

Epoetin Alfa

Clinical Evolution of a Pleiotropic Cytokine

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Recombinant human erythropoietin (epoetin alfa) has been used in clinical settings for more than a decade. Its indications have expanded considerably from its original use as hormone therapy in the treatment of anemia in adults with chronic kidney disease. Since the introduction of epoetin alfa, a greater understanding of anemia pathophysiology and the interactions of erythropoietin, iron, and erythropoiesis has been elucidated. Anemia is now independently associated with increased mortality and disease progression. Potential survival benefits associated with correction of anemia in various patient populations are leading to consideration of earlier, more aggressive treatment of mild to moderate anemia with epoetin alfa. Moreover, this agent's therapeutic use may extend beyond currently accepted roles. Epoetin alfa is undergoing evaluation with promising results in a variety of new clinical settings, including anemia associated with congestive heart failure, ribavirin–interferon alfa treatment of hepatitis C virus infection, and critical illness. Preclinical studies also have established erythropoietin and its recombinant equivalent to be a pleiotropic cytokine with antiapoptotic activity and neuroprotective actions in the central nervous system. The therapeutic potential of epoetin alfa appears yet to be fully realized.

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Recombinant human erythropoietin (epoetin alfa) was one of the first therapies brought to the clinic via recombinant DNA technology,^{1,2} with its initial introduction as a hormone therapy in the treatment of anemia in patients with chronic kidney disease (CKD).³⁻⁶ A decade has passed since several randomized controlled clinical trials confirmed the benefits of epoetin alfa therapy for anemia in zidovudine-treated patients with human immunodeficiency virus (HIV) infection,^{7,8} which was the first clinical application of the drug in a setting of elevated, yet still inadequate, endogenous erythropoietin levels.⁹ During this period, indications for epoetin alfa in the United States and worldwide have expanded considerably (**Table 1**).

Greater understanding of the pathophysiology of anemia in numerous diseases and conditions and the interactions of erythropoietin, iron, and erythropoiesis¹⁰ has accompanied the growing clinical investigation and therapeutic use of epoetin alfa. Anemia is also independently associated with increased mortality in various diseases and conditions. New insights into the relationships among hemoglobin (Hb) levels, symptoms of anemia, and quality of life (QOL) are prompting the reevaluation of tolerating lower Hb levels and the traditional use of Hb levels below 10 g/dL as the trigger for therapeutic intervention in many settings and patient populations. Observations across several diseases also raise the possibility that treatment and correction of anemia with epoetin alfa may be associated with improved survival.¹¹⁻¹³ In addition to ongoing clinical evaluation in various patient populations and conditions, preclinical studies have now established erythropoietin to be a pleiotropic cytokine with

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Table 1. Timeline of Approved Indications for Epoetin Alfa (Varies by Country and Formulation)

Year	Indication
1989	Anemia associated with chronic renal failure in patients undergoing hemodialysis*†
1990	Anemia in zidovudine-treated human immunodeficiency virus–infected patients‡ Anemia of chronic renal failure in adult patients undergoing peritoneal dialysis† and in those not requiring dialysis†‡
1992	Anemia in renal patients undergoing peritoneal dialysis†
1993	Anemia in patients with nonmyeloid malignancies receiving chemotherapy‡ Anemia of chronic renal failure in pediatric patients undergoing hemodialysis†
1994	Anemia in adult patients receiving chemotherapy† To increase yield of autologous blood from patients in predonation programs†
1996	Reduction of allogeneic blood transfusion in anemic patients undergoing elective noncardiac, nonvascular surgery‡
1998	Reduction of allogeneic blood transfusion in adult patients prior to major elective orthopedic surgery†
1999	Anemia in pediatric patients (≥1 month old) with chronic renal failure requiring dialysis*
2000	Reduction of anemia-related sequelae (eg, fatigue, decreased energy, and activity reduction) in adult chemotherapy patients‡

*In the United States, Epogen (epoetin alfa) is manufactured and marketed by Amgen Inc, Thousand Oaks, Calif.

†Outside of the United States, epoetin alfa is manufactured by Ortho Biologics, LLC, and distributed and marketed as EPREX or ERYPO by Ortho Biotech, Toronto, Ontario, and Janssen-Cilag, Issey-les-Moulineaux, France.

‡In the United States, PROCIT (epoetin alfa) is manufactured by Amgen Inc and distributed and marketed by Ortho Biotech Products, LP, Bridgewater, NJ.

antiapoptotic activity,¹⁴⁻¹⁶ as well as potential neuroprotective effects against central nervous system (CNS) injury. This review summarizes the developments and insights gained regarding the biology and clinical use of epoetin alfa since its initial introduction, focusing on clinical uses other than anemia in patients with advanced stages of CKD (ie, end-stage renal disease), as well as important areas of ongoing and new research that are anticipated to widen its therapeutic potential.

BIOLOGY OF ERYTHROPOIETIN

Erythropoietin is a glycoprotein produced primarily in the kidneys that stimulates the division and differentiation of committed erythroid progenitors in the bone marrow.¹⁷⁻¹⁹ Plasma erythropoietin levels remain relatively constant when Hb levels remain at or above 12 g/dL but begin to rise rapidly and markedly when the Hb level decreases below 12 g/dL (**Figure 1**).²⁰ It takes 3 to 4 days following erythropoietin stimulation for circulating reticulocytes to increase.²¹ Depending on the degree of anemia, maturation of circulating reticulocytes into mature red blood cells (RBCs) may take an additional 1 to 3 days.²⁰ Thus, any clinically significant increase in Hb levels is usually not observed in less than 2 weeks following erythropoietin stimulation and may require up to 6 weeks in some patients.

Epoetin alfa is the recombinant equivalent of the endogenous cytokine, with an identical amino acid structure and indistinguishable biologic activity both in vitro and in vivo.^{1,2,22} Over the last decade, greater efforts to more completely describe the biology of erythropoietin in humans have been undertaken, particularly to identify roles and actions of the cytokine in hematopoiesis and other biologic processes.

Erythropoietin has high affinity for the erythropoietin receptor expressed on the surface of erythroid cells. This receptor belongs to the cytokine receptor family that includes growth hormone, prolactin, various colony-stimulating factors, leptin, and several interleukins.^{15,23} In addition to its essential role in erythropoiesis, the erythropoietin receptor also is expressed in mast cells and megakaryocytes, as well as in nonhematopoietic tissues (eg, gastric mucosa, vascular smooth muscle, and brain neurons).^{16,24-27} In brain neurons, a role for erythropoietin receptor signaling during ischemia-associated neuronal angiogenesis has been suggested.^{28,29} In addition, erythropoietin acts to inhibit programmed cell death (apoptosis) of erythroid progenitor cells,³⁰ as well as in neurons following cerebral ischemia and metabolic stress.¹⁴ Other proposed neuroprotective mechanisms for erythropoietin include antioxidant³¹ and a direct neurotrophic effect.³²

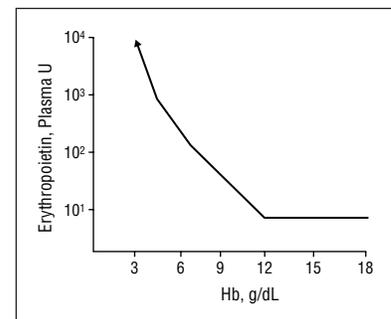


Figure 1. The response of erythropoietin secretion to anemia. Hb indicates hemoglobin. Reprinted with permission from Hillman and Finch.²⁰

DOSING OF EPOETIN ALFA

Epoetin alfa was initially administered intravenously 3 times weekly (TIW) to patients with CKD who were undergoing dialysis to mimic the normal physiologic environment and to allow the patient to receive the drug simultaneously with dialysis.³⁻⁵ Additional experience demonstrated that the drug also could be administered subcutaneously (SC) at the same or a somewhat reduced dose and schedule.³³ The TIW dosing regimen was used in clinical trials evaluating epoetin alfa for subsequent indications, but investigation of alternative, more convenient dosing schedules followed.³⁴⁻³⁶ Pharmacokinetic and pharmacodynamic studies in healthy subjects established that epoetin alfa administered SC at intervals of 7 to 10 days resulted in significant increases in reticulocyte counts^{34,36} and Hb levels.³⁴ A subsequent random-

ized, parallel-design study in healthy adults demonstrated that epoetin alfa, 150 U/kg SC TIW, and 40 000 U SC once weekly for 4 weeks were clinically equivalent regimens, producing similar increases in percentage of reticulocytes, Hb, and total RBCs.³⁷ Once-weekly epoetin alfa dosing has been shown to significantly increase Hb levels in anemic patients with CKD,³⁸ patients scheduled for major orthopedic surgery,³⁵ anemic patients with cancer receiving chemotherapy³⁹ or sequential or concurrent radiation plus chemotherapy,^{40,41} anemic HIV-positive patients (including patients receiving highly active antiretroviral therapy [HAART] with or without zidovudine),^{42,43} and hepatitis C virus (HCV)-infected patients who develop anemia while receiving ribavirin-interferon alfa therapy.⁴⁴ The efficacy and safety profiles of once-weekly epoetin alfa dosing in these populations were similar to those observed with TIW dosing. The once-weekly dosing regimen is now widely used in these patient populations (**Table 2**). Studies also are in progress in anemic patients with cancer receiving chemotherapy,^{45,46} patients with CKD not undergoing dialysis,⁴⁷ and HIV-positive patients to evaluate alternative epoetin alfa dosing regimens, including higher starting doses (eg, 60 000 U SC once weekly)^{45,46} and extended maintenance dosing intervals (eg, every 2-4 weeks).^{46,47}

Traditionally, patients with anemia were not treated until Hb levels dropped below 10 g/dL, at which time RBC transfusions often were administered empirically. Concerns about potential HIV and other in-

fections in the 1980s influenced the treatment of mild to moderate anemia because no alternative was available. Transfusions were generally withheld until Hb levels declined to 7 to 8 g/dL or the patient manifested symptoms of severe anemia. Normal physiologic stimulation of endogenous erythropoietin begins when Hb level falls below 12 g/dL. Based on this standard and data from anemic patients with cancer who demonstrate a significant relationship between QOL and Hb levels from 8 to 14 g/dL—with the greatest improvements in QOL occurring as Hb levels increased from 11 to 12 g/dL⁴⁸—it may be more appropriate to consider treating anemic patients at Hb levels lower than 12 g/dL rather than waiting until more severe anemia develops.^{48,49} This strategy would more closely mimic the body's normal response to inadequate tissue oxygenation and low Hb levels.²⁰

IRON REQUIREMENTS WITH EPOETIN ALFA USE

Transferrin saturation and serum ferritin should be monitored both prior to and during epoetin alfa therapy. In addition, patients who fail to respond or to maintain a response to recommended epoetin alfa doses should be evaluated for the presence of an underlying infectious, inflammatory, or malignant process; occult blood loss; underlying hematologic disease (eg, thalassemia and refractory anemia); vitamin deficiencies (folate and vitamin B₁₂); hemolysis; aluminum intoxication; and osteitis fibrosa cystica. In contrast to absolute iron deficiency, which results from inadequate iron stores,

functional iron deficiency describes the failure to provide iron quickly enough to meet the demands of erythropoiesis.⁵⁰ Inflammatory cytokines associated with the anemia of chronic disease are believed to inhibit the release of iron in storage, limiting the rate of RBC production. In particular, in clinical settings such as cancer and HIV and in patients with CKD undergoing dialysis, epoetin alfa stimulation of RBC production may surpass the rate of iron mobilization from iron stores to the labile iron pool, despite the existence of adequate iron in storage form.⁵¹ This results in a rapidly depleted labile iron pool, delaying a response to epoetin alfa and requiring iron supplementation to achieve or to maintain the effectiveness of epoetin alfa. Oral iron formulations cannot always provide iron quickly enough to support the accelerated erythropoiesis that occurs with epoetin alfa, and intravenous iron supplementation may be required.⁵¹⁻⁵⁴

CLINICAL EVOLUTION

Chronic Kidney Disease

As defined by the National Kidney Foundation (NKF), CKD describes patients with chronically reduced renal function, including those with chronic allograft dysfunction and those with end-stage renal disease.⁵⁵ Normochromic, normocytic anemia occurs in most patients with CKD and is associated with physiologic abnormalities including cardiac dysfunction, impaired cognitive function, impaired immune response, growth retardation in pe-

Table 2. Once-Weekly Epoetin Alfa Dosing and Administration Schema^{35,39,40,43}

Initial dosage	• Epoetin alfa, 40 000 U QW SC*
Evaluate at 4 weeks	• If Hb level increases ≤ 1 g/dL, increase epoetin alfa dosage to 60 000 U QW (maximum dosage)
	• If Hb level increases > 1 g/dL, continue epoetin alfa therapy, 40 000 U QW
If Hb level > 13 g/dL at any time	• Discontinue epoetin alfa therapy until Hb < 12 g/dL
	• Subsequently resume epoetin alfa therapy at 75% of original dose and then titrate to maintain desired Hb level
If Hb level increases > 1.3 g/dL during a 2-week period	• Decrease epoetin alfa dosage to 75% of original dose and then titrate to maintain desired Hb level
If Hb level increases < 1 g/dL from baseline after 8 weeks	• Discontinue epoetin alfa therapy

Abbreviations: Hb, hemoglobin; QW, once weekly; SC, subcutaneously.

*Prior to and during epoetin alfa therapy, patients' iron stores should be monitored (including transferrin saturation and serum ferritin). Most patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support epoetin alfa-stimulated erythropoiesis.

diatric patients, reduced QOL, and decreased patient survival.⁵³ In use since 1986,³ epoetin alfa has proven safe and effective for management of anemia in adult and pediatric patients with CKD, both prior to and during dialysis.^{4,5,56-60} Effective treatment of the anemia of CKD may improve survival (in predialysis patients and patients undergoing dialysis),^{11,61} decrease the risk of hospitalization,⁶² decrease morbidity,^{62,63} slow disease progression,^{11,64,65} and improve QOL.⁵⁵ The NKF guidelines now recommend target Hb levels of 11 to 12 g/dL and hematocrit (HCT) values ranging from 33% to 36%,⁵⁵ which are associated with marked improvement in oxygen utilization; muscle strength and function; cognitive and brain function⁶⁶⁻⁶⁹; cardiac function^{63,70,71}; sexual function; and QOL.⁵⁵

Early CKD

A novel approach to managing anemia and its complications in CKD is to start epoetin alfa therapy in patients with early CKD at the first indication that Hb levels are falling below normal.⁷² Because cardiovascular disease is common in patients with CKD and anemia is an independent risk factor for left ventricular hypertrophy in predialysis patients with CKD,⁷⁰ early treatment of anemic patients with CKD may prevent the cardiovascular dysfunction (eg, left ventricular hypertrophy, cardiac failure, and stroke) or its progression commonly observed in anemic patients with end-stage renal disease.⁷²⁻⁷⁴ As in diabetic patients with microalbuminuria who are treated for maximum blood pressure control and with angiotensin-converting enzyme inhibitors to prevent progression to macroalbuminuria or deteriorating renal function,⁷⁵ treatment of anemia in patients with early CKD may have the potential to alter the disease course. An additional goal in early CKD is to maintain exercise capacity and QOL. Patients also would likely be in better overall health when dialysis becomes necessary.

For an early treatment strategy to be optimally used, a clearer understanding of the scope of ane-

mia in early CKD is needed. In a recent preliminary analysis, 48% of 1716 patients with early CKD (serum creatinine concentration: women, ≥ 1.5 mg/dL [≥ 132.6 $\mu\text{mol/L}$], or men, ≥ 2.0 mg/dL [≥ 176.8 $\mu\text{mol/L}$], but ≤ 6 mg/dL [≤ 530.4 $\mu\text{mol/L}$] within the past 12 months) had an Hb level of 12 g/dL or lower, including 9% with an Hb level of 10 g/dL or lower.⁷⁶ As might be anticipated, a relationship between anemia severity and worsening renal function also was observed; approximately 52% of patients with a creatinine clearance of 30 mL/min or less also had an Hb level of 12 g/dL or lower.⁷⁶ These initial findings suggest a high prevalence of anemia in patients with earlier stages of CKD. In this context, Provenzano et al³⁸ recently conducted a large, prospective, multicenter study in patients with early CKD (serum creatinine concentration: women, ≥ 1.5 mg/dL [≥ 132.6 $\mu\text{mol/L}$]; men, ≥ 2.0 mg/dL [≥ 176.8 $\mu\text{mol/L}$], but ≤ 6 mg/dL [≤ 530.4 $\mu\text{mol/L}$] over 16 weeks) and showed that once-weekly epoetin alfa treatment improved Hb and HCT values from a baseline of 9.2 g/dL and 27.5%, respectively, to 11.9 g/dL and 36.2%, respectively, over 16 weeks. Transfusion rates were reduced from 11.1% to 0.5% in these patients, and QOL measures also showed improvement throughout the 16-week treatment period.

Treatment with epoetin alfa prior to initiation of dialysis also may improve survival in patients with CKD. A retrospective analysis performed on data from 4866 patients with end-stage renal disease, of whom 1107 (23%) were treated with epoetin alfa prior to initiation of dialysis,¹¹ showed that patients treated with epoetin alfa before starting dialysis had a lower mortality risk compared with patients who did not receive epoetin alfa treatment before dialysis (adjusted relative risk, 0.80). The greatest survival benefit was observed in patients with HCT values greater than 31.8% prior to dialysis (adjusted relative risk, 0.67; $P < .001$). Patients also received the most benefit during the first 19 months of dialysis (adjusted relative risk, 0.81), with no sustained survival advantage among patients undergoing dialysis for more than 31

months relative to patients who did not receive epoetin alfa prior to dialysis.

Early detection and intervention are key to the overall management strategy of patients with CKD.⁷⁷ This includes managing primary comorbidities (eg, diabetes and hypertension), preventing uremic complications (eg, anemia, acidosis, and malnutrition), and instituting appropriate measures to delay disease progression (eg, treatment with angiotensin-converting enzyme inhibitors, lipid management, and protein restriction). Correction of anemia plays a principal role in effectively managing many of these issues.⁷⁷

HIV/AIDS

Anemia is the most common hematologic abnormality of HIV infection, and its frequency and severity usually increase as infection progresses to immunologic and clinical AIDS.⁷⁸⁻⁸⁰ The first antiretroviral agent, zidovudine, was a well-recognized cause of bone marrow suppression and anemia, especially with the higher dosages used prior to the introduction of HAART.^{7,8} The evaluation of epoetin alfa as a potential therapy for anemia in patients with HIV or AIDS who were receiving zidovudine⁷ was prompted by the growing HIV/AIDS epidemic; the anticipated increase in transfusion requirements; concerns over the immunosuppressive effect of transfusions in this population; and the fact that, although elevated above normal, plasma erythropoietin levels in patients with HIV or AIDS were usually inadequate for the degree of anemia.⁹

Four placebo-controlled clinical trials including 255 evaluable patients demonstrated that epoetin alfa administered TIW significantly increased HCT ($P < .001$) and decreased transfusion requirements ($P = .003$) in patients with HIV or AIDS receiving zidovudine.^{8,81} These results were confirmed in an analysis of data from 1943 anemic patients with AIDS who participated in an open-label, multicenter, epoetin alfa treatment investigational new drug protocol.⁸² The increase in HCT values and reduction in transfu-

sion requirements were comparable with those observed in the controlled trials, and epoetin alfa therapy did not accelerate disease progression. A subgroup analysis of 523 patients who participated in the open-label study who were not receiving zidovudine found that the increase in HCT values and decrease in transfusion requirement also were comparable with those observed in patients receiving zidovudine.⁸³ Subsequent clinical trials have demonstrated that once-weekly epoetin alfa therapy (40 000-60 000 U SC for up to 16 weeks) also results in significant improvements in Hb and self-reported QOL parameters from baseline to final evaluation, regardless of whether antiretroviral therapy includes zidovudine, with QOL improvements corresponding to increases in Hb.^{42,43}

The introduction of HAART in 1996 had a dramatic impact on the treatment of HIV infection, significantly slowing disease progression as well as accompanying signs and symptoms and improving long-term prognosis for many patients. With the lower zidovudine dosages in current regimens, anemia was perceived as a less important clinical issue.⁸⁴ However, recent data suggest that mild to moderate anemia remains prevalent among HIV-positive patients receiving HAART therapy.⁸⁵⁻⁸⁸ In a subset analysis of data from the EuroSIDA study, a large prospective, observational study of more than 7300 nonselected HIV-positive patients in Europe, anemia resolved after 12 months in approximately 30% of patients who had anemia at initiation of HAART, but mild to moderate anemia remained evident in 46% of patients.⁸⁷

Many studies suggest that anemia is independently associated with disease progression and an increased risk of mortality in patients with HIV infection.^{12,79,86,89} The consistency of this observation regardless of heterogeneous patient populations, varied treatments, and different definitions of anemia underscores the strength of its reported association.⁸⁴ This association appears to be maintained in the HAART era,^{87,90-92} and data from recent studies further suggest that recovery from anemia may have a ben-

eficial impact on survival of HIV-positive patients.^{12,79,93} In an analysis of data from the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project, patients who recovered from anemia (Hb level >10 g/dL after diagnosis of anemia and Hb level of at least 1 g/dL higher than the level at the time of anemia diagnosis) had a significantly ($P < .001$, log-rank test) longer median survival time than patients who did not recover from anemia, regardless of initial CD4 cell count.⁷⁹ In a study of 2348 HIV-positive patients treated at a large urban HIV clinic from 1989 to 1996, use of epoetin alfa for the treatment of anemia ($n = 91$) was associated with a decreased risk of dying (relative hazard, 0.57; $P = .002$).¹² The observation was similar when only those patients who developed anemia ($n = 498$) were evaluated, adjusting for other prognostic factors. In 1203 patients from the cohort of HIV patients at this clinic who were monitored for a median of 2 years from 1996 to 1999 and included patients receiving HAART, patients with a Hb level of 9 to 11 g/dL had a 1.7-fold increase in the relative hazard for death; in addition, recovery from anemia (≥ 2 -g/dL increase in the Hb level) was associated with a relative reduction in risk of death of 40% compared with nonrecovery from anemia—a notable finding.⁹³

Collectively, these data highlight the ongoing importance of anemia monitoring in HIV-positive patients as the disease progresses, as well as the value of maintaining near-normal Hb levels to potentially improve QOL and functional ability and survival, despite recent advances in antiretroviral therapy.⁸⁴ Some experts suggest that treatment of anemia in HIV-positive patients should be considered at an Hb level lower than 12 g/dL in men and lower than 11 g/dL in women, increasing the Hb level to 12 g/dL or higher in men or 11 g/dL or higher in women.⁸⁴ Epoetin alfa may be appropriate initial therapy for treatment of HIV-related anemia when the Hb level is decreasing or has decreased slowly and also may be appropriate for patients who require repeated transfusions with associated frequent hospitalizations.⁸⁴

Cancer

Anemia is a frequent, often debilitating complication of cancer and its treatment. Fatigue, the most common symptom associated with anemia, affects most patients with cancer during the course of their disease and treatment, with many of these patients experiencing fatigue daily or reporting that fatigue significantly affects their daily routines.^{94,95} Historically, reporting of anemia as a toxic effect in chemotherapy studies was mainly focused on the more severe grades.⁹⁶ Mild to moderate anemia, however, occurs in 50% to 75% of adults receiving the most common single agents and combination regimens used to treat major nonmyeloid malignancies.⁹⁶ A recent systematic, quantitative review of available literature suggests that anemia may be an independent prognostic factor for survival in patients with cancer.⁹⁷ The overall estimated increased relative risk of death, after adjusting for other factors, was 65%; anemia was associated with significantly shorter survival times in patients with lung cancer, head and neck cancer, prostate cancer, or lymphoma. The anemia of cancer most closely resembles the anemia associated with chronic disease, with patients demonstrating serum erythropoietin levels that are elevated above normal but not as high as levels observed in patients with similar decreases in Hb level caused by iron deficiency or hemolytic anemia.⁹⁸ It appears that patients with cancer experience a blunted erythropoietin response to anemia,⁹⁸ as well as inadequate erythropoietin production,⁹⁹ making higher doses of epoetin alfa necessary to correct anemia in this setting.

Epoetin alfa (150-300 U/kg TIW) has been shown in randomized, double-blind, placebo-controlled clinical trials to effectively increase Hb levels and reduce transfusion requirements in anemic patients with cancer treated with cisplatin-containing or non-cisplatin-containing chemotherapy.^{100,101} Three additional large, prospective, community-based trials further established the efficacy of epoetin alfa (150-300 U/kg TIW

[N>4370] or 40 000-60 000 U once weekly [N=3012]) in increasing Hb levels and decreasing transfusion requirements in anemic patients with cancer receiving platinum or non-platinum chemotherapy.^{39,102,103} A recent randomized, double-blind, placebo-controlled trial confirmed the results of the community-based trials, showing that, compared with placebo, epoetin alfa significantly reduced transfusion requirements ($P=.006$), increased Hb levels ($P<.001$), and improved QOL ($P<.01$).¹³ Further, Kaplan-Meier estimates showed a trend in overall survival favoring epoetin alfa ($P=.13$), with Cox regression analysis demonstrating an estimated hazard ratio of 1.309 ($P=.052$), suggesting that the mortality risk during the median 26-month follow-up period was approximately 31% higher for patients receiving placebo than for those receiving epoetin alfa. This study was not powered to assess survival, however, and the protocol did not control for variables that may influence survival (eg, disease stage, bone marrow involvement, intensity of chemotherapy, and disease progression).

Epoetin alfa also is undergoing active investigation for the treatment of anemia in pediatric patients with Hodgkin disease, acute lymphocytic leukemia, and non-Hodgkin lymphoma who are receiving chemotherapy, as well as in patients with cancer who receive radiotherapy only. Randomized controlled trials show that epoetin alfa treatment can significantly reduce transfusion incidence, increase mean Hb level, and improve QOL in patients with multiple myeloma.¹⁰⁴⁻¹⁰⁶ Epoetin alfa also may allow disease downstaging in B-chronic lymphoproliferative disorders with long-term use.¹⁰⁷ Epoetin alfa administration in mice bearing multiple myeloma tumors has been shown to markedly prolong survival and reduce mortality, suggesting that epoetin alfa may act as an antitumor therapeutic agent in addition to its role in erythropoiesis.¹⁰⁸ Results of several clinical studies also suggest that use of epoetin alfa as an adjunct to radiotherapy can increase and maintain Hb levels and improve QOL during radiotherapy administered alone or either

sequentially or concomitantly with chemotherapy.^{40,41,109-112} Preliminary results in patients with head and neck cancer further suggest that epoetin alfa therapy may improve locoregional control and survival rates to levels observed in patients with normal pretreatment Hb levels.^{113,114} Additional clinical trials designed specifically to assess the potential impact of epoetin alfa on survival of patients with cancer are ongoing.

To confirm early clinical studies suggesting that epoetin alfa can effectively correct anemia in patients with advanced cancer without regard to chemotherapy use,^{100,115-118} Quirt et al¹¹⁹ recently demonstrated that epoetin alfa administration to patients with nonmyeloid malignancies, including a large cohort of anemic patients ($n=183$) not receiving chemotherapy, significantly improved Hb levels and decreased transfusion use, with increases in Hb levels positively correlating with significant improvements in QOL and changes in Eastern Cooperative Oncology Group performance scores. These results indicate that patients with cancer-related anemia who are not receiving chemotherapy can achieve substantial clinical benefits with epoetin alfa treatment.

Surgery

Despite significant improvements in the safety of the blood supply in recent years, efforts continue to refine existing blood conservation programs and develop new ways to minimize perioperative allogeneic blood exposure. Epoetin alfa has been shown in placebo-controlled trials to significantly decrease allogeneic transfusion requirements and increase preoperative Hb levels in mildly anemic (Hb level >10 g/dL to ≤ 13 g/dL) patients undergoing major elective orthopedic procedures.¹²⁰⁻¹²² In addition, epoetin alfa therapy resulted in comparable or significantly higher mean Hb levels preoperatively, postoperatively, and at discharge compared with preoperative autologous donation patients undergoing total joint arthroplasty surgery ($P<.001$).¹²³ These results suggest that epoetin alfa may effectively allow bloodless orthopedic surgery in many pa-

tients.¹²⁴ Epoetin alfa also has been shown to reduce perioperative exposure to allogeneic blood in patients undergoing radical retropubic prostatectomy.¹²⁵⁻¹²⁷ The results of these trials indicate that perioperative epoetin alfa administration is a safe, well-tolerated, effective, and cost-equivalent alternative to preoperative autologous donation.¹²⁸

Quality of Life

From the patient's perspective, QOL has become an increasingly important consideration in health care management and therapeutic decisions for individual patients. Numerous studies have now demonstrated a correlation between a positive response to epoetin alfa therapy and improved QOL (overall QOL, energy level, and activity level) in anemic patients with CKD,^{6,38,66} cancer,^{13,39,48,102,103,118} and HIV infection.^{8,43,129,130} Clinically relevant insights are emerging regarding the relationship between Hb levels and patient well-being and functional outcomes. In anemic patients with cancer treated with chemotherapy, significant improvements in self-reported QOL parameters and functional status have been reported by patients demonstrating a hematologic response to epoetin alfa,^{13,39,102,103} with improvements occurring independent of tumor response (**Figure 2**).^{102,103} An incremental analysis of the clinical and outcomes data from the combined results of the 2 community-based trials using TIW epoetin alfa dosing^{102,103} demonstrated a significant ($P<.01$), nonlinear relationship between Hb level and QOL over the Hb level range of 8 to 14 g/dL, with the greatest improvement in QOL occurring when the Hb level increased from 11 to 12 g/dL (range, 11-13 g/dL).⁴⁸ These studies in anemic patients with cancer indicate that Hb levels lower than 12 g/dL are associated with suboptimal degrees of overall QOL and functional abilities and are consistent with a large body of evidence in anemic patients with renal dysfunction that functional status is optimized at a Hb level of 12 g/dL. Collectively, these results have had a significant impact on the understanding of anemia and its relationship to patient well-being, sug-

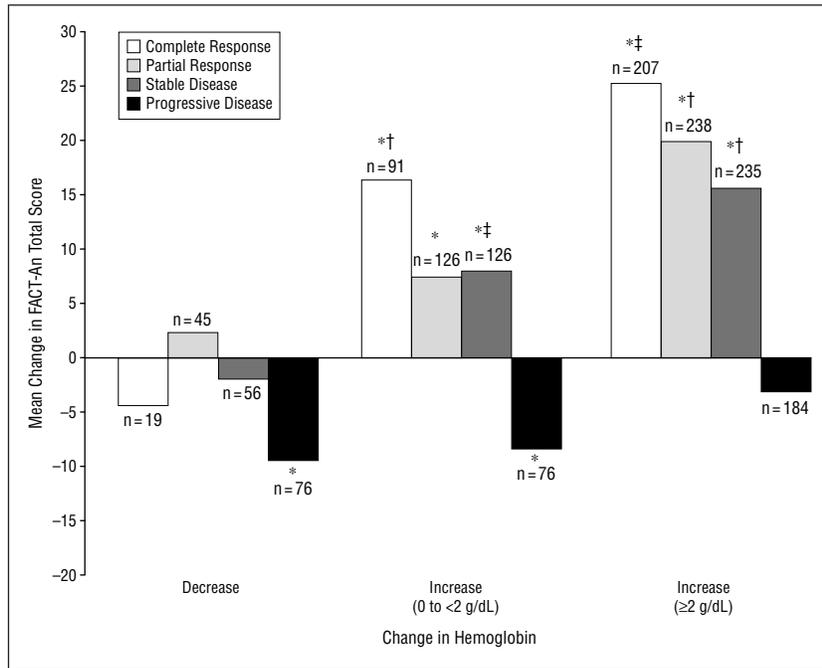


Figure 2. Quality of life parameters (Functional Assessment of Cancer Therapy–Anemia [FACT-An]) analyzed based on changes in hemoglobin levels and tumor response from baseline to final assessment. Asterisk indicates significantly ($P < .01$) different from baseline; dagger, significantly ($P < .01$) different from adjacent hemoglobin change group; and double dagger, significantly ($P < .05$) different from adjacent hemoglobin change group. Adapted with permission from Demetri et al.¹⁰³

Table 3. Hematologic and Clinical Findings in 26 Patients With Heart Failure at Baseline and Following Epoetin Alfa Therapy*¹⁴⁴

	Baseline	End of Study†
Hemoglobin, g/dL	10.16 ± 3.12	12.10 ± 1.21‡
LVEF, %	27.7 ± 4.8	35.4 ± 7.6‡
NYHA class (I-IV)	3.66 ± 0.47	2.66 ± 0.70§
No. of hospitalizations per patient	2.72 ± 1.21	0.22 ± 0.65§
Oral furosemide, mg/d	200.9 ± 120.4	78.3 ± 41.3§
IV furosemide, mg/mo	164.7 ± 178.9	19.8 ± 47.0§

Abbreviations: IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

*Data are mean ± SD value.

†Mean study duration, 7.2 ± 5.5 months (range, 4-15 months).

‡ $P < .001$ vs baseline, paired *t* test.

§ $P < .05$ vs baseline, paired *t* test.

gesting that optimal management of anemia contributes substantially to improving QOL and functional status and that more aggressive treatment of mild to moderate anemia in multiple patient populations may be warranted.

NEW AREAS OF RESEARCH

Congestive Heart Failure

Patients with congestive heart failure often develop anemia, which generally worsens with increasing heart failure severity.¹³¹⁻¹³⁵ The ane-

mia appears to occur despite plasma erythropoietin levels that increase progressively with increasing New York Heart Association (NYHA) severity.¹³⁵ Based on animal and human studies, the ischemic or hypertrophied heart seems to be more sensitive than healthy myocardium to anemia, including very small changes in Hb level, which result in a marked worsening of ischemia and impairment in cardiac function in the diseased heart.^{136,137} Conversely, chronic severe anemia results in salt and fluid retention that appears to improve when the ane-

mia is corrected.¹³⁸ In anemic patients with CKD, treatment with epoetin alfa has resulted in reductions in left ventricular hypertrophy, prevention of left ventricular dilatation, and improvement in left ventricular ejection fraction, stroke volume, and cardiac output.¹³⁹⁻¹⁴³

Thus, correction of anemia in patients with congestive heart failure may improve myocardial function.

In a recent retrospective analysis, the prevalence and significance of mild anemia (Hb level < 12 g/dL) in 142 patients with heart failure were shown to increase with heart failure severity, ranging from 9% in patients with NYHA class I heart failure to 79% of patients with NYHA class IV disease.¹⁴⁴ Of note, 19% of patients with mild heart failure (NYHA class II) and 53% of patients with moderate disease (NYHA class III) were anemic and had concomitant serum creatinine levels ranging from 1.9 to 2.4 mg/dL (168-212 μ mol/L), indicating some degree of renal insufficiency even in patients with relatively mild cardiac impairment. A subset of 26 patients with NYHA class IV heart failure, despite maximally tolerated therapy for at least 6 months and Hb levels lower than 12 g/dL, were enrolled in an intervention trial and received epoetin alfa (mean ± SD dosage, 5227 ± 455 U SC once weekly) and intravenous iron supplementation for a mean ± SD of 7.2 ± 5.5 (range, 4-15) months. In this subset, epoetin alfa therapy was associated with significant improvements in Hb levels and functional status and a 28% increase in left ventricular ejection fraction compared with baseline (**Table 3**). These improvements correlated with a significant reduction in oral and intravenous furosemide administration from baseline, a 92% decrease in hospitalizations compared with a similar period prior to initiation of epoetin alfa therapy, and a decrease in the rate of renal failure progression. No adverse events associated with epoetin alfa therapy were reported. Thus, treatment of anemia in patients with even mild to moderate heart failure may ameliorate progression of CKD and congestive cardiomyopathy. If successful treatment of anemia can improve car-

diac function and reduce hospitalizations in patients with congestive heart failure who have or develop anemia, epoetin alfa therapy may have an important role in the overall management of major cardiovascular disease. Further evaluation is warranted, and a randomized, controlled trial is ongoing.

CNS Disorders

There is considerable interest in agents that might have neuroprotective effects associated with various CNS insults such as head trauma, anoxic injury, and stroke. Epoetin alfa administered via intracerebroventricular injection appears to have such neuroprotective properties in animal models of hypoxic and/or ischemic stress.^{28,145} In studies using various *in vitro* and animal models of human CNS disorders, epoetin alfa had a protective effect against several forms of neuronal damage occurring in stroke, head trauma, epilepsy, and autoimmune encephalitis.^{28,29,145-147} Astrocytes and neurons also can produce erythropoietin under hypoxic or ischemic conditions.^{27,148-153} However, physiologic erythropoietin production alone cannot meet the oxygen demand needed to adequately respond to acute and severe hypoxic and/or ischemic neuronal stress, such as that which occurs following cerebrovascular accident, blunt head trauma, or status epilepticus.¹⁴⁶ Thus, it is possible that exogenous epoetin alfa administration following neuronal stress may augment the activity of endogenous erythropoietin in the CNS.

Intracerebrovascular injection is clearly not practical in the clinical setting and, until recently, systemically administered epoetin alfa had not been seriously evaluated in animal models because conventional wisdom suggested that large glycosylated molecules (eg, epoetin alfa) were not capable of crossing the blood-brain barrier. However, certain large proteins are transported into the CNS via binding to receptors on the capillary endothelium.^{154,155} Using immunocytochemistry techniques, the expression of erythropoietin receptors on human brain capillaries was

recently reported.¹⁴⁶ In addition, evidence suggesting a specific, saturable, receptor-mediated transport mechanism for epoetin alfa across the blood-brain barrier that was not dependent on the existence of injury or inflammation was reported.¹⁴⁶

Collectively, the preclinical data suggest that epoetin alfa possesses immunomodulatory, antiapoptotic, and anti-inflammatory properties in addition to the ability to stimulate erythropoiesis.¹⁴⁶ The neuroprotective effects may be conferred by erythropoietin receptors that have been shown to exist throughout the CNS.^{28,147} Further investigation of epoetin alfa in these and related CNS models is warranted to more specifically define its therapeutic potential in human CNS disorders.

Cognition

It is increasingly recognized that therapeutic interventions, such as coronary artery bypass surgery¹⁵⁶ or adjuvant chemotherapy in patients with breast cancer,¹⁵⁷⁻¹⁵⁹ are associated with a relatively high prevalence of cognitive impairment and a decline in cognitive functioning. The exact cause(s) of these cognitive deficits in the various affected patient populations has not been established, but reduced oxygen delivery to CNS tissues may be involved. Because of the neuroprotective effect of epoetin alfa in preclinical studies and its ability to improve QOL in anemic patients with cancer, clinical studies are ongoing to explore the potential relationship between decreases in Hb levels and cognitive function in patients with cancer receiving chemotherapy and a possible role for epoetin alfa in ameliorating cognitive deficits in anemic patients with cancer receiving chemotherapy. Jacobsen et al¹⁶⁰ recently reported that declines in Hb levels during the course of chemotherapy in patients with cancer were associated with increases in cognitive complaints (eg, problems with memory and concentration) and declines in cognitive abilities. In a randomized, double-blind, placebo-controlled pilot trial enrolling 100 patients with breast cancer receiv-

ing anthracycline-based adjuvant or neoadjuvant chemotherapy, O'Shaughnessy et al¹⁶¹ found that patients receiving epoetin alfa, 40 000 U SC once weekly, experienced improvements in mood, attenuations in the decline in QOL, and improvements in executive control cognitive function compared with patients receiving placebo. Based on these novel results, a larger follow-up, placebo-controlled clinical trial is under way.

Critical Care

Anemia occurs almost universally among critically ill patients and is associated with considerable RBC transfusion use¹⁶²⁻¹⁶⁶ and a potentially increased risk of mortality in the intensive care unit (ICU) setting.^{167,168} Two recent observational studies conducted in Europe¹⁶⁵ and the United States¹⁶⁶ described transfusion rates of 37% and 44%, respectively, in the ICU setting, with transfusions occurring more frequently in older patients and those with extended (≥ 7 days) ICU stays. In critically ill patients, the characteristic compensatory endogenous erythropoietin response to anemia is diminished^{169,170} and iron metabolism abnormalities are present, suggesting that the anemia is an underproduction anemia similar, if not identical, to anemia of chronic inflammatory disease.¹⁷¹ Typically, critically ill patients with anemia receive transfusions despite well-recognized potential adverse effects of allogeneic blood and an association between transfusion and increased risk of morbidity and mortality.¹⁶⁸ However, allowing critically ill patients to maintain a low but apparently tolerable Hb level (typically 7-10 g/dL) also may not be an acceptable option for positive clinical outcomes, particularly in patients with underlying or apparent comorbidities.^{167,168,172}

Critically ill patients with anemia still demonstrate a bone marrow response to epoetin alfa. Its potential role in the management of anemia in critically ill patients was initially assessed in a randomized, double-blind, placebo-controlled trial.¹⁷³ Patients were randomized to receive either epoetin alfa, 300 U/kg

SC (n=80), or placebo (n=80) once daily for the first 5 days and then once every other day for 2 weeks or until ICU discharge for those remaining in the ICU. Patients treated with epoetin alfa required significantly ($P<.02$) fewer RBC transfusions than patients receiving placebo. Patients in the epoetin alfa group received approximately half as many units (166 U) as patients in the placebo group (305 U). Despite this, patients receiving epoetin alfa demonstrated a significantly ($P<.001$) greater mean change in HCT from baseline (4.8% vs 1.4%), as well as a significantly ($P<.01$) higher final HCT (35.1% vs 31.6%), compared with patients receiving placebo. In a subsequent prospective, randomized, double-blind, placebo-controlled, multicenter study in 1302 critically ill patients, the patients receiving epoetin alfa, 40000 U once weekly (n=650), were significantly less likely to undergo transfusion than patients receiving placebo (n=652) (50.5% vs 60.4%; $P<.001$).¹⁷⁴ Patients in the epoetin alfa group had a 19% reduction in the total units of RBCs transfused (**Figure 3**) and a reduction in RBC units transfused per day alive (ratio of transfusion rates, 0.81; $P=.04$) compared with those receiving placebo. The increase in Hb level from baseline to study end was significantly higher in patients receiving epoetin alfa ($P<.001$). In both studies, there was no significant difference in mortality or frequency of ad-

verse events between the 2 treatment groups. The notable response to epoetin alfa in this setting provided further evidence that these patients have an impaired erythropoietin response to physiologic stimuli, as well as a limited ability to respond to endogenous erythropoietin. In this setting, epoetin alfa therapy may allow critically ill patients to achieve higher Hb levels while decreasing their need for RBC transfusions. Further research is needed to determine whether the reduction in RBC transfusion will result in improved clinical outcomes in some critically ill patients. Given the extent of transfusion in the critically ill, particularly in those with longer than 1-week length of stay in the ICU, the potential impact of epoetin alfa therapy on transfusion use in this setting could be substantial.

HCV Infection: Treatment-Related Anemia

Chronic HCV infection is now recognized as the leading cause of chronic liver disease in North America, resulting in cirrhosis, end-stage liver disease, and hepatocellular carcinoma.¹⁷⁵ Combination therapy with conventional interferon alfa or pegylated interferon alfa plus ribavirin, a guanosine analogue with activity against a range of viruses, is now considered standard reference therapy for HCV infection. However, a common and predictable adverse effect of ribavi-

rin is a dose-dependent, reversible anemia,¹⁷⁶ resulting in a drop in Hb levels to below 11 g/dL in 25% to 35% of patients and to below 10 g/dL in 8% to 9% of patients,¹⁷⁷⁻¹⁷⁹ requiring ribavirin dosage reduction or treatment discontinuation. In addition, data suggest that interferon alfa administration causes bone marrow suppression and a blunted reticulocytosis.^{180,181}

Concomitant treatment with epoetin alfa may ameliorate this anemia and allow HCV-infected patients to continue therapy with interferon alfa-2b plus ribavirin.^{44,182,183} In an open-label, randomized, multicenter, parallel-group study, 36 anemic HCV-infected patients (mean baseline Hb level, 11.0 g/dL) received epoetin alfa, 40000 U SC once weekly, along with combination ribavirin–interferon alfa-2b therapy, while 28 patients (mean baseline Hb level, 11.0 g/dL) received ribavirin–interferon alfa-2b and standard of care treatment for Hb level decreases.⁴⁴ At weeks 2, 4, 8, 12, and 16, patients receiving epoetin alfa had significantly ($P<.01$) higher Hb levels than at baseline, as well as significantly ($P<.05$) higher levels than those patients receiving the standard of care. In addition, mean ribavirin daily doses remained constant throughout the 16-week treatment period in patients receiving epoetin alfa but decreased in patients receiving the standard of care. In the on-treatment analysis, the mean ribavirin daily dose in patients receiving the standard of care was lower than that in patients receiving epoetin alfa throughout the study ($P<.05$ at week 16), with 83% of patients receiving epoetin alfa maintaining ribavirin daily doses of 800 mg or greater compared with 54% of patients receiving the standard of care ($P=.02$). These results suggest that epoetin alfa may be a valuable addition to the standard treatment regimen of HCV-infected patients who develop anemia with combination ribavirin–interferon alfa-2b therapy. By allowing maintenance of therapeutic doses of ribavirin, epoetin alfa may increase the likelihood of patients achieving sustained virologic responses to HCV treatment.

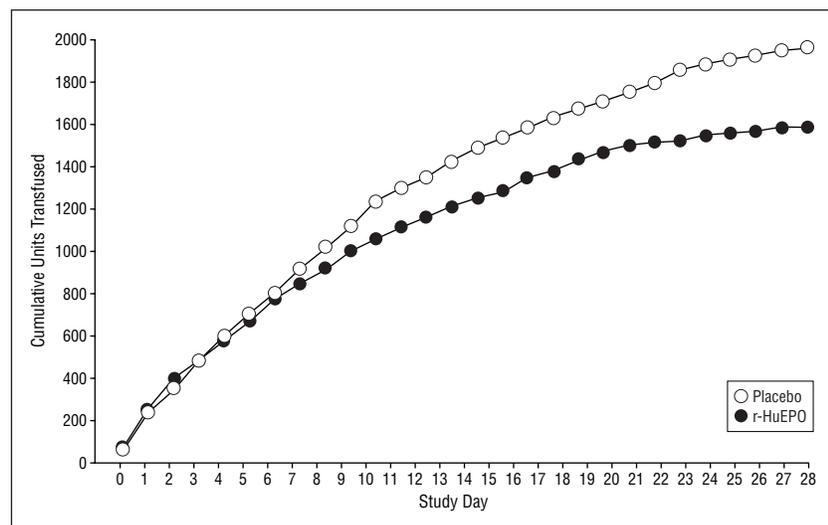


Figure 3. Cumulative units of red blood cells transfused in anemic critically ill patients receiving epoetin alfa (rHuEPO) or placebo. Reprinted with permission from Corwin et al.¹⁷⁴

Use in Pediatric Patients

Several clinical trials have confirmed the benefit of early epoetin alfa treatment (300-600 U/kg per week for 4-6 weeks) to decrease the need for blood transfusion in infants (weight from under 1000 g to 1750 g; gestational age \leq 33 weeks; baseline Hb level $<$ 10 g/dL; baseline HCT \leq 35%) with the anemia of prematurity.¹⁸⁴⁻¹⁸⁷ In these trials, infants receiving epoetin alfa received significantly fewer transfusions and experienced higher reticulocyte counts and serum erythropoietin levels compared with infants receiving transfusions alone or placebo.

Epoetin alfa is indicated for the treatment of pediatric patients aged 1 month to 16 years with anemia associated with CKD requiring dialysis.¹⁸⁸⁻¹⁹² The drug also has been used successfully to treat pediatric patients with anemia associated with CKD not requiring dialysis,^{191,193} HIV-infected pediatric patients,^{194,195} and those with cancer-associated anemia currently receiving chemotherapy.^{196,197} In each of these settings, epoetin alfa administration was associated with dose-dependent increases in Hb and HCT values and decreases in transfusion requirements.^{191,193-197} Ongoing studies are investigating the once-weekly administration of epoetin alfa to anemic pediatric patients with cancer.¹⁹⁸

Safety of Epoetin Alfa

Epoetin alfa is generally well tolerated and has demonstrated proven safety. The adverse effects reported in patients receiving epoetin alfa for its approved indications are generally consistent with the underlying disease (eg, CKD, cancer, and HIV) and its progression or with commonly reported sequelae following surgery. Rapid increases in HCT in patients with CKD may be associated with hypertension. The use of epoetin alfa is contraindicated in patients with uncontrolled hypertension.

In a randomized, prospective study of 1265 hemodialysis patients with clinically evident cardiac disease in which patients were

assigned to epoetin alfa treatment targeted to maintain an HCT of either $42\% \pm 3\%$ or $30\% \pm 3\%$, increased mortality (35%) was observed in the 634 patients randomized to the higher HCT compared with the 631 patients randomized to the lower target (29% mortality). The reason for the increased mortality is not known. The incidence of nonfatal myocardial infarctions (3.1% vs 2.3%), vascular access thrombosis (39% vs 29%), and all other thrombotic events (22% vs 18%) was also higher in the group randomized to 42% HCT.¹⁹² In cancer patients undergoing chemotherapy, the only adverse events that occurred with a statistically greater incidence in patients receiving epoetin alfa than in placebo-treated patients were diarrhea and edema. The most commonly reported adverse effects were pyrexia, vomiting, shortness of breath, paresthesia, and upper respiratory tract infection. The safety of perioperative use of epoetin alfa has been evaluated only in patients who received anticoagulant prophylaxis. Thus, the risk of postoperative thrombotic and/or vascular events cannot be excluded. The occurrence of pure RBC aplasia associated with the presence of anti-erythropoietin antibodies has been reported with recombinant human erythropoietin administered SC in a small number of patients with chronic renal failure.^{199,200} To date, no definitive causative factors have been identified.²⁰¹

Costs

The expansion of clinical uses of epoetin alfa has prompted further examination of the costs of therapy relative to traditional treatment options for anemia (primarily transfusions). Recent cost analysis studies have demonstrated that the costs of outpatient blood transfusions in patients with cancer have been underestimated.^{202,203} These findings imply that previous estimates of the cost-effectiveness of alternatives to transfusions, including epoetin alfa, were understated because the cost of transfusions was only partially captured.²⁰² Crémieux et al²⁰⁴ showed that epoetin alfa can be used cost-effectively to

treat anemic patients with cancer and that epoetin alfa is a cost-effective alternative to blood transfusions. Cost of erythropoietic treatment is an important issue, and additional pharmacoeconomic analysis on the use of erythropoietic agents across clinical uses could provide better perspective on their relative cost-effectiveness. Limited pharmacoeconomic data are available for use in most clinical settings, and direct comparisons of the various agents are not yet available. The issue is complicated in part because the cost of the agents and their reimbursement rates vary by institution, state, and country. In the United States, the average wholesale price as of February 2003 for available agents was \$13.35 per 1000 U for epoetin alfa (Procrit; Ortho Biotech Products, LP, Bridgewater, NJ) and \$124.69 per 25 μ g for darbepoetin alfa (Aranesp; Amgen, Thousand Oaks, Calif).²⁰⁵

CONCLUSIONS

Over the last decade, epoetin alfa has been used in over 1 million patients in the United States and in over 3 million patients worldwide. As one of the original recombinant DNA technology products made available for clinical use, epoetin alfa has proven to have a significant therapeutic role in treating anemia in many conditions beyond its initial use as hormone therapy in patients with anemia of CKD. Epoetin alfa is an accepted treatment for patients with HIV- and cancer-associated anemia, with the value of anemia therapy in these settings supported by the established relationship of anemia to QOL and functional outcomes. This relationship also has led to a reevaluation of traditional approaches to diagnosing and treating anemia, prompting more aggressive and earlier treatment of mild to moderate anemia in the disease course to minimize or avoid the adverse effect of anemia on patient well-being and functional status in established indications. The independent association between anemia and an increased risk of mortality in HIV infection, cancer, and CKD, along with the finding that correction of anemia with epoetin

alfa may be associated with improved survival in these settings, warrants continued research of the potential survival benefit of epoetin alfa therapy. Epoetin alfa also is undergoing evaluation in a variety of new clinical settings, including CHF, CNS disorders, critical care, HCV infection, and the anemia of prematurity, with promising results. It will be important to more fully evaluate the clinical effects of epoetin alfa on neuroprotection and cognition, since these avenues might provide new treatment approaches for a variety of conditions with inadequate therapies. Greater insight into the biology of erythropoietin and its recombinant equivalent, including antiapoptotic and neuroprotective actions, have led to its more accurate characterization as a pleiotropic cytokine. Epoetin alfa provides an important therapeutic option for anemia or its prevention in a variety of settings in which correction may have significant clinical and patient benefits. The potential uses and value of epoetin alfa therapy appear yet to be fulfilled.

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