

CHALLENGES IN TREATING CHEMOTHERAPY-INDUCED ANEMIA

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CLINICAL AND ECONOMIC CONSIDERATIONS FOR THE USE OF ERYTHROPOIESIS-STIMULATING AGENTS

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CHALLENGES IN TREATING CHEMOTHERAPY-INDUCED ANEMIA

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Practicing clinicians and healthcare administrators face many challenges in treating cancer patients, including management of chemotherapy-induced anemia. Information on how to best treat these patients comes from a variety of sources: clinical guidelines provide direction based on evidence-based literature, the US Food and Drug Administration (FDA) provides guidance on safe administration and use of erythropoiesis-stimulating agents (ESAs), and insurance providers drive treatment based on evidence and policy. With all of the directives on how to treat chemotherapy-induced anemia, integration of concepts and current data must be completed to determine the appropriate use of ESAs in cancer. The landscape surrounding erythropoietin agents is shifting as questions surround the safety and appropriate use of these agents in cancer patients. The clinical decision between blood transfusions and use of ESAs has become more difficult, as there are safety warnings concerning ESAs and questions regarding the safety of blood transfusions.

SAFETY

The American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO) has called for a meta-analysis of data to determine factors contributing to (1) the risks surrounding transfusions or adverse event of ESAs, or both; (2) faster tumor progression or shorter survival in some ESA-treated patients; and (3) a better understanding of effectiveness of ESAs for anemia not related to chemotherapy (anemia of cancer) and eventually help guide the design of new clinical trials. The Erythropoiesis Stimulating Agents in Cancer Patients: Individual Patient Data Meta-Analysis Collaborative Group presented a meta-analysis at the December 2008 ASH meeting. Their timely efforts analyzed data for 13,933 patients from 53 studies. ESAs increased on-study mortality by 17% (hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.06-1.30; $P = .002$) and worsened overall survival by 6% (HR, 1.06; 95% CI, 1.00-1.12; $P = .005$). Chemotherapy patients also had worse outcomes, with on-study mortality increasing by 10% (HR, 1.10; 95% CI, 0.98-1.24; $P = .12$) while overall survival decreased by 4% (HR, 1.04; 95% CI, 0.97-1.11; $P = .26$). Since the CI crossed 1 in the chemo-



Table 1

Benefits and Harms of the Use of RBC Transfusion

Outcomes	Assumed Control Group Risk (Liberal Transfusion Strategy)	Corresponding Risk (95% CI) (Restrictive Transfusion)	Relative Effect (95% CI)	NNTB or NNH (95% CI)
	Control (liberal strategy to keep hemoglobin 10-12 g/dL)	RBC transfusion (restrictive strategy to keep hemoglobin 7-9 g/dL)		
Benefits				
Patients exposed to RBC transfusion, %	86	50 (40-61)	0.58 (0.47-0.71)	3 (2-4)
Harms		Estimated frequency (per RBC unit of transfusion)		Estimated deaths (per 100 million units of transfusion)
Transfusion risks/deaths				
Febrile, nonhemolytic reactions		1/500		0
Transfusion-associated circulatory overload		1/100 to 1/700		30
Acute hemolytic reactions		1/12,000 to 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 3664-19,416

CI indicates confidence interval; NNTB/NNH, number of patients who need to receive treatment for 1 to be benefited/harmed (rounded to whole number); RBC, red blood cell.

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therapy subset, it appears from this meta-analysis that ESAs decrease survival in chemotherapy patients, but caution should be used in all patients using ESAs.^{1,3}

From the meta-analysis, Bohlius et al² determined the number needed to harm (NNH) for cancer patients with various prognoses. For low-risk patients who have a 5% chance of mortality within the next 4 months, the NNH was 121 (95% CI, 69-343). For medium-risk patients who have a 20% risk of mortality within months, the NNH was 34 (95% CI, 19-94). Finally, for high-risk patients with a 70% risk of mortality within 4 months, the NNH was 24 (95% CI, 14-67).³

These data confirmed the FDA warnings issued in March 2007 and proposed a framework for the ASH/ASCO 2007 guidelines. The guidelines included warnings derived from prior published or presented data that were then solidified as black box warnings in ESA labeling which: (1) shortened the time to tumor progression in patients with advanced head and neck cancers receiving radiation therapy when administered to target a hemoglobin level >12 g/dL (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression [ENHANCE] and Danish Head and Neck Cancer Study [DAHANCA] Group, 10 trials); (2) shortened overall survival and increased mortality attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to

“When treating patients for anemia related to chemotherapy, the possibility that ESAs may help improve hemoglobin levels and avoid the need for transfusion must be taken into consideration.”

target a hemoglobin level >12 g/dL (Breast Cancer Erythropoietin Trial [BEST]); and (3) increased the risk of death when administered to target a hemoglobin level of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy (Randomized Trial of Epoetin Alfa in Patients With Advanced Non-Small Cell Carcinoma of the Lung [EPOCAN-20] and Amgen 20010103 trials). The FDA warning established that treating patients to a hemoglobin level >12 g/dL can lead to negative consequences.^{4,9}

The Oncology Drug Advisory Committee (ODAC) of the FDA met after the letter in March 2007 to further analyze the safety data and clarify safety directives. It restated that patients with advanced breast, head and neck, lymphoid, and non-small-cell lung cancers (when hemoglobin levels are targeted at ≥ 12 g/dL), survival can be shortened and tumor progression more likely. Further warnings of changes in survival and tumor progression were made for ESAs at any targeted hemoglobin level (specifically <12 g/dL). Dosing should be targeted at the lowest dose to avoid blood transfusions. Anemia as a result of chronic disease is addressed as a nonindication. In March 2008,

this information was added to the product labeling.^{10,11}

In August 2008, a medication guide was drafted for epoetin alfa and darbepoetin alfa. The accompanying letter also stated that patients should not be started on ESAs unless their hemoglobin level is <10 g/dL. A warning was also added about not using ESAs when the expected outcome of chemotherapy is cure, as well as instructions on how to report an adverse event. The FDA plans to create a new Risk Minimization Action Plan or Risk Evaluation and Mitigation Strategy program for ESAs to better assess the true risks using these agents in anemia caused by chemotherapy. The overall risks and benefits of red blood cell transfusions (Table 1) should be outlined in addition to those outlined in the medication guides for the ESA products.¹²⁻¹⁵

EFFICACY

When treating patients for anemia related to chemotherapy, the possibility that ESAs may help improve hemoglobin levels and avoid the need for transfusion must be taken into consideration. Witzig et al¹⁶ demonstrated that weekly epoetin alfa significantly increased hemoglobin levels (10.9 g/dL for placebo, which was a change of 0.9 g/dL and



Table 2

Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion

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

ESA indicates erythropoiesis-stimulating agent. Reproduced with permission from The NCCN Clinical Practice Guidelines in Oncology™ Cancer- and Chemotherapy-Induced Anemia Guidelines (Version 2.2010). © 2009 National Comprehensive Cancer Network, Inc. NCCN.org <<http://www.nccn.org>>. Accessed November 20, 2009. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org <<http://www.nccn.org>>. ¹⁵

12.6 g/dL for epoetin alfa, a change of 2.8 g/dL by week 4 of the study; $P < .001$). Significant reductions in the percentage of patients undergoing transfusions was also described in a subset (110/329) of patients (27% transfused in the epoetin alfa arm, 40% in the placebo arm; $P = .012$). Patients were transfused at a median hemoglobin level of 8 g/dL, but transfusion triggers may differ in individual institutions and clinical situations, so the true benefit of the reduction in transfusions is difficult to determine. ^{16,17}

Although the efficacy of ESAs is well established, because safety

issues have been raised, adjunctive therapy could be more crucial to treatment of chemotherapy-related anemia. Auerbach et al¹⁸ conducted a trial evaluating the addition of intravenous and oral iron to ESAs. The study did not enroll enough patients to achieve the required statistical power, but the results provided compelling evidence for the use of intravenous iron. Of the patients who received intravenous iron, 68% responded (defined as an increase in hemoglobin ≥ 2 g/dL or maximal hemoglobin ≥ 12 g/dL). In the no iron and oral iron therapy groups, 25% ($P < .01$) and 36% ($P < .01$)

responded, respectively. This evidence shows that iron could potentially provide overall improvement in hemoglobin levels and possibly lessen the need for blood transfusions. The ASH/ASCO guidelines have not completely addressed intravenous iron therapy, but the data discussed appear to support concomitant use with ESAs.¹ The Mayo Clinic Cancer Research Consortium is completing a larger trial that should provide insight as to the use of oral iron and intravenous iron gluconate. ^{1,18,19}

Current clinical guidelines by ASH and ASCO were published after the safety warning by the FDA in March 2007, the ODAC meeting in May 2007, and the Centers for Medicare & Medicaid Services (CMS) National Coverage Decision (NCD) in July 2007.^{1,20} The hemoglobin level clinicians need to be aware of is 10 g/dL for Medicare patients, according to

“Although the efficacy of ESAs is well established, because safety issues have been raised, adjunctive therapy could be more crucial to treatment of chemotherapy-related anemia.”



the new NCD, but the ASH/ASCO guidelines leave the limit for treating chemotherapy-induced anemia at 12 g/dL. Some private insurers follow the ASH/ASCO guidelines as opposed to the CMS decision. Clinicians have shown their frustration over the new limit of 10 g/dL set by the CMS NCD. In May 2007, a total of 2600 patients, physicians, and other parties responded to the new NCD. Some concessions were made, but the limits to chemotherapy-related anemia and a restriction of treatment for patients with a hemoglobin level of <10 g/dL endured the suggestions.^{1,19,20} The ASH/ASCO guidelines support the dosing for epoetin alfa at 150 U/kg subcutaneously 3 times weekly and 40,000 units subcutaneously weekly. For darbepoetin alfa, they recommend 2.25 mcg/kg subcutaneously weekly or 500 mcg subcutaneously every 3 weeks. Alternative dosing can be utilized following the guidelines, which our clinic uses but continues to evaluate because of specific wording on dosing. New long-term studies are needed to evaluate whether giving ESAs on the same day of chemotherapy has a tumor progression benefit or adverse effect.¹

As to when to increase or decrease doses of ESAs, dosing should be reduced once the hemoglobin level approaches 11 g/dL and stopped once it is >12 g/dL to hopefully prevent any thromboembolic events. Increases in doses can be made at week 4 for epoetin and week 6 for darbepoetin, and clinicians must take this into account prior to

stopping therapy. Physicians should also consider erythropoietin levels to determine which patients will respond, as this may help to make better decisions as to who should receive therapy.^{1,16}

The other unanswered question is the use of the data concerning quality of life (QOL). This is a “soft” end point and difficult to measure. The objective end point of transfusion avoidance is much easier to assess. Future studies should focus on QOL outcomes so clinicians have better information to share with patients on the actual benefits of treatment. The QOL data do help in practice, but the actual impact is difficult to quantify. To further help clinicians answer questions about QOL benefits, this concept should continue to be a secondary end point in trials.

Guidelines from the National Comprehensive Cancer Network have addressed the risks and benefits of ESAs and transfusion medicine. The critical question for evaluating patients and creating institution policies surrounds the intent of the chemotherapy goals. If it is for curative intent, then ESAs are not indicated/appropriate. If the patient requires immediate resolution of symptoms from anemia (fatigue, chest pain, dyspnea, lightheadedness, syncope, and/or tachycardia), then a transfusion should be considered. If they are not symptomatic or do not require immediate attention, then iron studies should be completed and ESAs should be considered.

Dosing and titration are similar to previous versions of the guidelines and to the ASH and ASCO guidelines. The risks and benefits of both ESAs and transfusions should be considered as outlined in **Table 2**.^{1,13-15}

WEIGHING THE OPTIONS

After stepping back and taking in the impact of the last 2 years of new data analyses, guidelines, and safety updates, it appears that treating patients for chemotherapy-induced anemia can be difficult. Reducing the number of transfusions with a limited blood supply is the current primary goal of therapy. Patients provide feedback as to what they hope to receive from supportive care therapy, but with current guidelines and safety data, clinicians must continually re-evaluate the literature and treat with the patient’s best interests in mind. Patients in our clinic have read the warnings from the FDA concerning the discontinuation of ESA therapy 8 weeks following the last course of chemotherapy. For a variety of rationales, they cite that they “feel better” and wish to “avoid transfusions.” Future studies must take this into account (particularly the avoidance of transfusions) postchemotherapy. To quantify the impact of ESA therapy on transfusion avoidance, postchemotherapy trials need to continually consider the risks and benefits of supportive care therapy. Another question to take into account is the length of therapy beyond chemotherapy that would be safe



and appropriate. With the mass of data in nonchemotherapy-related anemia, we must make heads or tails of the clinical conundrum in which we are now practicing. Administrators should work closely with clinicians to determine the appropriate course of action to help ensure that patients receive the best possible care as new data and guideline updates emerge.

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CLINICAL AND ECONOMIC CONSIDERATIONS FOR THE USE OF ERYTHROPOIESIS-STIMULATING AGENTS

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INTRODUCTION

Erythropoiesis-stimulating agents (ESAs) are genetically engineered forms of erythropoietin that stimulate erythropoiesis through direct or indirect action on the erythropoietin receptor producing an increase in reticulocyte count, hemoglobin (Hb), and hematocrit levels.^{1,2} The first recombinant human erythropoietin was introduced in the United States in 1989.^{3,4} Currently, there are 3 available ESAs—epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp). The use of ESAs has been associated with a reduced need for blood transfusion, reduction in the frequency and severity of anemia-associated morbidity, and improvement in quality of life.^{2,4}

COMPARISON OF ESAs

ESAs were a biotechnology medical innovation, initially marketed for the treatment of anemia in end-stage renal disease.² Today, labeled indications for the use of these agents include the treatment of anemia associated with chronic renal failure in dialysis and nondialysis patients and the treatment of anemia in metastatic cancer patients (nonmyeloid malignan-

cies) due to concurrent chemotherapy. These agents are not indicated for use in cancer patients who are receiving lone hormonal therapy, therapeutic biologic therapy, or radiation therapy, and patients receiving myelosuppressive therapy when the expected outcome is cure. Additional US Food and Drug Administration (FDA)-approved indications for epoetin alfa include the treatment of anemia (1) associated with HIV therapy and (2) in those undergoing selective, noncardiac, and nonvascular surgeries, to reduce the need for allogeneic blood transfusions.⁵⁻⁷ However, these indications lack extensive study and will not be covered in detail in this review.

ESAs for the Treatment of Anemia Associated With Chronic Kidney Disease

The 2006 National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) guidelines define anemia of chronic kidney disease as an Hb level <13.5 g/dL in men or <12.0 g/dL in women.⁸ Two clinical trials, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study

and the Correction of Hb and Outcomes in Renal Insufficiency (CHOIR) study, revealed findings that led to changes for target Hb levels with ESA therapy.^{3,9,10} In September 2007, the 2006 KDOQI clinical practice guidelines on anemia and chronic kidney disease were updated to reflect the new evidence that supports a target Hb level in the range of 11.0 to 12.0 g/dL in dialysis and nondialysis patients receiving ESA therapy. This target range was selected to maintain flexibility in medical decision making and supports a patient-centered treatment approach. The guidelines were also updated to reflect the importance of not targeting Hb levels >13 g/dL due to an increased risk of serious cardiovascular events and death associated with ESA administration.^{1,3}

Full prescribing information outlines a weight-based calculation for dosing ESAs. In chronic renal failure patients, the recommended starting dose for epoetin alfa is 50 to 100 units/kg administered either subcutaneously or intravenously 3 times per week. The approved starting dose for darbepoetin alfa is 0.45 mcg/kg



Table

Dose Conversion From Epoetin Alfa to Darbepoetin Alfa⁵⁻⁷

Previous Dosage of Epoetin Alfa, units/week	Darbepoetin Alfa Dose, mcg/week	
	Pediatric	Adult
<1500	Not established	6.25
1500-2499	6.25	6.25
2500-4999	10	12.5
5000-10,999	20	25
11,000-17,999	40	40
18,000-33,999	60	60
34,000-89,999	100	100
≥90,000	200	200

Note: In patients receiving epoetin alfa 2-3 times per week, darbepoetin alfa is administered once weekly. In patients receiving epoetin alfa once weekly, darbepoetin alfa is administered once every 2 weeks.

once weekly or an alternate dosing of 0.75 mcg/kg every 2 weeks for nondialysis patients, administered either by the subcutaneous or intravenous route. The intravenous dosing route is the preferred method of administration for hemodialysis patients. Maintenance therapy should be individualized to maintain target hemoglobin levels. Increases in dosages should be limited to once every 4 weeks to allow sufficient time for changes in Hb levels. Doses should be titrated by 25%, and if a rapid rise in Hb (>1 g/dL per 2-week time period) occurs, therapy should be discontinued until the Hb level decreases. Therapy should be resumed at a dose that is 25% less than the previous dose.^{1,5-7} When adjusting doses, clinical judgment plays an important role because therapy is individualized. Retrospective cohort studies focusing on dosing regimens of epoetin alfa show

similar results in achieving Hb levels to those reported in clinical trials.³ In practice, extending dosing of darbepoetin alfa from once every 2 weeks to once monthly while maintaining Hb levels may be possible in hemodialysis or nondialysis patients. An advantage to the use of darbepoetin alfa compared with epoetin alfa is its longer serum half-life, which allows for dosing of the medication once weekly or every 2 weeks. Estimated dosing conversion from one agent to the other is outlined in the **Table**.

ESAs for the Treatment of Chemotherapy-Related Anemia

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) updated their guidelines in 2007 to address the thromboembolic risks associated with ESAs and the use of darbepoetin alfa,

which was not included in the original ASCO/ASH guidelines published in 2002. Initiation of ESA therapy is recommended in patients with an Hb level that is approaching or falling below 10 g/dL.¹¹

The FDA-approved starting dose of epoetin alfa is 150 units/kg 3 times per week or 40,000 units weekly via subcutaneous administration. Subcutaneous administration of darbepoetin alfa is recommended at an initial dose of 2.25 mcg/kg once weekly or an alternative dosing of 500 mcg once every 3 weeks. Adjustment of doses should be aimed at maintaining the lowest Hb level to avoid red blood cell transfusion. Dose escalation of epoetin alfa 3 times per week by an increase of 300 units/kg 3 times per week is suggested if there is no reduction in transfusion requirements or no increase in Hb levels after 8 weeks of therapy.



The recommended weekly dose of epoetin alfa should be increased to 60,000 units if Hb levels do not increase by 1 g/dL or more after 4 weeks of therapy. If after 6 weeks of therapy with weekly dosing of darbepoetin alfa there is a greater than 1-g/dL rise in Hb level, then it is recommended to increase the dose to 4.5 mcg/kg. The epoetin alfa dose should be reduced by 25% when the Hb level approaches 12 g/dL or increases >1 g/dL in 2 weeks. The darbepoetin alfa dose should be reduced by 40% when the Hb level exceeds 11 g/dL or rises >1 g/dL in 2 weeks. Doses of ESAs should be withheld when the Hb level exceeds 12 g/dL.^{5-7,11} Two randomized controlled trials comparing ESA use in cancer patients with anemia due to chemotherapy were inconclusive with respect to superiority of one agent over another.^{12,13}

Disadvantages of ESAs

In recent clinical studies, the use of ESAs has been associated with an increased risk of serious cardiovascular events, thromboembolic events, tumor progression, and death.⁴ These risks were associated with a rapid rise in Hb (>1 g/dL over 2 weeks) and maintenance of higher Hb levels. Disease-related concerns associated with ESAs for cancer patients and chronic renal failure patients have led the FDA to mandate a black box warning on ESA product labeling. It is advised to individualize dosing in patients with renal failure so the Hb level is achieved and maintained within target range. Higher Hb levels were associated with increased risk of death and

“Since the arrival of the first ESA, the financial impact on institutions and payers has been significant. ESAs account for the single largest expenditure for Medicare (\$1.8 billion).”

serious cardiovascular events.⁵⁻⁷ These data are further supported by recent findings in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), which linked a target Hb level of approximately 13 g/dL in patients given darbepoetin alfa with an increased incidence of stroke.¹⁴ The FDA has warned that ESA use in patients with breast, non-small-cell lung, head and neck, lymphoid, and cervical cancers can shorten overall survival and/or increase the risk of tumor progression. Additionally, ESAs are not indicated for cancer patients when the anticipated outcome is cure. Discontinuation of ESA therapy is recommended when chemotherapy is complete. In all patient populations, the appropriate use of ESAs is defined as Hb levels not surpassing the target range of 10 to 12 g/dL and not exceeding an increase in Hb levels >1 g/dL per 2-week period during therapy.⁵⁻⁷

COST COMPARISON

Since the arrival of the first ESA, the financial impact on institutions and payers has been significant. ESAs account for the single largest expenditure for Medicare (\$1.8 billion).¹⁵ In 2007, the Centers for Medicare & Medicaid Services (CMS) issued a statement regarding reimbursement, which

closely followed the black box warning from the FDA, suggesting that reimbursement is becoming more closely tied to drug safety. CMS further issued changes to the Medicare claims-processing policy for ESAs administered to patients receiving dialysis, capping the maximum cumulative dose per billing cycle at 400,000 units for epoetin alfa and 1200 mcg for darbepoetin alfa. Furthermore, as of January 2008, CMS requires a 50% dose reduction in patients whose Hb level persists at >13 g/dL for 3 consecutive months.¹⁶ While CMS stops short of denying claims in this circumstance, the claim will be paid at a reduced rate. In addition, Medicare will only reimburse costs for ESAs in chronic kidney disease and cancer-induced anemia when ESAs are initiated at an Hb level of >10 g/dL. Implementation of bundled payments by Medicare promotes an additional incentive to reduce the expense of these medications by removing financial incentives and encouraging providers to operate in a more cost-conscious manner.¹⁷ Much of the literature to date has focused on claims data and cost-minimization strategies with few studies examining cost-effective utilization. Studies have been criticized for using average wholesale price or wholesale acquisition cost to con-



“In the inpatient setting, a strategy of cost minimization should be used when diagnosis-related groups are used for reimbursement.”

duct the cost comparisons, which tends to favor epoetin alfa over darbepoetin alfa. Manufacturer rebates and discount programs have led to poor price transparency in the US market, making it difficult for direct comparisons of these 2 products. Some studies in Canada and Europe suggest that using either of these agents may be cost-effective, but this has not been demonstrated in the United States.² In addition, most studies fail to account for baseline Hb levels, which can bias the results.¹⁸ In a few randomized trials and observational studies that controlled for cost, the advantage typically favored epoetin alfa.²

The setting in which a patient receives ESA therapy can play an important role in determining the choice of agent. When choosing between agents, both the direct and indirect acquisition costs should be weighed

along with clinical efficacy and reimbursement. According to marketing information from the manufacturer, darbepoetin alfa offers the advantage of extended interval dosing relative to epoetin alfa. Evidence, however, suggests that extended interval dosing with epoetin alfa can be successful in some patients. Research has also shown that patients receiving epoetin alfa achieved goal more rapidly than patients administered darbepoetin alfa, with lower overall indirect costs despite more frequent administration. These results, however, may not translate for all patient populations or disease states associated with the use of ESAs.^{2,13,19,20}

In the inpatient setting, a strategy of cost minimization should be used when diagnosis-related groups are used for reimbursement. With the flexible dosing

schedule of epoetin alfa, patients could be treated in a cost-effective manner by using divided dosing via a hospital-approved protocol. This has the potential to reduce the number of units that are administered in the inpatient setting, thus minimizing cost. Establishing patient-specific doses is another methodology that can reduce waste and should be a standard, as it is consistent with the Joint Commission Medication Management Standards as well as cost-effective. The 340b program can also be used to maximize savings to an organization that qualifies as a disproportionate share under the Medicare Cost Report. Financial savings from this program could drive the use of one agent versus another in the outpatient setting, especially if the patient is seen in a health system clinic. Because the subcutaneous route of administration requires approximately 30% of the intravenous dose to maintain comparable Hb levels, the route of administration should also be further examined.²¹

CONCLUSION

After more than 20 years in the market, a review of literature shows a rapidly changing landscape with ESAs, with the need for additional research being the most repetitive theme. It is no wonder that ESAs continue to be a high-profile topic given the evolving information and complex array of factors that play a role in the cost-effective use of these molecules. Key factors that will influence stakeholders

“Research has also shown that patients receiving epoetin alfa achieved goal more rapidly than patients administered darbepoetin alfa, with lower overall indirect costs despite more frequent administration.”



include patients' quality of life, efficacy, safety, cost of ESAs, and outcomes. Certainly, when ESAs first appeared on the market, they were hailed as wonder drugs due to their ability to reduce the number of blood transfusions, while benefiting patients by reducing fatigue. While these agents are effective in raising Hb levels, recent studies have raised concerns that ESAs may increase the risk of complications such as thromboembolic events, stroke, and lead to rapid tumor progression in some types of cancer. Entry of "biosimilar" agents into the market will likely further complicate and compound these issues, but may lead to price reductions due to competition. As healthcare reform takes shape in the United States, cost-effective medication management will continue to be an integral part of a cost-avoidance strategy. The large expenditure of healthcare dollars on ESAs will likely continue to receive scrutiny, especially in the presence of an ever-increasing diabetic population and the aging baby boom generation that will see an increased prevalence of cancer.

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