ABSTRACT

Approximately one third to one half of patients with cancer are anemic, a condition that diminishes the ability to engage in daily activities and undermines the overall quality of life. Although cancer-related anemia has many causes, one of the most important is inadequate production and impaired utilization of erythropoietin. At any given level of anemia, patients with cancer produce much less erythropoietin compared with a healthy person and, as a result, are unable to compensate for the impaired production and shortened lifespan of red blood cells that occur in this situation. Supplemental recombinant erythropoietin can stimulate the production of red blood cells, correct anemia, and improve quality of life. New dosing regimens offer increased convenience to patients and may hasten drug response. (Advanced Studies in Medicine. 2002;2(17):612-619)

The causes of anemia, a common complication of cancer, are varied, ranging from blood loss to inadequate red blood cell production. The consequences of anemia, while equally diverse, all contribute to undermine quality of life and, perhaps, response to antineoplastic therapies. Although the causes of cancer-related anemia are many, impaired erythropoietin production and impaired responsiveness of erythroid progenitor cells to this hormone are central to its pathophysiology. Therefore, alleviating the anemia of cancer requires an understanding of how erythropoietin stimulates red blood cell formation and how the production of and response to this glycoprotein are altered in patients with cancer.

ANEMIA AND CANCER

The prevalence of cancer-related anemia, while not rigorously documented, appears to be substantial. In an audit of more than 2700 patients with a variety of solid tumors and who were receiving chemotherapy at 28 oncology centers in the United Kingdom, 33% of the patients were sufficiently anemic to require blood transfusion. The incidence of transfusion varied widely by tumor type; the incidence was 19% for breast cancer and 43% for lung cancer. Seven percent of patients with breast cancer and 22% with lung cancer required more than 1 transfusion. The overall proportion of patients with a hemoglobin level below 11 g/dL increased from 17% at the start of chemotherapy to 38% by the sixth cycle, despite transfusion in 33% of the
patients. Of those patients receiving transfusion, 25% required hospitalization.

Other reports suggest that among patients with solid tumors, anemia is most common in those with lung cancer (52%) or ovarian cancer (51%). These patients are also the most likely to require blood transfusion (28% and 25%, respectively). Patients treated with platinum-based chemotherapy agents are at especially high risk for developing anemia. Reported transfusion rates in these patients range from 47% to 100%, depending on the cumulative dose of platinum and other risk factors, particularly a low baseline hemoglobin level (<11 g/dL) or a reduction in the hemoglobin level of 1 g/dL to 2 g/dL after the first cycle of chemotherapy. In one study, more than 50% of 81 patients referred for radiation therapy were anemic.

The Consequences of Anemia

Although severe anemia has traditionally been treated with blood transfusion, mild-to-moderate anemia often goes untreated. This lack of treatment may result from a desire to avoid unnecessary use of a therapy that, despite improvements in donor screening, carries definite risks, including immediate and delayed hemolytic reactions, alloimmunization, contamination by infectious agents, iron overload, volume overload, graft-versus-host disease, and immunosuppression.

An equally valid explanation, however, is that many physicians consider the clinical consequences of mild-to-moderate anemia to be minimal. This perception is being challenged by new data on the negative influence of anemia on patients’ performance of everyday activities and quality of life. Anemic patients can experience dyspnea, tachycardia, dizziness, anorexia, hypersensitivity to cold, and, perhaps most commonly, fatigue (Table 1). Of the symptoms of anemia, fatigue is identified by patients as having the most profound and intrusive effect, limiting their ability to work and engage in daily activities to a greater degree than even nausea and pain. In addition, anemia impairs tissue oxygenation and organ function, increases postoperative mortality, increases the likelihood of transfusion after chemotherapy, eliminates the possibility of donating blood for autologous transfusion, increases susceptibility to thrombocytopenic bleeding, and, in certain instances, increases iron absorption.

There appears to be a link between anemia and mortality. In studies of patients with solid tumors, those with anemia had worse outcomes after radiation therapy, including reduced overall survival and less effective locoregional tumor control. Because hypoxia has been shown to limit the radiosensitivity of cells, the poorer outcome may be related to reduced tumor oxygenation in patients with cancer-related anemia.

An analysis of 60 studies reporting survival of patients with cancer according to hemoglobin level showed that anemia was associated with a 65% increase in the risk of death. The relative risk varied by tumor type, from 19% among anemic patients with lung cancer to 75% among patients with head and neck cancer. Whether these findings suggest a causal link or merely reflect the association between anemia and advanced-stage disease is not yet clear.

Role of Erythropoietin

Many factors cause anemia in patients with solid tumors (Table 2), including intrinsic or iatrogenic blood loss; nutritional deficiencies, primarily involving iron or folic acid; autoimmune, traumatic, or drug-induced hemolysis; and bone marrow failure due to tumor encroachment, myelofibrosis, or marrow necrosis. Infection, inflammation, and hypersplenism also cause anemia. In some cases, the

Table 1. Consequences of Anemia

- Impaired tissue oxygenation
- Impaired organ function
- Impaired quality of life
- Increased postoperative mortality
- Increased probability of blood transfusion after chemotherapy
- Inability to donate blood for autologous transfusion
- Increased susceptibility to thrombocytopenic bleeding
- Increased iron absorption (some forms of anemia)
One of the common denominators among the disparate causes for cancer-related anemia is abnormal production and utilization of erythropoietin, the glycoprotein hormone that stimulates production of red blood cells and maintains their viability.\textsuperscript{8,9} Erythropoietin is a 166-amino acid protein that is heavily glycosylated. The circulating, biologically active form of the protein comprises 165 amino acids glycosylated on 3 N-linked groups and 1 O-linked group. The N-linked carbohydrates maintain erythropoietin in a biologically active conformation, and their sialic acid residues ensure survival in the circulation.

Erythropoietin is produced primarily in the kidneys by peritubular interstitial cells and, to a lesser extent, in the liver by fibroblastoid interstitial cells and hepatocytes.\textsuperscript{10-12} Normally, plasma erythropoietin levels are maintained at a constant level by basal production of the hormone. Plasma levels are characterized by a diurnal variation, with the highest levels observed in the morning. Although the normal plasma erythropoietin level is constant in a given individual, the level varies widely from one person to another (normal range, 4–26 mU/mL).\textsuperscript{11}

Erythropoietin production increases in response to tissue hypoxia. Normally, an inverse relationship exists between the plasma level of erythropoietin and hemoglobin or hematocrit, as well as between erythropoietin and arterial oxygen saturation.\textsuperscript{11} A hypoxia-triggered increase in erythropoietin production normally causes an increase in red blood cell production; a decrease in the plasma erythropoietin level occurs with restoration of tissue oxygenation.

Erythropoietin interacts with erythroid progenitor cells in the bone marrow through specific surface receptors to promote cell proliferation and differentiation and to maintain cell viability.\textsuperscript{11-13} The burst-forming unit-erythroid is the earliest erythroid progenitor cell to express erythropoietin receptors. Because burst-forming unit-erythroid cells contain few erythropoietin receptors, an increased concentration of erythropoietin is required to trigger these dormant cells into cycle. The colony-forming unit-erythroid cell, the other target of erythropoietin, expresses a large number of erythropoietin receptors. Therefore, a much smaller amount of the hormone is needed to maintain cell viability.\textsuperscript{13}

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<th>How Cancer Influences Erythropoiesis</th>
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<td>Erythropoietin production is impaired in several situations, including renal parenchymal disease, inflammation, infection, surgery, and blood hyperviscosity.\textsuperscript{11} In cancer, the causes for reduced production are multifaceted. At any level of anemia, patients with cancer produce much less erythropoietin than normal. As a result, they are unable to compensate for the impaired production and shortened lifespan of red blood cells (Table 3).\textsuperscript{8,9}</td>
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<td>The release of inflammatory cytokines in response to malignancy may cause impaired erythropoietin production in patients with cancer.\textsuperscript{8,9,13} These cytokines—primarily tumor necrosis factor, interferon gamma, and interleukin 1— not only reduce erythropoietin production, but also suppress the response of erythroid progenitor cells to the hormone.</td>
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<td>Compounding the deleterious effects of inflammatory cytokines are the effects of cancer therapy on erythropoiesis. Many chemotherapeutic agents not only impair erythropoietin production, but also reduce progenitor cell proliferation. Platinum-based chemotherapeutic agents are reported to cause can-</td>
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<th>Table 2. Causes of Anemia in Patients With Cancer</th>
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<td>▶ Abnormalities in erythropoietin production and utilization</td>
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Data from references 2, 8, and 9.
cer-related anemia through myelosuppression and damage to the renal tubules where erythropoietin is produced. Irradiation can damage erythroid progenitor cells.

Inflammatory cytokines play an additional, although probably not central, role in cancer-related anemia through disordered iron metabolism. Iron is bound to transferrin during transport from the reticuloendothelial system to the bone marrow, where the complex is internalized by developing erythroid cells. The iron molecule is used in the erythroid cells for hemoglobin synthesis or is stored in the cytoplasm as ferritin. Serum ferritin provides a measurement of storage iron, with normal values of 20 mcg/L to 100 mcg/L in women and 30 mcg/L to 300 mcg/L in men. Transferrin saturation reflects the iron content of circulating transferrin. Values below 20% are associated with decreased delivery of iron to the bone marrow.

Normally, tissue iron deficiency is characterized by low transferrin saturation and a low serum ferritin level. In cancer, as in many chronic inflammatory disorders, reduced transferrin saturation is usually associated with a normal or elevated serum ferritin level, a combination characteristic of the so-called anemia of chronic disease. The anemia of chronic disease is a hypoproliferative anemia that may be normocytic and normochromic or microcytic and hypochromic. This disease is characterized by reduced levels of serum iron, reduced transferrin saturation, increased reticuloendothelial iron stores, normal or elevated serum ferritin levels, increased erythrocyte free protoporphyrin, and reduced gastrointestinal iron absorption.

These observations have supported the belief that abnormal iron metabolism plays a major role in the anemia of chronic disease. Other evidence, however, refutes this concept. Although iron absorption is reduced and reticuloendothelial iron stores are increased, there is no actual impairment of iron delivery to the bone marrow and no marked impairment in the utilization of iron by erythroid cells. Lack of impairment has been demonstrated by the ability of recombinant erythropoietin therapy to correct the anemia of chronic disease, which would not be possible if iron deficiency were an important element in this form of anemia. It is likely, therefore, that reduced iron absorption, decreased erythroblast transferrin receptor expression, and iron sequestration by the reticuloendothelial system actually represent the consequences of impaired erythropoietin production in this situation, which is caused by the inflammatory cytokines.

**Patient Outcomes**

Treatment with recombinant human erythropoietin is generally recognized as appropriate for patients with a hemoglobin level below 10 g/dL or for patients with anemia-related symptoms despite a higher hemoglobin level. Other potential recipients include patients with a low baseline hemoglobin level (10 g/dL to 12 g/dL) who are beginning chemotherapy and patients who are receiving platinum-based chemotherapy and have had a marked decrease (1 g/dL to 2 g/dL) in hemoglobin from baseline to the second cycle of treatment. These patients are at high risk for becoming anemic and requiring blood transfusion during chemotherapy.

The value of supplemental erythropoietin in patients with cancer-related anemia is now being judged not only by its effects on the hemoglobin or hematocrit, but also by its influence on quality of life. Data from several large studies, both randomized placebo-controlled trials and community-based observational studies, indicate that correcting cancer-related anemia with recombinant human erythropoietin improves overall quality of life, as well as participation in physical activity, energy level, and psychosocial well-being.

Recently, Littlewood et al reported on a randomized, double-blind, placebo-controlled clinical trial of 375
patients with cancer-related anemia who were receiving nonplatinum chemotherapy for solid or nonmyeloid hematologic malignancies. Study participants had a hemoglobin level of 10.5 g/dL or below, or 12.0 g/dL or below in conjunction with a decrease of 1.5 g/dL or more with each cycle of chemotherapy. Patients were randomized to treatment with either epoetin alfa, 150 IU/kg to 300 IU/kg by subcutaneous injection 3 times per week for 12 to 24 weeks, or placebo. Compared with placebo, epoetin alfa significantly reduced the need for blood transfusion (P = .0057) and increased hemoglobin levels (P < .001). Equally important, all key measures of quality of life, including energy level, the ability to perform daily activities, and fatigue, were significantly better in patients treated with epoetin alfa (P < .01).

These data support an earlier analysis by Henry and Abels of 3 randomized, double-blind, placebo-controlled trials of recombinant erythropoietin for the treatment of anemia in a total of 413 patients with cancer. Those patients receiving chemotherapy were treated with epoetin alfa (150 U/kg subcutaneously) 3 times per week for 12 weeks. In patients who were not undergoing chemotherapy, the epoetin dose was 100 U/kg, and the duration of treatment was 8 weeks. In all cases, epoetin alfa produced a significantly greater increase in hematocrit compared with placebo (P < .004). When the results from these 2 chemotherapy trials were considered together, epoetin therapy was associated with a significant reduction in the need for blood transfusion after the first month of therapy (P ≤ .009). Quality of life improved significantly among patients who responded to epoetin therapy with at least a 6–percentage point increase in hematocrit (P < .05).

Community-based studies have also demonstrated the value of treating cancer-related anemia with epoetin alfa. Gabrilove et al prospectively evaluated data from 3012 patients with nonmyeloid malignancies undergoing chemotherapy at 600 community-based oncology practices in the United States. In this non-randomized open-label study, patients received epoetin alfa 40 000 U once weekly, or 60 000 U once weekly after 4 weeks if the hemoglobin response was inadequate. After 16 weeks of therapy, epoetin alfa produced a significantly greater increase in hemoglobin levels compared with placebo (P < .004). When the results from these 2 chemotherapy trials were considered together, epoetin therapy was associated with a significant reduction in the need for blood transfusion after the first month of therapy (P ≤ .009). Quality of life improved significantly among patients who responded to epoetin therapy with at least a 6–percentage point increase in hematocrit (P < .05).

More recently, Glaspy et al retrospectively analyzed data from these latter 2 community-based studies to determine if the selection of chemotherapeutic agent influenced the effectiveness of epoetin alfa. Data from 4298 of the 4712 patients were included in the study. The results showed that epoetin alfa therapy was associated with a significant increase in mean hematocrit levels and a significant decrease in the need for blood transfusion (P < .001). Patients also reported significantly increased energy level, activity level, and overall quality of life. These improvements correlated with the magnitude of the hemoglobin increase and were independent of tumor response. Demetri et al reported similar results in a study of 2370 patients with nonmyeloid malignancies who were being treated with chemotherapy in 621 community-based oncology practices in the United States. Epoetin alfa therapy was associated with an improvement in quality of life that not only correlated significantly with hemoglobin levels but also was independent of tumor response.

![Figure. Effects of Erythropoietin on Quality of Life](image)

Results of linear analog scale assessment scores. Scores are based on a scale of 1–100 mm. P < .001 for all.
analysis; of these patients, 1601 received a platinum-based chemotherapeutic agent and 2697 received a nonplatinum-based agent. The investigators found that in patients receiving erythropoietin, hemoglobin levels increased from baseline to final evaluation by a mean of 1.6 g/dL to 2.0 g/dL; the need for blood transfusion was reduced after 2 months, and quality of life improved by 20% to 43%. All of these changes were statistically significant and none was influenced by the type of chemotherapy the patient received.

Despite their importance in defining the value of erythropoietin therapy, quality-of-life analyses have suffered from methodological weaknesses. Recently, researchers studying outcomes have scrutinized the available data and, in some cases, found it wanting.

Bottomley et al, of the Quality-of-Life Unit of the European Organization for Research and Treatment of Cancer Data Center in Brussels, conducted a critical review of 13 trials of erythropoietin therapy in patients with cancer.25 They concluded that, although evidence showed that erythropoietin therapy had positive effects on quality of life, methodological limitations inherent in most of the studies hampered interpretation of the data. They called for new studies of more robust design to evaluate the quality-of-life benefits of erythropoietin therapy.

Seidenfeld et al, of the Blue Cross and Blue Shield Association Technology Evaluation Center, conducted a meta-analysis of 22 controlled clinical trials of varying quality (all were randomized, but not all were placebo controlled).26 The researchers concluded that erythropoietin therapy reduced the need for blood transfusion in patients with cancer-related anemia but that lower-quality trials overestimated the magnitude of this benefit compared with higher-quality trials. Only those studies whose participants had mean baseline hemoglobin concentrations of 10 g/dL or below reported statistically significant effects of epoetin treatment on quality of life. The evidence was insufficient to determine if initiating erythropoietin therapy earlier spared more patients from blood transfusion or resulted in better quality of life.

Yount et al, from the Center on Outcomes, Research, and Education at Evanston Northwestern Healthcare and Northwestern University, Evanston, Illinois, reviewed literature published between November 2000 and October 2001.27 The investigators concluded the evidence supported a positive effect of epoetin therapy on quality of life in patients with cancer; however, they also called for future studies with more rigorous methodological design to clarify and strengthen the association.

**Darbepoetin Alfa**

The standard dosing schedule for recombinant erythropoietin has been 3 times per week. However, Gabrilove et al recently reported that once-weekly epoetin alfa therapy appeared to be similarly effective in increasing hemoglobin levels, decreasing blood transfusion requirements, and improving quality of life in patients with cancer-related anemia.21 This was a major advance with respect to patient convenience, and newer analogs of recombinant erythropoietin, such as darbepoetin alfa, may offer even more convenient dosing options for patients with cancer-related anemia.

Darbepoetin alfa's effects are identical to those of native erythropoietin. Darbepoetin, however, differs from native or recombinant erythropoietin in having 2 additional N-linked carbohydrate side chains with additional sialic acid residues. Darbepoetin's structural differences provide additional metabolic stability in vivo and markedly extend its half-life.6,28 In patients with renal failure, darbepoetin alfa has a half-life of approximately 26 hours following intravenous administration—an estimated 3-fold increase compared with epoetin alfa.6,28 Subcutaneous administration has been shown to further extend the half-life of darbepoetin to 49 hours in patients with renal failure. In a study of patients with nonmyeloid cancers undergoing multiple cycles of chemotherapy, subcutaneous darbepoetin was found to have a half-life exceeding 40 hours.6

Data are now available from small studies investigating the safety and effectiveness of darbepoetin administered once per week to treat cancer-related anemia in patients with solid tumors who are and who are not undergoing chemotherapy.6,29,30 These studies show that darbepoetin produced a dose-dependent increase in hemoglobin levels. In one study focusing on patients with nonmyeloid malignancies who were not undergoing chemotherapy, the proportion of patients responding to darbepoetin ranged from 61% in the group treated with 1.0 mcg/kg per week to 83% in the group treated with 4.5 mcg/kg per week.29

Darbepoetin's prolonged half-life and greater in vivo biological activity present the opportunity for even less frequent dosing. Preliminary evidence from studies investigating the use of higher doses delivered...
at 2-week or 3-week intervals suggests that an equivalent proportion of patients achieve the target hemoglobin response when darbepoetin is administered every 2 weeks or 3 weeks compared with weekly dosing. Evidence also shows that darbepoetin alfa administered once every 2 weeks produces a hemoglobin response equivalent in both magnitude and speed to that achieved with once-weekly dosing of epoetin alfa; response rates of approximately 54% have been reported with 2-week dosing regimens and 50% with 3-week dosing regimens.

Other approaches being evaluated include a further reduction in dosing frequency to every 4 weeks and a new 2-part regimen that combines loading and maintenance phases. In the loading phase, darbepoetin is administered weekly until the target hemoglobin response is achieved, then every 2 weeks or 3 weeks thereafter. At the 2002 meeting of the American Society of Clinical Oncology, Glaspy et al reported the results of a clinical study of 122 patients with solid tumors and a hemoglobin level of 11 g/dL or below who received darbepoetin alfa 4.5 mcg/kg weekly for 4 weeks, followed by 3.0 mcg/kg every 2 weeks. The researchers observed a rapid and sustained hemoglobin response and relief of fatigue in patients receiving this front-loaded approach to therapy. (See Poster Presentations in this issue for details.)

**Conclusion**

Clinical understanding of the consequences of cancer-related anemia has been broadened to include its negative impact on quality of life, most often because of fatigue. Fortunately, these negative effects can be corrected with recombinant human erythropoietin and its newer analogs. Future studies should define the most efficient means of exploiting these important biologic agents.

**References**


