

Cancer-related anemia

When dollars and cents— not science—dictate treatment

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In an increasingly cost-conscious clinical environment, practitioners may be reluctant to prescribe erythropoietic agents for patients with mild anemia unless reimbursement guidelines are changed. In our institution, reimbursement requirements force us to wait for hemoglobin levels to fall to < 10 g/dL before initiating treatment with this mainstay of anemia therapy. These requirements often result in delayed treatment, which is clearly unacceptable, particularly when compared with reimbursement regulations in neighboring states. This article addresses the appropriate timing of intervention with erythropoietic therapy, the optimization of schedule and dose, and their impact on overall quality of life.

Erythropoietin is a glycoprotein hormone that participates in regulating erythropoiesis. It is produced primarily in the kidneys in response to hypoxia and acts by binding to its receptor with consequent activation of the intracellular signal transduction pathways.¹ Recombinant human erythropoietin (epoetin alfa [Epoen, Procrit]) is used to treat anemia of various etiologies. It is a glycoprotein manufactured by recombinant DNA technology with an amino acid sequence identical to isolated natural erythropoietin.² Clinical trials have shown that epoetin alfa increases the hemoglobin concentration in patients with cancer-related anemia. The National Comprehensive Cancer Network (NCCN)³ and the American Society of Clinical Oncology (ASCO) in conjunction with the American Society of Hematology (ASH)⁴ have developed evidence-based clinical practice guidelines for the use of epoetin alfa in patients with cancer.

Cancer-related anemia

Anemia is now recognized as a common occurrence in patients with cancer. The National Cancer Institute considers normal hemoglobin levels as 14–18 g/dL for men and 12–16 g/dL for women. Adult males tend to have slightly higher hemoglobin levels due to the effects of circulating androgen. This hormone enhances the secretion of erythropoietin from the kidneys and causes precursor cells to be more responsive to it. Severity of anemia is usually characterized as⁵:

- mild (hemoglobin level: 10 g/dL—normal limit);
- moderate (hemoglobin level: 8–10 g/dL);
- severe (hemoglobin level: 6.5–7.9 g/dL);
- life-threatening (< 6.5 g/dL).

There is a relatively high incidence of mild to moderate anemia, particularly among those receiving myelosuppressive chemotherapy, where the incidence can be as high as 50%–67% of patients.⁵ The European Cancer Anemia Survey (ECAS), conducted in 24 countries, enrolled 15,367 cancer patients. Study authors reported that, particularly in those patients receiving chemotherapy, anemia occurred frequently in both solid tumor and hematologic malignancy patients (74% and 78%, respectively) during the course of their disease.⁶ Overall, 66% of patients with solid tumors and 72% of patients with hematologic malignancies were anemic (hemoglobin level < 12 g/dL) at some point during the 6-month survey.⁶

A number of factors may contribute to the development of anemia in cancer patients: bone marrow infiltration by tumor cells, myelosuppressive effects of chemotherapy or radiotherapy, hemolysis, bleeding, nutritional deficiencies, low endogenous erythropoietin levels, and the anemia of chronic disease, or a combination of these. Anemia, being

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a multisymptom syndrome, adversely affects patients with cancer in several ways by its effects on their functional capacity, with fatigue being one of the cardinal side effects. In a survey performed by Curt et al,⁷ cancer survivors reported it to be the side effect that affected them the most after completion of chemotherapy, with 91% of the 379 patients saying that it prevented them from leading a normal life. Similarly, in a Canadian survey of 913 cancer patients who had received treatment within the previous 2 years, 78% reported that fatigue was the most common and most distressful symptom.⁸

“...anemia may lead to poor tolerance of chemotherapy and radiation therapy and decreased locoregional tumor control.”

Fatigue can have a significant negative effect on quality of life in cancer patients. Studies also have suggested that anemia in cancer patients may lead to poor tolerance of chemotherapy and radiation therapy and decreased locoregional tumor control.⁹ Evidence from current data indicates that aggressive treatment of anemia is an important aspect of cancer therapy.

In spite of these findings and the high incidence of anemia in patients with cancer, anemia remains undertreated across all hemoglobin levels. A survey of US physicians showed that only 35% of patients with hemoglobin levels < 10 g/dL and 15% of patients with hemoglobin levels between 10 and 12 g/dL received erythropoietic therapy.¹⁰ Cancer-related anemia also is undertreated in Europe: The ECAS, mentioned above, showed that only 47% of patients with hematologic malignancies and 36% of those with solid tumors received treatment for their anemia, and the treatment was initiated primarily at low hemoglobin levels (mean, 8.8

g/dL for patients with hematologic malignancies and 9.6 g/dL for those with solid tumors).⁶

In the 1990s, epoetin alfa was approved by the US Food and Drug Administration (FDA) and since then has been widely used for the treatment of cancer-related anemia. Although red-blood-cell transfusion is also a treatment option and continues to be used, especially for treatment of symptomatic acute anemia, its use is not without problems. Its limitations are short-term resolution of symptoms, risk of transmission of infections, limited availability of adequate blood supplies, and conflict with religious beliefs of some patients.

However, before initiating therapy with an erythropoietic agent, other causes of anemia in patients with cancer should be investigated and corrected if possible. It is advisable to conduct an appropriate history, including a thorough drug-exposure history, and physical examination. Relevant diagnostic testing aimed at identifying other causes of anemia should be initiated, as indicated. This may include careful review of the peripheral blood smear (and, in some cases, bone marrow examination), a complete blood count with indices, reticulocyte count, iron studies, ferritin level, serum B₁₂ and folate levels, serum creatinine level, serum lactate dehydrogenase level, fractionated bilirubin level, and testing stools for occult blood.^{3,4} These tests should be followed by appropriate treatment of any cause identified during the evaluation.³

The effects of epoetin alfa

Data from several large, multicenter, clinical trials have shown that epoetin alfa increases hemoglobin levels, decreases transfusion requirements, and improves quality of life in anemic cancer patients receiving chemotherapy.¹¹⁻¹⁶ In a randomized, double-blind, placebo-controlled clinical trial by Littlewood et al,¹¹ 375 patients with solid or nonmyeloid hema-

tologic malignancies and hemoglobin levels of ≤ 10.5 g/dL, or > 10.5 g/dL but ≤ 12.0 g/dL after a hemoglobin decrease of ≥ 1.5 g/dL per cycle since starting nonplatinum chemotherapy, were randomized 2:1 to receive epoetin alfa (150–300 U/kg) or placebo 3 times per week for 12–24 weeks. Treatment of anemia with epoetin alfa, compared with placebo, significantly decreased transfusion requirements (24.7% vs 39.5%, respectively, *P* < 0.0057) and increased hemoglobin levels (2.2 g/dL vs 0.5 g/dL, respectively, *P* < 0.001). The study also showed improvement in all primary cancer- and anemia-specific quality-of-life domains.¹¹

In another randomized, placebo-controlled trial by Abels et al,¹³ involving 413 patients, quality-of-life parameters showed significant improvement in epoetin-treated patients whose hematocrit increased by ≥ 6 percentage points. Similar benefits of epoetin alfa therapy on hemoglobin levels and quality of life have also been seen in cancer patients not receiving chemotherapy.^{13,17} Further analyses have revealed that improvements in quality-of-life parameters appear to be independent of response of the tumor to chemotherapy.^{12,15}

Response rates to epoetin alfa therapy

Epoetin alfa increases hemoglobin levels in approximately two thirds of patients treated for chemotherapy-induced anemia. In a study by Gabrielove et al,¹⁴ the overall response rate to epoetin therapy was 68%. Of the patients responding to epoetin alfa, approximately 45%–49% had an increase in hemoglobin level of ≥ 1.0 g/dL within the first 4 weeks of therapy,^{11,14,18} and approximately 67% experienced an increase in hemoglobin level ≥ 2.0 g/dL at 8 weeks.¹⁸ Several pretreatment and early treatment factors (eg, serum erythropoietin level, hemoglobin level, serum ferritin, serum transferrin saturation,

type of chemotherapy, and bone marrow involvement) have been looked at to predict the response to epoetin alfa therapy. Review of these possible predictors of response to epoetin alfa found no clinically useful pre- or early-treatment measurement capable of predicting response.^{19,20}

Clinical practice guidelines

The ASCO/ASH guidelines are based on data included in a report prepared by the Blue Cross Blue/Shield Association Technology Evaluation Center. The panel reviewed and summarized many clinical studies involving patients with cancer-related anemia and provided recommendations for the use of recombinant erythropoietin in patients with cancer. Briefly, the ASCO/ASH guidelines recommend the use of recombinant erythropoietin in patients with chemotherapy-associated anemia when the hemoglobin level is ≤ 10.0 g/dL, with the decision to treat less severe anemia (hemoglobin level > 10.0 g/dL but < 12.0 g/dL) to be determined by the clinical circumstances.⁴

Guidelines which were published by the NCCN also recommend the use of erythropoietic therapy for cancer-related anemia but suggest intervention for hemoglobin levels ≤ 11.0 g/dL.³ It is important to check the baseline iron status for iron deficiency and to routinely monitor it thereafter. NCCN guidelines suggest iron supplementation, if indicated (ferritin level < 100 ng/mL; transferrin saturation $< 20\%$).³

Dosing of epoetin alfa

Historic data comparisons have shown that a once-a-week dose schedule of epoetin alfa is as effective as the FDA-approved thrice-weekly (TIW) regimen in terms of increasing hemoglobin levels and decreasing transfusion requirements.^{14,18,21,22}

Commonly used dosing schedules (given by subcutaneous injection) are:

■ **TIW regimen:** Start treatment with epoetin alfa 10,000 U TIW (or 150 U/kg TIW). Consider increasing the dose to 20,000 U TIW (or 300 U/kg) if a response (hemoglobin level increase by ≥ 1 g/dL) is not seen after 4–8 weeks of therapy.

■ **Weekly (QW) regimen:** Start treatment with epoetin alfa 40,000 U QW. Consider increasing the dose to 60,000 U QW if a response (hemoglobin level increase by ≥ 1 g/dL) is not seen after 4–8 weeks of therapy. This schedule is uniformly used at our own institution.

Dosages should be titrated to maintain hemoglobin levels at or near 12 g/dL. NCCN guidelines recommend reducing the dose of epoetin alfa by 25% if the hemoglobin concentration increases by more than 1 g/dL in a 2-week period.³ Further, the guidelines recommend holding erythropoietic therapy if the hemoglobin level exceeds 12 g/dL and then reinitiating therapy (at a 25% lower dose than was used previously) when the hemoglobin concentration falls below 12 g/dL.³

In the absence of a hemoglobin response (ie, a less than 1–2 g/dL rise in hemoglobin level), even with the dose escalation, consider discontinuing epoetin treatment, as it is unlikely that the patient will respond to further treatment. These patients should be investigated for tumor progression, bone marrow involvement, or iron deficiency.⁴

Alternative dosing regimens of epoetin alfa are being investigated. Encouraging results were seen in a pilot study performed by Patton et al²³ in anemic cancer patients receiving chemotherapy, evaluating the response rate of epoetin alfa (60,000 U QW) until the hemoglobin level was clinically stable (ie, hemoglobin level increase ≥ 2.0 g/dL) followed by a maintenance dose of 120,000 U every 3 weeks. Further studies will help to identify the most effective and convenient dosing schedule that can offer the greatest flexibility.

Impact of epoetin alfa on survival

Whether epoetin alfa therapy has any effect on survival of cancer patients is less clear. In the study by Littlewood et al, described above, there was a trend toward prolonged overall survival favoring epoetin alfa, compared with placebo, but the protocol was not powered to assess this parameter as an endpoint and did not control for variables that could influence survival.¹¹

A study by Glaser et al²⁴ included patients receiving chemoradiation for squamous cell carcinoma of the oral cavity and oropharynx. This study showed higher response and survival

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rates in patients whose pretreatment hemoglobin level was ≥ 14.5 g/dL and also in patients whose pretreatment hemoglobin level was < 14.5 g/dL but who were treated with epoetin alfa, compared with patients with prechemoradiation hemoglobin levels < 14.5 g/dL who did not receive epoetin alfa. Some studies have demonstrated an association between hemoglobin levels and survival^{25,26} and that the hemoglobin concentration may be an independent prognostic factor for treatment outcomes.²⁷

However, two recent studies have shown conflicting results. In a multicenter, double-blind, randomized, placebo-controlled trial by Henke et al,²⁸ a total of 351 patients (hemoglobin level < 12 g/dL in women and < 13 g/dL in men) with head and neck carcinoma receiving radiotherapy were assigned to epoetin beta 300 IU/kg TIW ($n = 180$) or subcutaneous placebo ($n = 171$), from 10 to 14 days before irradiation and continuing throughout

radiotherapy. Even though epoetin beta improved hemoglobin concentrations (in 82% of patients), locoregional disease progression-free survival was found to be poorer with epoetin beta than with placebo (adjusted relative risk, 1.62; $P = 0.0008$).

In August 2003, a breast cancer trial with epoetin alfa was terminated early when patients on epoetin were found to have a higher death rate than those taking placebo.²⁹ In this randomized, double-blind, placebo-controlled study by Leyland-Jones,²⁹ the aim was to assess the effect of 12 months of treatment with epoetin alfa on survival in 939 patients receiving first-line chemotherapy for metastatic breast cancer. An analysis of survival rates at 12 months showed a statistically significant difference ($P = 0.0117$) between patients in the placebo treatment group (76%) and those in the group given epoetin alfa (70%).²⁹ The results of this trial must be interpreted with caution, however, due to concerns raised regarding po-

darbepoetin alfa also increases hemoglobin levels and decreases transfusion requirements,³⁰ and these responses appear to be similar to those seen with epoetin alfa.³¹⁻³³

In a pooled analysis of three darbepoetin alfa clinical trials reviewed by Mirtsching et al,³¹ patients (with hemoglobin levels ≤ 11 g/dL) received either darbepoetin alfa at 3.0 $\mu\text{g}/\text{kg}$ every 2 weeks ($n = 260$) or recombinant human erythropoietin given as 40,000 U QW or 150 U/kg TIW ($n = 115$). Hematopoietic responses in both groups were similar (71% vs 71%). No clinically significant differences between the fixed doses and weight-based doses of darbepoetin alfa were observed in a recent randomized phase II study.³⁴

Darbepoetin alfa has been demonstrated to be safe and effective in alleviating cancer-related anemia at dose intervals of once every 1 or 2 weeks. Various initial doses, given by subcutaneous injection, that have been evaluated in cancer patients are 2.25 $\mu\text{g}/\text{kg}$ QW, 3.0 $\mu\text{g}/\text{kg}$ every 2 weeks, or a fixed dose of 200 μg every 2 weeks. If there is no response, these initial doses can be titrated up to 4.5 $\mu\text{g}/\text{kg}$ QW, 5.0 $\mu\text{g}/\text{kg}$ every 2 weeks, or a fixed dose of 300 $\mu\text{g}/\text{kg}$ every 2 weeks, respectively.

New regimens are also being evaluated in various clinical trials. A recent double-blind, placebo-controlled, randomized study by Kotasek et al³⁵ showed that darbepoetin alfa administered every 3 weeks has a tolerable safety profile and effectively ameliorates chemotherapy-related anemia. In a phase II trial, Hesketh et al³⁴ reported encouraging results by using a front-loading darbepoetin dose of 4.5 $\mu\text{g}/\text{kg}$ (or a fixed dose of 325 μg) given by subcutaneous injection once a week until patients achieved a hemoglobin concentration of ≥ 12.0 g/dL and then maintaining them on a 4.5 $\mu\text{g}/\text{kg}$ (or a fixed dose of 325 μg) subcutaneous dose given every 3 weeks.

Reimbursement

Medicare reimbursement for epoetin alfa depends on the geographic jurisdiction. Medicare has listed various indications and limitations of coverage, including ICD-9 codes that support reimbursement. For example, in Oklahoma, Louisiana, Arkansas, Missouri, and New Mexico, epoetin alfa and darbepoetin alfa are indicated for the treatment of symptomatic anemia for patients with nonmyeloid malignancies with hemoglobin levels of < 10 g/dL (<http://www.oknmmedicare.com/provider/medpol/polmanindex1.asp>).³⁶ Erythropoietic therapy is also indicated to decrease the need for transfusions in patients who have anemia and have received myelosuppressive therapy.³⁶ Reimbursement for epoetin alfa will be denied if it is used to prevent anemia or the use of transfusion, and its use will not be covered to treat other types of anemia apart from the approved indications.³⁶ Self-administration is not covered.³⁶

There are also various documentation requirements. Reimbursement is as per every 1,000 U of epoetin alfa used, and Medicare usually reimburses 80% of the charges. It is recommended that physicians review the guidelines of their own jurisdiction for further details, since indications and other regulations differ from state to state.

Given the findings of some studies in recent years that have shown beneficial effects of early intervention with epoetin alfa,³⁷⁻³⁹ it is our opinion that current guidelines for reimbursement based on the level of hemoglobin need to be revised. Littlewood et al¹¹ showed that anemic cancer patients with higher hemoglobin levels (> 10.5 g/dL but ≤ 12.0 g/dL) at the initiation of epoetin alfa therapy had lower transfusion rates (7.1% vs 28.2%), achieved a higher peak hemoglobin level (13.8 g/dL vs 12.7 g/dL), and reached the target hemoglobin level of ≥ 12 g/dL more quick-

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tential prognostic factor imbalances between the two treatment groups.

Many of these studies had serious design problems and the results cannot be considered conclusive, so further investigation of the impact of erythropoietic therapy on survival is needed before drawing any definite conclusion. Such studies are under way.

Darbepoetin alfa

Darbepoetin alfa (Aranesp) is the second erythropoietic agent to be approved for the treatment of chemotherapy-related anemia. It is a hyperglycosylated analog of recombinant human erythropoietin with the same mechanism of action as erythropoietin but with a longer terminal half-life. Clinical trials have shown that

ly (4 weeks vs 12 weeks). In addition, fewer patients required doubling of their starting dosage (15% vs 25%) than patients who received treatment when their hemoglobin levels fell to ≤ 10.5 g/dL.³⁷

Straus et al³⁸ conducted a randomized, open-label, multicenter trial comparing the effectiveness of epoetin alfa treatment administered to two groups of chemotherapy patients: an "early group" with mild anemia (hemoglobin level ≥ 10 mg/dL and ≤ 12 g/dL) and a "late group" with moderate anemia (hemoglobin level < 9.0 g/dL). The early group had more patients with a hematologic response (70.4% vs 25.4%) and required fewer transfusions (17.8 vs 26.1%). Hemoglobin increases also significantly correlated with quality-of-life changes. Further, the early group had significantly greater reductions than the late group in number of days spent in bed (52.2% vs 3.1%), with a trend toward reductions in overnight hospital stays, clinic visits, and calls to physicians.³⁸

Two additional studies evaluated the effects of initiating epoetin alfa treatment concurrently with chemotherapy, regardless of baseline hemoglobin level.^{39,40} Richart et al³⁹ reported that patients who received epoetin alfa from the initiation of chemotherapy were able to maintain a higher hemoglobin level and experienced less fatigue, compared with those who received epoetin alfa when their hemoglobin level was < 10 g/dL; there was no difference in transfusion requirements. In an open-label, nonrandomized, multicenter, community-based study by Hudis et al,⁴⁰ once-weekly epoetin alfa therapy (at doses of 40,000 U) maintained hemoglobin levels, significantly improved quality of life compared with baseline, and was well tolerated.

Together, these findings suggest that epoetin alfa can maintain or improve hemoglobin levels and attenuate decreases in quality of life when administered early during—or even

prior to—the course of chemotherapy and/or to patients with mild to moderate anemia. Despite these data, in an increasingly cost-conscious clinical environment, practitioners may be reluctant to prescribe epoetin alfa for patients with mild anemia unless reimbursement guidelines are changed.

In our institution, reimbursement requirements force us to wait for patient hemoglobin levels to fall to < 10 g/dL before we can initiate therapy with either epoetin alfa or darbepoetin alfa. These requirements often result in delayed treatment (following multiple cycles of chemotherapy and with hemoglobin concentrations in the 10–12 g/dL range for many weeks) during chemotherapy administration. This is clearly unacceptable from both a physiologic and patient care viewpoint, particularly when compared with reimbursement regulations in neighboring states that allow administration for hemoglobin levels of < 12 g/dL. In our viewpoint, erythropoietic therapy should be considered for early or even prophylactic benefit in patients with any hemoglobin concentration that is less than normal who are about to be offered chemotherapy. We believe patients should then be kept on the lowest effective dose and schedule that maintain their hemoglobin level within the normal range. If additional data confirm the value of this approach, it would warrant changes in both the existing guidelines and reimbursement models.

Summary

Treatment of cancer-related anemia with erythropoietic agents leads to significant increases in hemoglobin levels and reductions in the need for blood transfusions, with resultant clinically significant improvements in quality of life. The impact of these changes on overall survival of treated patients needs to be further investigated. Additional alternate effective dosing regimens of epoetin alfa and

darbepoetin alfa continue to be under investigation, and further studies are warranted to evaluate prophylactic use of these agents in maintaining normal hemoglobin levels throughout chemotherapy administration. Recent evidence has indicated biologic effects of erythropoietin on a variety of non-erythroid cells, including those of the nervous system, where it might have a possible role in protecting against hypoxic injury. The potential benefits of epoetin alfa on improvement of mood and cognitive function in cancer patients are being explored, and results of these studies might provide useful insights.

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