



Use of Darbepoetin and Epoetin in Non-Nephrology Patients – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline

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Executive Summary

Guideline Overview

Recommendations for the appropriate indications, dosage, administration and monitoring parameters for the use of darbepoetin alfa and epoetin alfa in adult and pediatric non-nephrology patients in the ambulatory and inpatient setting

Key Practice Recommendations

General Recommendations

1. Darbepoetin is the least costly, generally best-reimbursed, and most cost-effective agent for anemia management (compared to conventional epoetin) and the preferred agent
2. Epoetin is significantly more costly and is generally not as well reimbursed as darbepoetin, and therefore should be restricted to use under the following circumstances listed in this guideline

Adult Use

1. Darbepoetin Indications and Dosing
 - a. Anemia due to chemotherapy in patients with non-myeloid malignancies (see Appendix A)
 - i. Goal is to maintain a stable hemoglobin (Hgb) concentration; lowest dose necessary should be used to avoid transfusions^{1,2} (Class I, Level of Evidence A)
 - ii. Targeted Hgb concentrations greater than 10 g/dL in oncology patients are not recommended^{1,2} (Class III, Level of Evidence A)
 - iii. Recommended starting dose and schedule¹ (Class I, Level of Evidence A):
 1. Darbepoetin 2.25 mcg/kg subcutaneously every week until completion of chemotherapy course OR
 2. Darbepoetin 500 mcg subcutaneously every three weeks until completion of chemotherapy course
 - iv. Recommended dose adjustments are listed in Table 1¹ (Class I, Level of Evidence A)
 - v. Supplemental IV or oral iron supplementation should be administered when serum ferritin is <30 ng/mL and transferrin saturation is < 20%; supplemental IV or oral iron supplementation should be considered when serum ferritin is 30-800 ng/mL and transferrin saturation is 20-50%² (Class I, Level of Evidence A)
 - vi. For patients receiving chemotherapy, darbepoetin should be discontinued following completion of a chemotherapy course¹⁻³ (Class I, Level of Evidence A)
 - b. Myelodysplastic syndrome (MDS) (see Appendix B)
 - i. Use of darbepoetin should be considered in patients who meet requirements for initiation³⁻¹² (Class I, Level of Evidence A)

1. Documented diagnosis of both low grade MDS and anemia
 2. Low risk myelodysplasia with less than 5% blasts
 3. Pretreatment erythropoietin levels ≤ 500 mU/mL
 4. Hgb concentration < 10 g/dL
 - ii. The starting dose of 150 to 300 mcg subcutaneously weekly is recommended³ (Class I, Level of Evidence A)
 - iii. Two months after initiating erythropoiesis-stimulating agent (ESA) therapy, a therapeutic response defined as an increase in clinically significant Hgb levels or a decrease in transfusion requirements must be documented to continue ESA treatment
 - c. Severe autoimmune hemolytic anemia due to cold agglutinins
 - i. Darbepoetin may be considered as some patients benefit from modest doses to support an increased rate of bone marrow RBC production¹³ (Class IIb, Level of Evidence C)
 - d. Ribavirin-induced anemia
 - i. Darbepoetin may be considered to avoid ribavirin dose adjustments that compromise antiviral activity, however no evidence exists ESAs improve sustained viral response¹⁴⁻¹⁶ (Class IIb, Class of Evidence C)
2. Epoetin Indications and Dosing
- a. Anemia due to chemotherapy in patients with non-myeloid malignancies
 - i. Darbepoetin therapy is preferred due to cost¹⁷ (see General Recommendations) (Class I, Level of Evidence A)
 - b. Myelodysplastic syndrome (MDS)^{3-12,18}
 - i. Darbepoetin therapy is preferred due to cost¹⁹ (see General Recommendations) (Class I, Level of Evidence A)
 - c. Anemia due to zidovudine in HIV-infected patients
 - i. Therapy should be considered if measured endogenous serum erythropoietin levels ≤ 500 mUnits/mL and receiving zidovudine doses of 4,200 mg or less per week^{2,3,19} (Class I, Level of Evidence A)
 - ii. The starting dose of 100 units/kg subcutaneously three times weekly is recommended¹⁹(Class I, Level of Evidence A)
 - d. Religious beliefs prohibiting blood transfusions²⁵ (Class IIb, Level of Evidence C)
 - i. Time to start of treatment, dosages, route of administration and treatment duration varied widely among case reports; thus if clinically indicated a standardized dosing regimen may be considered²⁵ (Class IIb, Level of Evidence C)²⁵
3. Monitoring Parameters
- a. Iron Status
 - i. Evaluate iron status in all patients before and during treatment and maintain iron repletion^{1,2,19} (Class I, Level of Evidence A)

- ii. Goals of therapy for ESAs should include serum ferritin \geq 100 ng/mL and transferrin saturation is \geq 20% saturation¹ (Class I, Level of Evidence A)
 - b. Blood Pressure
 - i. Blood pressure should be controlled prior to initiating ESA therapy and monitor periodically during therapy^{1,19} (Class I, Level of Evidence A)
 - c. Hemoglobin
 - i. Hgb should be monitored weekly until it has stabilized and maintenance dose has been established^{1,19} (Class I, Level of Evidence A)
 - ii. After an adjustment in dose, Hgb should be monitored weekly for at least four weeks until stabilized; following stabilization Hgb may be monitored monthly^{1,19} (Class I, Level of Evidence A)
- 4. Warnings/Cautions
 - a. ESAs increase the risk for death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence, particularly when administered to target a Hgb of >12 g/dL; it is recommended to use the lowest dose of ESA to increase the Hgb concentration to the lowest level sufficient to avoid the need for RBC transfusion^{1,19,26-28} (Class I, Level of Evidence A)
- 5. Eligibility Period
 - a. For patients receiving chemotherapy, ESAs should be discontinued following completion of a chemotherapy course^{1-3,19} (Class I, Level of Evidence A)
- 6. Special Considerations for Oncology Indication^{1,19}
 - a. Prescribing of ESAs for patients with chemotherapy-induced anemia is restricted to UW Heath prescribers who have completed training and are currently enrolled in the ESA APPRISE Oncology Program^{1,19,29} (Class I, Level of Evidence A)
 - b. Approved prescribers must counsel each patient regarding risks of ESA therapy prior to new course^{1,19,29} (Class I, Level of Evidence A)
 - c. Prescriber and patient must sign approved ESA APPRISE acknowledgement form (available from website) prior to initiation and administration of ESAs; a copy of the signed acknowledgement form must be made available in patient's medical record and given to patient^{1,19,29} (Class I, Level of Evidence A)
 - d. Prior to each administration of an ESA, a medication guide should be distributed to the patient per product labeling^{1,19,29} (Class I, Level of Evidence A)

Pediatric Use

1. Darbepoetin Indications and Dosing

- a. Use of darbepoetin in pediatric patients is not indicated as safety and effectiveness have not been established¹⁹ (Class III, Level of Evidence A)
- 2. Epoetin Indications and Dosing
 - a. Treatment of anemia in patients 5 to 18 years old due to concomitant myelosuppressive chemotherapy¹⁹ (Class I, Level of Evidence A)
 - i. The starting dose of epoetin 600 units/kg intravenously weekly until completion of a chemotherapy course is recommended¹⁹ (Class I, Level of Evidence A)
 - b. Anemia due to zidovudine in HIV-infected pediatric patients¹⁹ (Class I, Level of Evidence A)
 - i. The starting dose of epoetin 50 to 400 units/kg subcutaneously or intravenously 2 to 3 times per week is recommended¹⁹ (Class I, Level of Evidence A)
 - c. Reduction of blood transfusions in pediatric patients with acute kidney injury³⁰⁻³² (Class IIb, Level of Evidence C)
 - i. Use may be considered but effectiveness is not well established³⁰⁻³² (Class IIb, Level of Evidence C)
 - ii. Initiation of therapy may be considered if Hgb is less than 10 g/dL³⁰⁻³² (Class IIb, Level of Evidence C)
 - iii. No specific pediatric dosing recommendations are present with acute kidney injury; initial dosing strategies and dose adjustments may be based on anemia in chronic kidney disease^{17,30-32} (Class IIb, Level of Evidence C)
- 3. See adult section for monitoring parameters, warnings/cautions and documentation requirements

Companion Documents

Anemia Management in Chronic Kidney Disease – Adult – Inpatient/Ambulatory
Clinical Practice Guideline

Scope

Disease/Condition(s): Adult or pediatric non-nephrology patients requiring darbepoetin alfa or epoetin alfa

Clinical Specialty: Hematology, Oncology, Hepatology, HIV, Pediatrics

Intended Users: Physicians, Physician Assistants, Advanced Practice Nurses, Pharmacists

CPG objective(s): To standardize and provide recommendations for the appropriate indications, use and monitoring for darbepoetin alfa and epoetin alfa for adult and pediatric patients across UW Health

Target Population: Adult or pediatric inpatient or ambulatory patients with indication for darbepoetin alfa or epoetin alfa therapy

Interventions and Practices Considered:

This guideline provides management recommendations for non-nephrology adult and pediatric patients requiring darbepoetin alfa or epoetin alfa in order to help standardize care in the inpatient and ambulatory setting

Methodology

Methods Used to Collect/Select the Evidence:

Searches of electronic databases (e.g., national and international guidelines for darbepoetin and epoetin use and cancer and chemotherapy induced anemia)

Methods Used to Assess the Quality and Strength of the Evidence:

Weighting according to rating scheme (scheme given below)

Rating Scheme for the Strength of the Evidence:

A rating scheme must be used to indicate the strength of the evidence. Recommended rating systems include the GRADE system or the United States Preventive Services Task Force (USPSTF) grading system.

Rating Scheme for the Strength of the Recommendations:

A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1) have been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline¹

Figure 1: Quality of Evidence and Strength of Recommendation Grading Matrix*

		SIZE OF TREATMENT EFFECT →			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology

Methods Used to Analyze the Evidence:

National Guideline Reviews, Systemic Reviews, Expert Opinion

Methods Used to Formulate the Recommendations:

See the “Rating Scheme for the Strength of Evidence.”

Definitions (optional):

1. Erythropoiesis-stimulating agent (ESA): Medications used to stimulate the production of red blood cells such as epoetin alfa (epoetin) and darbepoetin alfa (darbepoetin)

Introduction

Darbepoetin alfa (also referred to as darbepoetin) and erythropoietin alfa (also referred to as epoetin alfa or epoetin) are both synthetic, recombinant forms of the glycoprotein hormone erythropoietin and are hematopoietic agents that principally affect erythropoiesis (erythropoiesis-stimulating agents or ESAs).² Unlike transfusion which immediately boosts the hemoglobin level, ESAs can take weeks to elicit a response, but they are effective in maintaining a target hemoglobin level with repeated administration.² Darbepoetin differs structurally from the endogenous hormone and epoetin by the addition of two carbohydrate chains. This structural modification results in a longer terminal half-life allowing darbepoetin to be less frequently administered. Possible benefits of ESAs include avoidance of blood transfusion; however risks in some disease states include thromboembolism, hypertension/seizures and possible increased mortality.²

This guideline is intended to define the appropriate indications for use of ESAs at UWHC for non-nephrology patients, taking into consideration available clinical data on efficacy, cost to UWHC and reimbursement by third-party payers. A separate guideline is available that addresses the use of these two products in nephrology patients.

Recommendations

General Recommendations

1. Darbepoetin is the least costly, generally best-reimbursed, and most cost-effective agent for anemia management (compared to conventional epoetin) and the preferred agent
2. Epoetin is significantly more costly and is generally not as well reimbursed as darbepoetin, and therefore should be restricted to use under the following circumstances listed in this guideline

Adult Use

1. Darbepoetin Indications
 - a. Anemia due to chemotherapy in patients with non-myeloid malignancies^{1,2} (see Appendix A)
 - i. The goal of ESA therapy for anemic cancer patients receiving concurrent chemotherapy is to reduce transfusion requirements and benefit should be weighed with the risk profile, including an increased incidence of thromboembolic reactions^{33,34} (Class IIa, Level of Evidence A)
 - ii. Treatment goal is to maintain a stable Hgb concentration; lowest dose necessary should be used to avoid transfusions; a minimum of two additional months of planned chemotherapy is required^{1,2} (Class I, Level of Evidence A)
 - iii. ESA therapy should not be prescribed for an improvement in quality of life (QOL) or improved cancer outcomes as available evidence does not support this¹ (Class III, Level of Evidence A)
 - iv. ESAs should not be used when anticipated outcome is cure as ESAs may promote tumor growth in an off-target manner² (Class III, Level of Evidence A)
 - v. Cancer patients not receiving active chemotherapy or undergoing radiation treatment should not receive ESAs as administration of ESAs in this patient population has offered no benefit and shortened time to death² (Class III, Level of Evidence A)
 - vi. Supplemental IV or oral iron supplementation should be administered when serum ferritin is <30 ng/mL and transferrin saturation is < 20%; supplemental IV or oral iron supplementation should be considered when serum ferritin is 30-800 ng/mL and transferrin saturation is 20-50%² (Class I, Level of Evidence A)
 - b. Myelodysplastic syndrome (MDS)⁴⁻¹² (see Appendix B)

1. Darbepoetin 2.25 mcg/kg subcutaneously every week until completion of chemotherapy course OR
 2. Darbepoetin 500 mcg subcutaneously every three weeks until completion of chemotherapy course
- iv. Recommended dose adjustments are listed in Table 1¹
(Class I, Level of Evidence A)

Table 1: Darbepoetin Dose Adjustments for chemotherapy-associated anemia

Dose Adjustment	Weekly Schedule	Every 3 Week Schedule
<ul style="list-style-type: none"> • If Hgb increases greater than 1 g/dL in any 2-week period OR • If Hgb reaches a level needed to avoid RBC transfusion 	Reduce dose by 40%	Reduce dose by 40%
If Hgb exceeds a level needed to avoid RBC transfusion	<ul style="list-style-type: none"> • Withhold dose until Hgb approaches a level where RBC transfusions may be required • Reinitiate at a dose 40% below the previous dose 	<ul style="list-style-type: none"> • Withhold dose until Hgb approaches a level where RBC transfusions may be required • Reinitiate at a dose 40% below the previous dose
If Hgb increases by less than 1 g/dL <u>and</u> remains below 10 g/dL after 6 weeks of therapy	Increase dose to 4.5 mcg/kg/week	No dose adjustment
<ul style="list-style-type: none"> • If there is no response as measured by Hgb levels or if RBC transfusions are still required after 8 weeks of therapy • Following completion of a chemotherapy course 	Discontinue darbepoetin	Discontinue darbepoetin

- b. Myelodysplastic syndrome
 - i. The starting dose of 150 to 300 mcg subcutaneously weekly is recommended³ (Class I, Level of Evidence A)
 - ii. Two months after initiating ESA therapy, a therapeutic response defined as an increase in clinically significant Hgb levels or a decrease in transfusion requirements must be documented to continue ESA treatment
- c. Ribavirin-induced anemia
 - i. Darbepoetin may be considered to avoid ribavirin dose adjustments that compromise antiviral activity, however no

evidence exists ESAs improve sustained viral response¹⁴⁻¹⁶
(Class IIb, Class of Evidence C)

1. During the first two weeks of ribavirin treatment, darbepoetin may be used for hemoglobin declines of > 2 g/dL or for hemoglobin < 10 g/dL, before ribavirin dose adjustment is attempted
2. Between weeks 2 and 12 of ribavirin treatment, darbepoetin may be used for hemoglobin < 10 g/dL before ribavirin dose adjustment is attempted
3. After 12 weeks of ribavirin therapy, ribavirin dose adjustment should be attempted as an initial response to hemoglobin value < 10 g/dL; if hemoglobin values do not respond to a ribavirin dose adjustment and hemoglobin remains < 10 g/dL, darbepoetin should be initiated
4. Cardiac patients may require earlier darbepoetin initiation or more aggressive darbepoetin dosing

3. Epoetin Indications

- a. Anemia due to chemotherapy in patients with non-myeloid malignancies
 - i. Epoetin is indicated in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, however darbepoetin therapy is preferred due to cost¹⁷ (see General Recommendations) (Class I, Level of Evidence A)
- b. Myelodysplastic syndrome^{3-12,18}
 - i. Epoetin is indicated in patients with low risk MDS, however darbepoetin therapy is preferred due to cost¹⁷ (see General Recommendations) (Class I, Level of Evidence A)
- c. Anemia due to zidovudine in HIV-infected patients
 - i. Epoetin therapy is only recommended for HIV-infected patients with measured endogenous serum erythropoietin levels ≤ 500 mUnits/mL and receiving zidovudine doses of 4,200 mg or less per week; at initiation of therapy, Hgb concentration must be less than 10 g/dL^{2,3,19} (Class I, Level of Evidence A)
- d. Religious beliefs prohibiting blood transfusions (Class IIb, Level of Evidence C)
 - i. Elective surgical patients who decline blood-derived products because of religious beliefs, epoetin may be used if clinically indicated (i.e., anticipated blood loss, etc.) as several cases have been reported where recombinant human erythropoietin has been successfully administered to critically ill Jehovah's Witnesses; however time to start of treatment, dosages, route of administration and treatment duration varied widely among case reports; thus if clinically indicated a standardized dosing regimen may be considered²⁵ (Class IIb, Level of Evidence C)²⁵

4. Epoetin Dosing and Administration

- a. Zidovudine-treated HIV-infected patients
 - i. The starting dose of 100 units/kg subcutaneously three times weekly is recommended¹⁹(Class I, Level of Evidence A)
 - ii. Prior to starting epoetin therapy, an endogenous serum erythropoietin level should be drawn as patients with levels > 500 mUnits/mL are unlikely to respond to epoetin therapy³⁵ (Class I, Level of Evidence A)
 - iii. Dose Adjustments
 - 1. If Hgb does not increase after 8 weeks of therapy, recommend increasing epoetin dose by approximately 50 to 100 Units/kg at 4 to 8 week intervals until Hgb reaches a level needed to avoid RBC transfusions or 300 Units/kg¹⁹ (Class I, Level of Evidence A)
 - 2. Withholding epoetin if Hgb exceeds 12 g/dL is indicated; recommend resuming therapy at a dose 25% below the previous dose when Hgb declines to less than 11 g/dL¹⁹ (Class I, Level of Evidence A)
 - 3. No added clinical benefit has been demonstrated if epoetin doses exceed 300 units/kg three times weekly; epoetin should be discontinued if an increase in Hgb is not achieved at a dose of 300 units/kg three times weekly for 8 weeks¹⁹ (Class I, Level of Evidence A)

5. Monitoring Parameters

- a. Iron Status
 - i. Evaluate iron status in all patients before and during treatment and maintain iron repletion^{1,2,19} (Class I, Level of Evidence A)
 - ii. Goals of therapy for ESAs include serum ferritin \geq 100 ng/mL and transferrin saturation is \geq 20% saturation¹ (Class I, Level of Evidence A)
- b. Blood Pressure
 - i. Blood pressure should be controlled prior to initiating ESA therapy and monitor periodically during therapy^{1,19} (Class I, Level of Evidence A)
- c. Hemoglobin
 - i. Hemoglobin should be monitored weekly until it has stabilized and maintenance dose has been established^{1,19} (Class I, Level of Evidence A)
 - ii. After an adjustment in dose, Hgb should be monitored weekly for at least four weeks until stabilized; following stabilization Hgb may be monitored monthly^{1,19} (Class I, Level of Evidence A)
 - iii. Targeted Hgb concentrations should not exceed 10 g/dL in oncology patients as adverse outcomes have been noted in trials when Hgb concentrations exceed 12 g/dL; clinical trial data evaluating patients with head and neck cancer documented accelerated tumor progression with ESA therapy compared to placebo³⁶ and a subsequent trial

evaluating metastatic breast cancer patients receiving chemotherapy noted an increase in mortality due to disease progression and decreased overall survival³⁷ (Class III, Level of Evidence A)

iv. Lack or loss of hemoglobin response

1. Initiate a search for causative factors causing refractoriness prior to increasing dose, including: infection, inflammatory processes, occult blood loss, hemolysis or severe aluminum toxicity¹⁻³ (Class I, Level of Evidence A)
2. In absence of another etiology, the patient should be evaluated for evidence of pure red cell aplasia and serum should be tested for the presence of antibody to recombinant erythropoietins¹⁻³ (Class I, Level of Evidence A)

6. Warnings/Cautions

- a. ESAs increase the risk for death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence, particularly when administered to target a Hgb of >12 g/dL thus it is recommended to use the lowest dose of ESA that will gradually increase the Hgb concentration to the lowest level sufficient to avoid the need for RBC transfusion^{1,19,26-28} (Class I, Level of Evidence A)
- b. Given use of ESAs in cancer patients has shortened overall survival and/or increased risk of tumor progression in patients with advanced head and neck, breast, non-small cell lung, and cervical cancers when administered to target a Hgb of >12 g/dL, ESAs should not be used for the treatment of anemia in cancer patients other than those with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy^{1,19} (Class I, Level of Evidence A)
- c. ESAs are contraindicated in patients with uncontrolled hypertension as approximately 40% of patients required initiation or intensification of antihypertensive therapy during early phase of treatment and hypertensive encephalopathy and seizures have been reported; ESAs may need to be reduced or withheld if blood pressure is difficult to control and patients should be advised regarding importance of compliance with antihypertensive therapy^{1,19,26} (Class I, Level of Evidence A)

7. Eligibility Period

- a. For patients receiving chemotherapy, ESAs should be discontinued following completion of a chemotherapy course^{1-3,19} (Class I, Level of Evidence A)

8. Special Considerations for Oncology Indication^{1,19}

- a. Prescribing of ESAs for patients with chemotherapy-induced anemia is restricted to UW Health prescribers who have completed training and are currently enrolled in the ESA APPRISE Oncology Program^{1,19,29} (Class I, Level of Evidence A)

- b. Approved prescribers must counsel each patient regarding risks of ESA therapy prior to new course^{1,19,29} (Class I, Level of Evidence A)
- c. Prescriber and patient must sign approved ESA APPRISE acknowledgement form (available from website) prior to initiation and administration of ESAs; a copy of the signed acknowledgement form must be made available in patient's medical record and given to patient^{1,19,29} (Class I, Level of Evidence A)
- d. Prior to each administration of an ESA, a medication guide should be distributed to the patient per product labeling^{1,19,29} (Class I, Level of Evidence A)

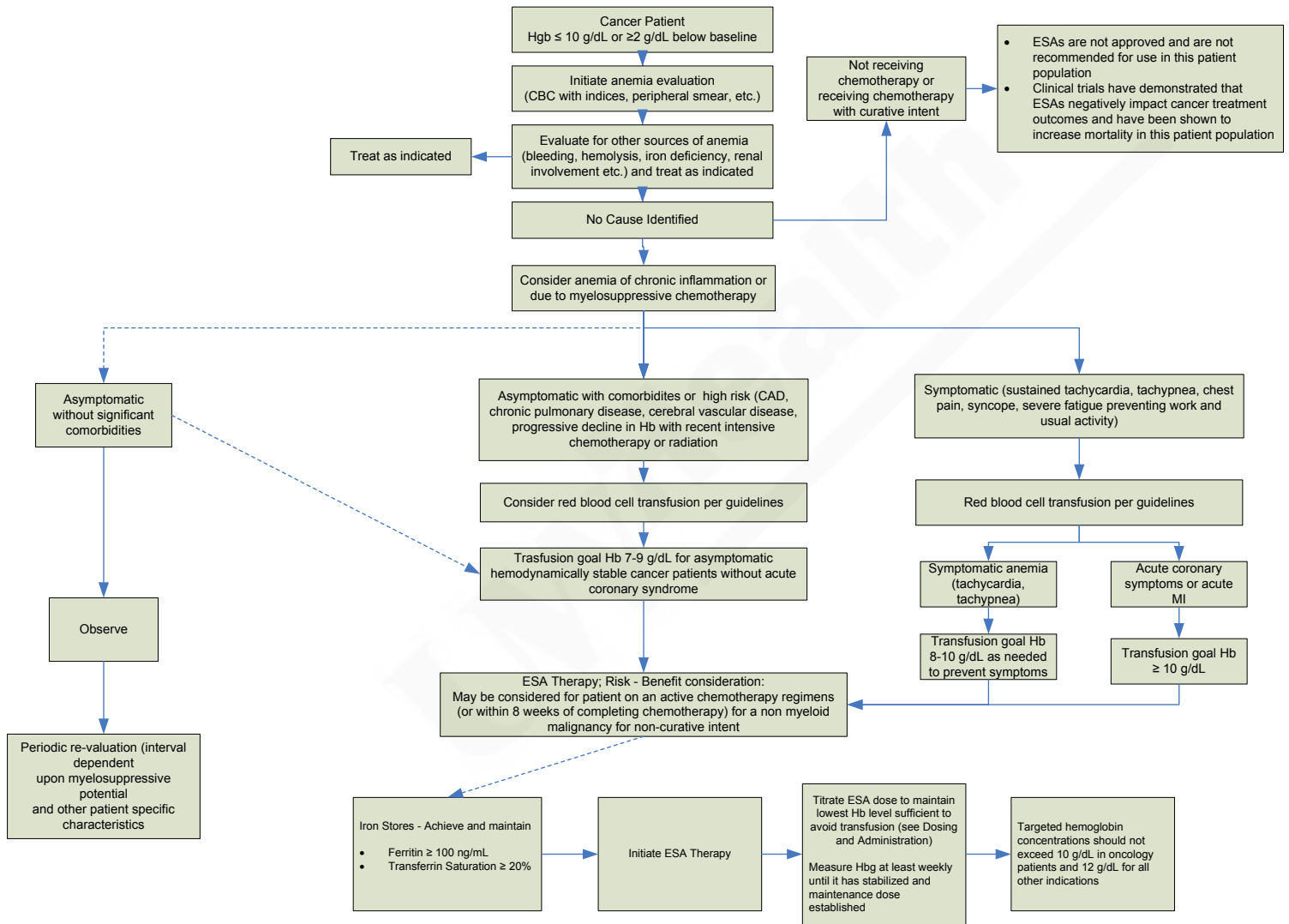
Pediatric Use

1. Darbepoetin Indications
 - a. Use of darbepoetin in pediatric patients is not indicated as safety and effectiveness have not been established¹⁹ (Class III, Level of Evidence A)
2. Epoetin Indications
 - a. Treatment of anemia in patients 5 to 18 years old due to concomitant myelosuppressive chemotherapy¹⁹ (Class I, Level of Evidence A)
 - b. Anemia due to zidovudine in HIV-infected pediatric patients based off increases in Hgb levels and decreases in blood transfusions¹⁹ (Class I, Level of Evidence A)
 - c. Reduction of blood transfusions in pediatric patients with acute kidney injury³⁰⁻³² (Class IIb, Level of Evidence C)
 - i. Pediatric nephrology service should be consulted for use in this population³⁰⁻³² (Class I, Level of Evidence A)
 - ii. Use may be considered but effectiveness is not well established³⁰⁻³² (Class IIb, Level of Evidence C)
 - iii. Continuation of therapy after resolution of renal insufficiency is not recommended as it exposes the patient to unnecessary risks of drug adverse effects and increases the cost of therapy³⁰⁻³² (Class III, Level of Evidence C)
 - iv. Patients should be evaluated for the need for epoetin on a daily basis and upon hospital discharge based on Hgb, serum creatinine, urine output and renal function³⁰⁻³² (Class I, Level of Evidence A)
3. Epoetin Dosing and Administration
 - a. Pediatric cancer patients (5 to 18 years) receiving chemotherapy
 - i. The starting dose of epoetin 600 units/kg intravenously weekly until completion of a chemotherapy course is recommended¹⁹ (Class I, Level of Evidence A)
 - ii. The following dose adjustments are recommended¹⁷ (Class I, Level of Evidence A)
 1. If Hgb does not increase by >1 g/dL and remains <10 g/dL after initial 4 weeks; increase to 900 units/kg/dose (maximum dose: 60,000 units)

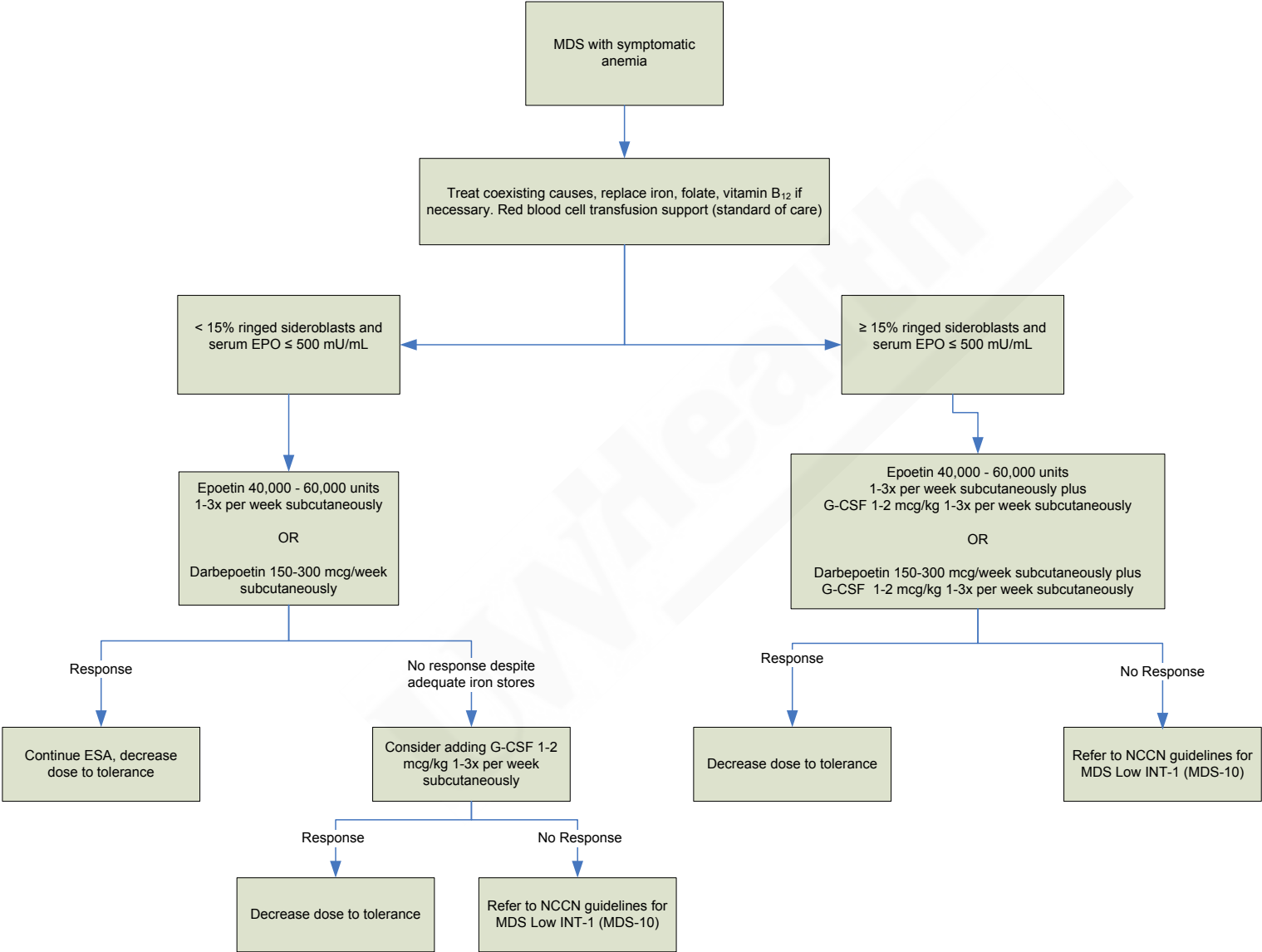
2. If Hgb exceeds a level needed to avoid RBC transfusion: Withhold dose; resume treatment with a 25% dose reduction when Hgb approaches a level where transfusions may be required
 3. If Hgb increases >1 g/dL in any 2-week period or Hgb reaches a level sufficient to avoid RBC transfusion; reduce dose by 25%
 4. Discontinue after 8 weeks of treatment if RBC transfusions are still required or there is no Hgb response
- b. Pediatric patients with HIV infection receiving zidovudine
- i. The starting dose of epoetin 50 to 400 units/kg subcutaneously or intravenously 2 to 3 times per week is recommended¹⁹ (Class I, Level of Evidence A)
 - ii. The following dose adjustments are recommended¹⁷ (Class I, Level of Evidence A)
 1. Withhold dose if Hgb exceeds 12 g/dL, may resume treatment with a 25% dose reduction once Hgb <11 g/dL; titrate to minimum effective dose to maintain a Hgb sufficient to avoid RBC transfusions
- c. Reduction of blood transfusions in patients with acute kidney injury
- i. Initiation of therapy may be considered if Hgb is less than 10 g/dL³⁰⁻³² (Class IIb, Level of Evidence C)
 - ii. No specific pediatric dosing recommendations are present with acute kidney injury; initial dosing strategies and dose adjustments may be based on anemia in chronic kidney disease; reduce or interrupt treatment if Hgb approaches or exceeds 11 g/dL^{17,30-32} (Class IIb, Level of Evidence C)
 - iii. It is not recommended to continue epoetin beyond resolution of renal insufficiency or in admitted patients with Hgb >12 g/dL regardless of renal function³⁰⁻³² (Class III, Level of Evidence C)
 - iv. Epoetin alfa may be discontinued once acute kidney injury has resolved and renal function has returned to baseline³⁰⁻³² (Class IIb, Level of Evidence C)
4. See adult section for monitoring parameters, warnings/cautions and documentation requirements

Appendix A: ESA Algorithm: Treatment of Anemia in Adult Cancer Patients
 Modified from NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines V.2.2015

Appendix A: ESA Algorithm for the Treatment of Anemia in Cancer Patients



Appendix B: Algorithm for the Treatment of Symptomatic Anemia in Adult Patients with Myelodysplastic Syndrome
 Modified from NCCN MDS Guidelines V. 2.2015



UW Health Implementation

Potential Benefits:

This guideline has been developed based on best evidence based recommendations. By implementing the parameters set forth in the guideline, non-nephrology adult and pediatric patients will receive ESAs appropriately and safely.

Potential Harms:

Side effects and adverse events associated with various medical/drug treatments.

Implementation Tools/Plan

1. Guideline will be housed on UConnect in a dedicated folder for Clinical Practice Guidelines.
2. Links to this guideline will be created in appropriate HealthLink or equivalent tools.
3. Pharmacists will be educated about these guidelines via department inservices.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

References

1. Darbepoetin (Aranesp) Package Insert. Amgen Inc. Revised May 2012.
2. National Comprehensive Cancer Network. The NCCN Cancer and Chemotherapy-Induced Anemia Clinical Practice Guidelines in Oncology. Available at: <http://www.nccn.org>. Version 2.2015. Accessed [October 1, 2014].
3. National Comprehensive Cancer Network. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology. Available at: <http://www.nccn.org>. Version 1.2015. Accessed [November 1, 2014].
4. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. *Br J Haematol* 1998;103:1070-4.
5. Clavio M, Nobili F, Balleari E, et al. Quality of life and brain function following high-dose recombinant human erythropoietin in low-risk myelodysplastic syndromes: a preliminary report. *Eur J Haematol* 2004;72:113-20.
6. Hast R, Wallvik J, Folin A, Bernell P, Stenke L. Long-term follow-up of 18 patients with myelodysplastic syndromes responding to recombinant erythropoietin treatment. *Leuk Res* 2001;25:13-8.

7. Musto P, Falcone A, Sanpaolo G, et al. Efficacy of a single, weekly dose of recombinant erythropoietin in myelodysplastic syndromes. *Br J Haematol* 2003;122:269-71.
8. Spiriti MA, Latagliata R, Niscola P, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol* 2005;84:167-76.
9. Stasi R, Brunetti M, Bussa S, et al. Response to recombinant human erythropoietin in patients with myelodysplastic syndromes. *Clin Cancer Res* 1997;3:733-9.
10. Stasi R, Brunetti M, Terzoli E, Abruzzese E, Amadori S. Once-weekly dosing of recombinant human erythropoietin alpha in patients with myelodysplastic syndromes unresponsive to conventional dosing. *Ann Oncol* 2004;15:1684-90.
11. Terpos E, Mougiou A, Kouraklis A, et al. Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: a phase II trial in 281 patients. *Br J Haematol* 2002;118:174-80.
12. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2007). © 2007 National Comprehensive Cancer Network I. Available at: <http://www.nccn.org>. Accessed [June 7, 2007]. To view the most recent and complete version of the guideline, go online to www.nccn.org.
13. Gertz MA. Management of cold haemolytic syndrome. *Br J Haematol*. 2007; 138(4):422-9.
14. Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302-11.
15. Del Rio RA, Post AB, Singer ME. Cost-effectiveness of hematologic growth factors for anemia occurring during hepatitis C combination therapy. *Hepatology* 2006;44:1598-606.
16. Dieterich DT, Wasserman R, Brau N, et al. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastroenterol* 2003;98:2491-9.
17. Epoetin alfa monograph. *Pediatric and Neonatal Lexi-Drugs*. Accessed November 14, 2014.
18. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol* 2008;26:3607-13.
19. Epoetin alfa (Epogen) Package Insert. Amgen Inc. Revised May 2012.
20. Christodoulakis M, Tsiftsis DD. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. *Ann Surg Oncol* 2005;12:718-25.
21. Feagan BG, Wong CJ, Kirkley A, et al. Erythropoietin with iron supplementation to prevent allogeneic blood transfusion in total hip joint arthroplasty. A randomized, controlled trial. *Ann Intern Med* 2000;133:845-54.
22. Hardwick ME, Morris BM, Colwell CW, Jr. Two-dose epoetin alfa reduces blood transfusions compared with autologous donation. *Clin Orthop Relat Res* 2004;240-4.
23. Qvist N, Boesby S, Wolff B, Hansen CP. Recombinant human erythropoietin and hemoglobin concentration at operation and during the postoperative period: reduced need for blood transfusions in patients undergoing colorectal surgery--prospective double-blind placebo-controlled study. *World J Surg* 1999;23:30-5.
24. Weber EW, Slappendel R, Hemon Y, et al. Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: the European Epoetin Alfa Surgery Trial (EEST). *Eur J Anaesthesiol* 2005;22:249-57.

25. Ball AM, Winstead PS. Recombinant human erythropoietin therapy in critically ill Jehovah's Witnesses. *Pharmacotherapy* 2008;28:1383-90.
26. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;12:Cd003407.
27. 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;299:914-24.
28. Grant MD, Piper M, Bohlius J, et al. AHRQ Comparative Effectiveness Reviews. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
29. <https://www.esa-appraise.com/ESAAppriseUI/ESAAppriseUI/default.jsp>.
30. Pape L, Ahlenstiel T, Kreuzer M, et al. Early erythropoietin reduced the need for red blood cell transfusion in childhood hemolytic uremic syndrome: a randomized prospective pilot trial. *Pediatr Nephrol* 2009;24:1061-4.
31. Balestracci A, Martin SM, Toledo I, Alvarado C, Wainsztein RE. Early erythropoietin in post-diarrheal hemolytic uremic syndrome: a case-control study. *Pediatr Nephrol* 2014.
32. Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999;27:2346-50.
33. 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;94:1211-20.
34. Vansteenkiste J, Tomita D, Rossi G, Pirker R. Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline. *Support Care Cancer* 2004;12:253-62.
35. Henry DH, Beall GN, Benson CA, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. *Ann Intern Med* 1992;117:739-48.
36. 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;362:1255-60.
37. 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;23:5960-72.