotherapy				
ENHANCE,[47] head and neck, n=351	Epoetin beta (300 IU/kg x 3/wk), 7-9 wk	<12 (women) <13 (men)	≥14 (women) ≥15 (men)	Decreased OS, HR for death = 1.39, P = 0.02; locoregional progression, HR = 1.69, P = 0.007
DAHANCA 10,[48] head and neck, n=522	Darbepoetin alfa (150 µg/wk), Terminated early	≤14.5	>15.5	Increased locoregional failure, RR = 1.44, P = 0.03
Chemoradiotherapy				
GOG-191,[51] cervical cancer, n=113	Darbepoetin alfa (40 000 U/wk), Terminated early	<12	>14	Decreased OS, 61% vs 75%; decreased PFS, 58% vs 65%
No therapy/palliative radiotherapy				
EPO-CAN-20,[49] non-small cell lung cancer, n=70	Epoetin alfa (40 000 U/wk), 12 wk	<12.1	>14	Decreased OS, HR for death = 1.84, P = 0.04
Amgen 103,[50] non-myeloid cancer, n=989	Darbepoetin alfa (6.75 µg/kg/4 wk), 16 wk	≤11	>13	Decreased OS, HR for death = 1.3, P = 0.008

Hb = hemoglobin; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

Source: adapted from Bennett et al, JAMA 299: 914-924, 2008.

Risk of hypertension/seizures. Seizures have been reported in patients with chronic renal failure receiving ESAs. There is a 2.5% incidence of seizure in patients on dialysis during the first 90 days of therapy. [12] While it is unclear whether cancer patients receiving ESA therapy are at risk for seizures, hemoglobin levels should be monitored before and during the use of ESAs to decrease the risk of these adverse events (ANEM-A 4 of 5).

Risk of pure red cell aplasia. Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count, a loss of bone marrow erythroblasts, neutralizing antibodies against

erythropoietin, and resistance to ESA therapy. From 1998 to 2004, however, a marked rise in incidence (191 cases) was observed, 90% of which occurred with Eprex, an epoetin alfa product used outside of the United States. [61,62] Causation was attributed to formulations without human serum albumin (HAS), subcutaneous administration, and uncoated rubber stoppers. [63] 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. [64] This resulted in a class label change for all ESAs. Toxicity has been reported predominantly in patients with chronic renal failure receiving subcutaneous ESAs.

The NCCN panel recommends that any cancer patient who develops a sudden loss of response to ESA, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect. ESAs should be withheld while plasma is sent to ESA-producing pharmaceutical companies for evaluation of assays for binding and neutralizing antibodies to erythropoietin. ESAs should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESA products as antibodies may cross-react. (ANEM-A 4 of 5)

Treatment of Anemia in the Cancer Patient

Recommendations for cancer-related anemia (ANEM-2)

The NCCN panel recommends transfusion as the only appropriate treatment for anemia in patients with solid tumors who are not undergoing chemotherapy; ESAs are not indicated for these patients. The panel recommends that these patients should be transfused according to symptom assessment and institutional or published guidelines. For anemia associated with myelodysplastic syndromes, clinicians are referred to the NCCN Myelodysplastic Syndromes Guidelines. For patients with other hematologic malignancies, transfusion may be performed as necessary based on institutional or published guidelines, with an emphasis on treatment of the underlying malignancy (see relevant NCCN guidelines from the NCCN Guidelines Table of Contents). There is insufficient clinical data for specific recommendations on persistent anemia in transfusion-dependent patients who show good response to therapy.

Recommendations for chemotherapy-induced anemia requiring rapid correction

Transfusion with PRBC is the recommended treatment for patients needing immediate correction of anemia. Institutional or published guidelines for PRBC transfusion should be followed. Risks and benefits of transfusion should be discussed with the patient.

Recommendations for symptomatic chemotherapy-induced anemia not requiring immediate intervention

For symptomatic patients not requiring immediate correction, treatment options include PRBC transfusion (patients receiving therapy with curative or non-curative intent) and ESA therapy (chemotherapy with non-curative intent only).

The panel considers ESA therapy for prevention of transfusion in symptomatic patients as a category 1 recommendation (see ANEM-6). Patients for whom ESA therapy is considered should be counseled in a shared decision-making environment regarding the risks and benefits of ESA therapy. (See Benefits of ESA therapy and Risks of ESA therapy; and ANEM-B.) Serum iron parameters (eg, serum iron, total iron binding capacity, and serum ferritin) should be measured in patients receiving ESA therapy, and iron supplementation should be administered as indicated (See section on Iron monitoring and supplementation). Periodic re-evaluation for symptoms and risk factors for anemia is recommended for these patients.

Recommendations for asymptomatic patients receiving myelosuppressive chemotherapy

Options for asymptomatic patients with risk factors for the development of symptomatic anemia requiring transfusion include observation or consideration of ESA therapy (chemotherapy with non-curative intent only). Patients for whom ESA therapy is considered should be counseled on the risks and benefits. Serum iron parameters should be measured in patients receiving ESA therapy for consideration of iron supplementation (See Iron monitoring and supplementation). Asymptomatic patients without risk factors for development of symptomatic anemia should undergo periodic re-evaluation for symptoms and risk factors (see ANEM-5).

ESA Therapy: Administration and Response Assessment

Dosing schedules

At present, two ESAs are available in the U.S.: epoetin alfa and darbepoetin alfa. The consensus of the panel is that either agent can be used in ESA therapy. Recommended initial dosing schedules for patients receiving chemotherapy are summarized on ANEM-A.

The most common initial dosing schedules for epoetin alfa evaluated in clinical trials of cancer patients are 150 units/kg three times weekly administered subcutaneously [9,40] and 40,000 units once weekly SC. [45,49,51,65] Both of these initial dose schedules are currently recommended. Other dosing ranges and schedules of epoetin alfa may be considered, including an extended dosing of 80,000 U SC every 2 weeks.[66] and a dose of 120,000 U SC once every 3 weeks. [67]

Although darbepoetin doses were initially administered at 2.25 mcg/kg SC every week, [41,46,68] there has been interest in using fixed doses and higher doses at decreased frequency. A randomized trial compared weekly dosing at 2.25 mcg/kg vs. fixed dosing at 500 mcg every three weeks in 705 patients with non-myeloid malignancies with a hemoglobin level <11 g/dL. The percentage of patients achieving the target hemoglobin level (≥11 g/dL) was 77% in the weekly arm and 84% for patients receiving darbepoetin alfa every three weeks. [68] Currently the NCCN panel recommends both schedules. A number of studies have demonstrated the safety and efficacy of alternative dosing schedules for darbepoetin alfa. These include a fixed weekly dose of 100 mcg,[41] a fixed dose of 200 mcg biweekly,[69] and 300 mcg every 3 weeks. [70]

Response assessment and dose titration

Response to ESA therapy is assessed to determine whether the initial dose should be reduced, escalated, or withheld. (See ANEM-7 and ANEM-A) Decisions related to ESA dose adjustment are based on the goal of a gradual increase in hemoglobin level to avoid transfusion.

ESAs require at least 2 weeks of treatment before there is an increase in the number of RBCs. [12] Hemoglobin levels should be measured weekly until they stabilize. Dose reduction should be implemented if the hemoglobin level increases by 1 g/dL or more during a 2 week period. Doses of epoetin alfa and darbepoetin alfa should be decreased by 25% to 50%,[12] although individualized dose titrations may be needed.

Conversely, the ESA dose should be increased according to ANEM-A 1 of 5 for patients receiving chemotherapy who show no response (less than 1 g/dL in hemoglobin increase) in hemoglobin level following 4 weeks of epoetin alfa or 6 weeks of darbepoetin alfa. Under the recommended schedules, patients were escalated from 150 to 300 units/kg three times weekly or from 40,000 to 60,000 units weekly for epoetin alfa, and from 2.25 to 4.5 mcg/kg weekly for darbepoetin alfa. Iron supplementation can be considered to improve response to ESA therapy (See Iron monitoring and supplementation). A subsequent response at 8 or 9 weeks for patients on ESA dosing schedules of every 2 or 3 weeks may necessitate a dose titration with

the goal to avoid transfusion. Individuals receiving weekly doses of ESA therapy can be evaluated for subsequent response at 8 or 9 weeks. The same dose reduction formulas as described above should be followed. ESA therapy should be discontinued in patients showing no response despite iron supplementation after 8 or 9 weeks of therapy, and PRBC transfusion should be considered. ESAs should be discontinued when chemotherapy is complete and anemia has resolved, usually within 6 weeks.

Iron monitoring and supplementation

A "functional" iron deficiency often arises after continued erythropoietin use, and iron supplementation will eventually be required in most patients to maintain optimal erythropoiesis. [71,72] This is because rapid ESA-stimulated RBC production can surpass the rate of iron stabilization from stores to the usable iron pool in the reticuloendothelial system. Release of iron can be further delayed by inflammatory cytokines released in the tumor setting. The overall result is a blunted erythropoietin response to anemia. 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, in order to rule out absolute iron deficiency which may respond to oral iron therapy.

Iron can be administered in oral form or parenteral form (low-molecular weight iron dextran, ferric gluconate, and iron sucrose). Substantial evidence from five recent studies suggests that IV iron is superior to oral iron. Patients participating in these trials had serum ferritin levels ranging from ≥ 10 ng/ml to ≤ 800 ng/ml. A prospective, multicenter, open-label trial randomized 157 patients with chemotherapy-induced anemia receiving epoetin alfa to (1) no iron, (2) oral iron, (3) iron dextran IV bolus, (4) iron dextran total dose infusion. [73] Mean hemoglobin level increase achieved for these groups was 0.9 g/dL, 1.5 g/dL, 2.5 g/dL and 2.4 g/dL, respectively. Increases in hemoglobin levels were greater with IV iron (groups 3 and 4) compared to oral supplementation or no iron ($P < 0.02$) while there was no difference between the oral and no iron groups ($P = 0.21$). In a second open-label study by Henry and colleagues, 187 anemic cancer patients receiving chemotherapy and epoetin alfa were randomized to no iron, oral ferrous sulfate three times daily, or weekly IV ferric gluconate. IV iron produced a significantly greater hemoglobin response than oral or no iron (mean hemoglobin increase 2.4 g/dL, 1.6 g/dL, 1.5 g/dL, respectively). [74] Response rate was also higher in the IV arm (73%) compared to oral (45%) or no iron (41%). A third study was conducted on 67 patients with lymphoproliferative malignancies not undergoing chemotherapy. [75] Patients were randomized to weekly epoetin beta with or without IV iron sucrose. Although an oral iron arm was not included, IV iron resulted both in higher mean change in hemoglobin level from baseline (2.76 g/dL versus 1.56 g/dL, $P= 0.0002$) and in a higher hemoglobin level response rate (87% versus 53%, $P = 0.0014$) compared to the no-iron group. Two additional studies were published in 2008. Bastit et al reported their open-label trial on 396 patients with nonmyeloid malignancies undergoing chemotherapy (hemoglobin level less than 11 g/dL). [76] These were treated with darbepoetin alfa with or without IV iron (iron sucrose or ferric gluconate) every three weeks for 16 weeks. Again, hematopoietic responses and time to reach target hemoglobin level was improved in the IV iron arm. Most significantly, IV iron was also associated with fewer RBC transfusions (9% versus 20%, $P = 0.005$). In a study by Pedrazzoli et al, [77] 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/IV iron group showed a higher hematopoietic response rate (93% versus 70%, $P = 0.0033$) compared to the control group. These studies

demonstrated that concurrent IV iron may enhance hematologic response to ESAs, although there is insufficient evidence to determine whether iron supplementation can allow an ESA dose decrease.

In the NCCN guidelines, IV iron products are recommended for iron repletion in cancer patients with absolute iron deficiency (ferritin < 30 ng/ml and transferrin saturation < 15%). It can also be considered in combination with erythropoietic drugs for patients with functional iron deficiency ferritin ≤ 800 ng/ml and transferrin saturation < 20%) (see ANEM-5). Common adverse events following FDA approved doses of parenteral iron include hypotension, nausea, vomiting and/or diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness.[78-80] Most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferrum®). [81] The recommended iron dextran product is low molecular weight iron dextran (INFed®). [82] 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. Recommendations for administering parenteral iron therapy are listed on ANEM-C.

References

1. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 2004;116 Suppl 7A:11S-26S.

2. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. Am J Health Syst Pharm. 2007;64:S5-13; quiz S28-30.

3. Steensma DP. Is anemia of cancer different from chemotherapy-induced anemia? J Clin Oncol. 2008;26:1022-1024.

4. Wilson J, Yao GL, Raftery J, et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess. 2007;11:1-202, iii-iv.

5. Moullet I, Salles G, Ketterer N, et al. Frequency and significance of anemia in non-Hodgkin's lymphoma patients. Ann Oncol. 1998;9:1109-1115.

6. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer. 2004;40:2293-2306.

7. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst. 1999;91:1616-1634.

8. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol. 1998;16:3412-3425.

9. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. J Clin Oncol. 1997;15:1218-1234.

10. Hill SR, Carless PA, Henry DA, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2002:CD002042.

11. Pawson R, Brunskill S, Murphy MF, Doree C, Hyde C, Daly J. Different threshold levels for red blood cell transfusions in patients with haematological malignancy (Protocol). The Cochrane Library. 2008:10.

12. FDA label information on ESAs: http://www.fda.gov/cder/drug/infopage/RHE/.

13. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. Support Care Cancer. 1996;4:82-96.

14. Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol. 2004;15:979-986.

15. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94:528-538.

16. Jefferies S, Rajan B, Ashley S, Traish D, Brada M. Haematological toxicity of cranio-spinal irradiation. Radiother Oncol. 1998;48:23-27.

17. Cable R, Carlson B, Chambers L, et al. Practice Guidelines for Blood Transfusion: A compilation from recent peer-reviewed literature. American Red Cross. 2002:52.

18. Wiesen AR, Hospenthal DR, Byrd JC, Glass KL, Howard RS, Diehl LF. Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. Ann Intern Med. 1994;121:278-230.

19. Kader AS, Lim JT, Berthelet E, Petersen R, Ludgate D, Truong PT. Prognostic significance of blood transfusions in patients with esophageal cancer treated with combined chemoradiotherapy. Am J Clin Oncol. 2007;30:492-497.

20. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409-417.

21. Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med. 2001;29:227-234.

22. Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. N Engl J Med. 2006;355:1303-1305.

23. Djulbegovic B. Reasoning and Decision Making in Hematology. . New York: Churchill Livingstone, Inc. 1992.

24. Goodnough LT, Bach RG. Anemia, transfusion, and mortality. N Engl J Med. 2001;345:1272-1274.

25. Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. Lancet. 2003;361:161-169.

26. Rao SV, Chiswell K, Sun JL, et al. International variation in the use of blood transfusion in patients with non-ST-segment elevation acute coronary syndromes. Am J Cardiol. 2008;101:25-29.

27. Fatalities reported to the FDA following blood collection and transfusion. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM113904.pdf Annual summary for fiscal year 2008

28. Busch MP, Glynn SA, Stramer SL, et al. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion. 2005;45:254-264.

29. Dodd RY. Current risk for transfusion transmitted infections. Curr Opin Hematol. 2007;14:671-676.

30. Hillyer CD, Josephson CD, Blajchmann MA, Vostal JG, Epstein JS, Goodman JL. Bacterial contamination of blood components: risks, strategies, and regulation. Joint ASH and AABB Educational Session in Transfusion Medicine. American Society of Hematology Education Program Book 2003. 2003.

31. King KE, Shirey RS, Thoman SK, Bensen-Kennedy D, Tanz WS, Ness PM. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion. 2004;44:25-29.

32. Parsyan A, Candotti D. Human erythrovirus B19 and blood transfusion - an update. Transfus Med. 2007;17:263-278.

33. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. Curr Opin Hematol. 2003;10:412-418.

34. Popovsky MA. Transfusion Medicine. Bethesda: AABB Press. 1996.

35. Shander A, Popovsky MA. Understanding the consequences of transfusion-related acute lung injury. Chest. 2005;128:598S-604S.

36. Yazer MH, Podlosky L, Clarke G, Nahirniak SM. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. Transfusion. 2004;44:10-15.

37. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med. 2008;168:2377-2381.

38. Jabbour E, Kantarjian HM, Koller C, Taher A. Red blood cell transfusions and iron overload in the treatment of patients with myelodysplastic syndromes. Cancer. 2008;112:1089-1095.

39. Vekeman F, Bookhart BK, White J, et al. Impact of limiting erythropoiesis-stimulating agent use for chemotherapy-induced anemia on the United States blood supply margin. Transfusion. 2009;49:895-902.

40. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a

randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2001;19:2865-2874.

41. Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst. 2002;94:1211-1220.

42. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006;98:708-714.

43. FDA press release: FDA receives new data on risks of anemia drugs consistent with previous data on tumor growth and death. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116830.htm

44. NCI Cancer Bulletin. http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_051507/page2.

45. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol. 2005;23:5960-5972.

46. Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol. 2003;122:394-403.

47. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet. 2003;362:1255-1260.

48. Overgaard J, Hoff C, San Hansen H. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC): the Danish Head and Neck Cancer Group DAHANCA 10 (Abstract). . Eur J Cancer Suppl. 2007;5.

49. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007;25:1027-1032.

50. Smith RE, Jr., Aapro MS, Ludwig H, et al. Darbepoetin Alfa for the Treatment of Anemia in Patients With Active Cancer Not Receiving Chemotherapy or Radiotherapy: Results of a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Oncol. 2008.

51. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol. 2008;108:317-325.

52. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008;299:914-924.

53. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. Lancet. 2009;373:1532-1542.

54. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ. 2009;180:E62-71.

55. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000;160:809-815.

56. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients

receiving outpatient chemotherapy. J Thromb Haemost. 2007;5:632-634.

57. Levine MN, Gent M, Hirsh J, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. N Engl J Med. 1988;318:404-407.

58. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol. 1991;9:286-294.

59. Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol. 2007;25:5490-5505.

60. Glaspy J, Osterborg A, Ludwig H, et al. Evaluation of the association between hemoglobin (Hb) events and safety outcomes in cancer patients (pts) with chemotherapy-induced anemia (CIA): an integrated analysis of patient-level data from 6 randomized, placebo-controlled trials (RCTs) of darbepoetin (Abstract). European Journal of Cancer (Suppl). 2007;5.

61. Bennett CL, Cournoyer D, Carson KR, et al. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood. 2005;106:3343-3347.

62. Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med. 2004;351:1403-1408.

63. McKoy JM, Stonecash RE, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion. 2008;In press.

64. FDA on ESA-associated PRCA. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=430

65. Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol. 2001;19:2875-2882.

66. Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80 000 U Q2W) vs weekly dosing (40 000 U QW) in patients with chemotherapy-induced anemia. Curr Med Res Opin. 2006;22:1403-1413.

67. Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. J Clin Oncol. 2006;24:1079-1089.

68. Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst. 2006;98:273-284.

69. Thames WA, Smith SL, Scheifele AC, Yao B, Giffin SA, Alley JL. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naive patients and patients switched from epoetin alfa. Pharmacotherapy. 2004;24:313-323.

70. Boccia R, Malik IA, Raja V, et al. Darbepoetin alfa administered every three weeks is effective for the treatment of chemotherapy-induced anemia. Oncologist. 2006;11:409-417.

71. Henry DH. Supplemental Iron: A Key to Optimizing the Response of Cancer-Related Anemia to rHuEPO? Oncologist. 1998;3:275-278.

72. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352:1011-1023.

73. 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;22:1301-1307.

74. Henry DH, Dahl NV, Auerbach M, Tchekmedyian S, Laufman LR. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist. 2007;12:231-242.

75. Hedenus M, Birgegard G, Nasman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia. 2007;21:627-632.

76. Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol. 2008;26:1611-1618.

77. Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. J Clin Oncol. 2008;26:1619-1625.

78. Ferrlecit package insert. Watson Pharma Inc. 2006.

79. Venofer package insert. American Regent Inc. 2007.

80. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol. 2004;76:74-78.

81. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant. 2006;21:378-382.

82. Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet. 2007;369:1502-1504.

Appendix

Since the relationship between risks and benefits of ESA therapy varies with the clinical scenario, one tool that has been proposed to assist patients and physicians in making a choice utilizes a preference-based rather than effective-based (ie. where benefits clearly outweigh the risks) approach. The decision to use ESA support versus transfusion will depend on the patient's values and preferences. Tables A and B are available to further assist patients and physicians in making decisions; they are not intended to replace physician judgment and a standard discussion between the physician and patient.

Applying evidence on benefits and risks to Individualize administration of erythropoietin agents

The following is an example to illustrate how Table A can be applied to tailor administration of ESA to a particular patient. Only a single beneficial effect (avoidance of RBC transfusions) and single harmful effect (thrombosis) will be considered. Combination of multiple benefits and harms require more complex modeling and decision-support systems.

Assume that you are seeing a 61 year old man recently diagnosed with anemia due to myeloma. He presents with hemoglobin 8.5 g/dL. You want to start treatment with MPT (melphalan-prednisone-thalidomide) which is one of the treatment options recommended by the NCCN Multiple Myeloma Guidelines. You are concerned that MPT will further decrease your patient's hemoglobin. You estimate that there is at least a 70% chance that your patient will require RBC transfusion if you give MPT without ESA. However, you are also aware of the increased risk of thrombosis with MPT, which you estimate to be about 12% over 4-6 months.[1] Warfarin or low-molecular weight heparin can reduce this risk by 90% (i.e. to absolute risk of 1.2%). To apply Table A to this case:

Risks for RBC transfusion without ESA: 70% (over 4-6 months)

Risks for RBC transfusion with ESA: 42% (over 4-6 months)

This is equal to NNTB ~ 4 meaning that for every 4 patients treated with ESA, one will avoid RBC transfusion.

Risk of thrombosis with chemotherapy (MPT) (on warfarin) (without ESA): 1.2%

Risk of thrombosis with chemotherapy (MPT) (on warfarin) (with ESA): 1.9%

This is equal to NNH~ 146 indicating that for every 146 patients treated with ESA, one will suffer from thrombosis.

Does this mean that you should administer ESA to your patient (since NNTB<NNH)? (NB an ideal NNTB=1, which means that every treated patient will benefit; and ideal NNH=∞, meaning that no one will be harmed).

The answer to this question depends on your patient's values and preferences. Your recommendation is known as preference-based as opposed to effective-based recommendations (where benefits clearly outweigh risks regardless of patients' preferences). For example, you can ask your patient about his relative values (RV) for one outcome vs. the other i.e. how many times he values avoiding thrombosis over RBC transfusion. If [NNT <NNH/RV],[2] then you should administer ESA. In your case, this would mean that only if your patient values avoiding getting thrombosis 36.5 less times than receiving transfusion than you would be justified giving him ESA.

Table A. Benefits and harms of the use of erythropoeitic stimulating agents (ESA) in the cancer setting.[f1]

Outcomes	Assumed control group risk (outcomes without ESA)	Corresponding risk (with ESA) (95% CI)	Relative effect[f2] (95% CI)	NNTB[f2] or NNH[f2] (95% CI)	No. of participants (# RCTs)[f2]
Benefits[f1]	**Control** (observation and transfusion when required)	**Epoetin/ Darbepoetin**			
Patients receiving red blood cell transfusions	30%[f3]	18% (16 to 20)	RR= 0.60 (0.53 to 0.67)	8 (7 to 10)	5,063 (32)
	50%	30% (27 to 34)		5 (4 to 6)	
	70%	42% (37 to 47)		4 (3 to 5)	
Fatigue[f4]	10%[f3]	7% (6-8)	OR= 0.66[f5] (0.56 to 0.77) Standardized Mean Difference = -0.23 (-0.32 to -0.14) (z=5.08;p<0.001)	33 (25-50)	2,926 (9)
	20%	13% (11 to 15)		14 (11-20)	
	30%	20% (17 to 23)		10 (8 -14)	
Harms[f1]					
Thrombotic events[f6]	2%[f3]	3.14% (2.6% to 3.7%)	RR[3] = 1.57 (1.31 to 1.87)	88 (58 to 161)	8,172 (38)
	5%	8% (7% to 9%)		33 (25 to 50)	
	20%	31% (26% to 37%)		9 (6 to 17)	
Mortality (overall)[f7]	1%	1.1% (1% to 1.2%)	HR[3] = 1.10 (1.01 to 1.20)	1000 (500 to 10,000)	13,611 (51)
	5%	5.5% (5.1% to 6%)		200 (100 to 2,000)	
	20%	22% (20.2% to 24%)		50 (25 to 500)	

[f1]Only data on most important outcomes for decision-making shown (see text for other benefits and harms associated with ESA). [3-7]

[f2] Abbreviations: CI = Confidence interval; No.= Number; RR = Relative risk; OR = odds ratio, HR = hazard ratio; RCT = randomized controlled trials; NNTB/NNH = number of patients that need to receive treatment in order for one to be benefited/harmed (NB values for NNTB/NNH are rounded to whole number) [Table constructed according to GRADE method].[8] Each row provides calculation for the separate baseline risks.

[f3] Representative baseline risks included. The tailoring of data from this table to individual patient circumstances depends on that particular patient's estimates of the baseline risks for outcomes without [ESA] treatment. This is a key factor for individualizing treatment decisions. RBC transfusion rate: average (range across all trials in control arms):47% (0-100%).[7] Fatigue: baseline risk i.e. proportion of cancer patients with fatigue assumed (not specified in Minton et al[5]); Thrombotic events: average thrombotic rate (range across all trials in control arms): 5% (0-23%).[4,7]

[f4] Although there is likely to be a relationship between fatigue and quality of life [QOL], the effect of ESA on fatigue should not be equated as the effect on QOL. At this time, the effect of ESA on QOL is uncertain largely because problems with the quality of trials such as large amount of missing data.[5,6]

[f5] Converted from SMD (standardized mean difference).

[f6] The annual average risk of thromboembolic complications in the general population is 0.1%, while in cancer patients that received at least one cycle of chemotherapy, the risk is 0.8%/month, representing an annual risk of 9.6%.[9] In hospitalized cancer patients with neutropenia the risk of the development of thromboembolic complications is 8%.[10]

[f7] Does not take into account life expectancy. Note that NNTB/NNH is typically much smaller where baseline risk is higher (where life expectancy is expected to be shorter). Clinical circumstances will determine a relationship between NNTB/NNH and life expectancy. For example, although NNH in adjuvant setting can be high (less harmful than in the palliative setting), total years of lives lost is expected to be considerably larger, which is the reason caution is advocated in the curative/adjuvant setting (see text and Algorithms).

Table B. Benefits and harms of the use of red blood cell transfusion.[f1]

Outcomes	Assumed control group risk (liberal transfusion strategy)	Corresponding risk (95% CI) (restrictive transfusion)	Relative effect[f2] (95% CI)	NNTB[f2] or NNH[f2] (95% CI)
Benefits[f3]	**Control** (liberal strategy to keep hemoglobin between 10 – 12 g/L)	**Red Blood Cell Transfusion** (restrictive strategy[f4] to keep hemoglobin between 7 - 9 g/L)		
% patients exposed to RBC transfusion	86%[f5]	50% (40%-61%)	0.58 [0.47-0.71]	3 [2-4]
Harms[f3]		**Estimated frequency (per RBC unit of transfusion)**		**Estimated deaths (per 100 million units of transfusion)**
Transfusion risks/deaths[f5,f6]				
Febrile, non-hemolytic reactions		1/500		0
Transfusion-associated circulatory overload		1/100 to 1/700		30
Acute hemolytic reactions		1/12,000-1/35,000		159
Delayed hemolytic reactions		1/2300 to 1/7000		26
Transfusion-related lung injury		1/4000		100
Transfusion-transmitted sepsis		1/250,000		100-200
Hepatitis A		1/1,000,000		0
Hepatitis B		1/220,000		0-14
Hepatitis C		1/2,200,000		50-1700
HIV		1/200,000 to 1/2,200,000		50-500
				Aggregate NNH[f7] **3,664-19,416**

[f1] This table is based on systematic review of the literature of RBC transfusion that did not specifically examine cancer setting. It is supplemented by data from selective citations and the narrative literature review. [11-27]

[f2] Abbreviations: RR = Relative risk; NNTB/NNH = number of patients that need to receive treatment in order for one to be benefited/harmed (NB values for NNTB/NNH are rounded to whole number); RCT = randomized controlled trials.

[f3]Only data on most important outcomes for decision-making shown (see text for other benefits and harms associated with RBC transfusion).

[f4]It is generally believed that RBC transfusion can be safely withheld in patients without cardiovascular diseases even when hemoglobin is as low as 6-8 g/dL [13] Cochrane systematic review [16] originally published in 2000 included 10 RCTs (n=1780 patients found that mortality, rates of cardiac events, morbidity, and length of hospital stay did not differ between RBC strategies. However, trials were of poor methodological quality (and 80% of data came from one RCT). Subsequently, an additional trial (n=357)[15] was published confirming safety of restrictive RBC policy, with the possible exception of patients with acute myocardial infarcts and unstable angina. In this trial, non-significant increase death rate (by about 5%;p=0.38) was noted in "restrictive RBC treatment arm". This may have been a false-negative result since the trial was underpowered to detect 5% difference in mortality [The trial was design to detect 17% difference in mortality].[13]

[f5] Representative baseline risks included. The tailoring of data from this table to individual patient circumstances depends on that particular patient's estimates of the baseline risks for outcomes without [liberal] RBC transfusion. This is a key factor for individualizing treatment decisions.

[f6]Other risks associated with RBC transfusions include iron-overload (unlikely to occur in patients restricted to limited time period corresponding to chemotherapy treatment), rare infectious risks such as West Nile virus as well as unknown risks from yet undiscovered microbiological organisms.

[f7] Assuming that a typical patient will receive 10 units of RBC and that the causes of deaths are mutually exclusive (i.e. the patient cannot die twice or from two or more diseases at the same time), we need to transfuse between 3,664 to 19,416 patients (with 10 RBC units) to incur one death. This NNH is, *on average,* much higher than NNH associated with ESA (see Table 3). As a consequence, the risk of death associated with RBC transfusion is about 3.6 (3,664/1,000) to 388 (19,416/50) times lower than that with ESA.

Appendix References

1. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006;367:825-831.

2. Djulbegovic B, Hozo I, Lyman GH. Linking evidence-based medicine therapeutic summary measures to clinical decision analysis. MedGenMed. 2000;2:E6.

3. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008;299:914-924.

4. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006;98:708-714.

5. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer related fatigue. Cochrane Database Syst Rev. 2008:CD006704.

6. Rizzo JD, Somerfield MR, Hagerty KL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J Clin Oncol. 2008;26:132-149.

7. Seidenfeld J, Piper M, J. B. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidenced-based Practice Center under Contract No. 290-02-0026) Agency for Healthcare Research and Quality, 2006. http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=4&DocID=35.

8. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.

9. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer. 2005;104:2822-2829.

10. Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol. 2006;24:484-490.

11. Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. N Engl J Med. 2006;355:1303-1305.

12. Djulbegovic B. Reasoning and Decision Making in Hematology. . New York: Churchill Livingstone, Inc. 1992.

13. Goodnough LT, Bach RG. Anemia, transfusion, and mortality. N Engl J Med. 2001;345:1272-1274.

14. Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. Lancet. 2003;361:161-169.

15. Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med. 2001;29:227-234.

16. Hill SR, Carless PA, Henry DA, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2002:CD002042.

17. Rao SV, Chiswell K, Sun JL, et al. International variation in the use of blood transfusion in patients with non-ST-segment elevation acute coronary syndromes. Am J Cardiol. 2008;101:25-29.

18. Fatalities reported to the FDA following blood collection and transfusion. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM113904.pdf Annual summary for fiscal year 2008.

19. Busch MP, Glynn SA, Stramer SL, et al. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion. 2005;45:254-264.

20. Dodd RY. Current risk for transfusion transmitted infections. Curr Opin Hematol. 2007;14:671-676.

21. Hillyer CD, Josephson CD, Blajchmann MA, Vostal JG, Epstein JS, Goodman JL. Bacterial contamination of blood components: risks, strategies, and regulation. Joint ASH and AABB Educational Session in Transfusion Medicine. American Society of Hematology Education Program Book 2003. 2003.

22. King KE, Shirey RS, Thoman SK, Bensen-Kennedy D, Tanz WS, Ness PM. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion. 2004;44:25-29.

23. Parsyan A, Candotti D. Human erythrovirus B19 and blood transfusion - an update. Transfus Med. 2007;17:263-278.

24. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. Curr Opin Hematol. 2003;10:412-418.

25. Popovsky MA. Transfusion Medicine. Bethesda: AABB Press. 1996.

26. Shander A, Popovsky MA. Understanding the consequences of transfusion-related acute lung injury. Chest. 2005;128:598S-604S.

27. Yazer MH, Podlosky L, Clarke G, Nahirniak SM. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. Transfusion. 2004;44:10-15.