

Anemia in Cancer: Update on Studies of Erythropoiesis-Stimulating Agents

Harold J. Burstein, MD, PhD

Management of anemia in cancer patients continues to be an important component of comprehensive cancer care. Cancer patients are at risk from anemia for several reasons. Marrow failure syndromes or marrow infiltration by tumor can directly cause suppression of red blood cell production. Chronic illness such as advanced cancer contributes to anemia of chronic disease. Patients with bleeding complications from tumors may be iron deficient, and functional iron deficiency is also common in patients with cancer. Lastly, patients receiving myelosuppressive chemotherapy also experience direct inhibition of normal erythropoiesis.

Ongoing clinical studies, clinician education programs, and direct-to-consumer marketing serve to raise awareness for the importance of managing anemia in cancer patients. Oncologists and patients continue to revise upward their expectations for quality of life during chemotherapy treatment. Commercially available erythropoiesis-stimulating agents (ESAs) have been shown to minimize chemotherapy-related anemia with clinically important consequences, including a lower risk of transfusion and improvements in health-related quality of life. For those reasons, strategies to optimize the use of erythropoietins in patients with cancer are the source of much ongoing investigation. The reports in this issue of *The Journal of Supportive Oncology* highlight clinical advances in the use of ESAs.

Clinical Findings

SCHEDULING

There continues to be substantial interest in different treatment schedules for ESAs. Two abstracts highlighted the use of extended dosing with long-acting darbepoetin alfa (Aranesp),

showing that every-2 or every-3-week therapy is comparable with weekly administration (Schwartzberg et al, page 22; Canon et al, page 26). The use of every-3-week darbepoetin alfa was also found to be effective in the treatment of cancer patients receiving chemotherapy for gastrointestinal tumors (Malik et al, page 26), a group of patients who often have substantial preexisting as well as treatment-induced anemia. According to a study by Henry et al (page 16), epoetin alfa (Procrit) can be used effectively at 40,000 U weekly or 80,000 U every 2 weeks, with comparable rates of rise in hemoglobin levels and reductions in the number of red blood cell transfusions between these two schedules.

MYELOYDYSPLASTIC SYNDROME

The use of ESAs for myelodysplastic syndrome (MDS) continues to be a fertile area of research. Gabrilove and colleagues (pages 14 and 26) demonstrated that in patients with low-risk MDS, administration of darbepoetin alfa on an every-3-week schedule could reduce anemia at 6-month and 1-year follow-ups. A pooled analysis comparing results from studies using either epoetin alfa or darbepoetin alfa as treatment for MDS-related anemia demonstrated comparable overall efficacy between these two strategies (Mundle et al; page 26).

CHEMOTHERAPY-INDUCED ANEMIA

Erythropoietic therapy remains an important component of supportive care for patients with chemotherapy-induced anemia. Among breast cancer patients receiving chemotherapy, earlier initiation of epoetin alfa when the hemoglobin level was in the 11–12 g/dL range, as opposed to the 10–11 g/dL range, predictably was associated with a lesser need for transfusion and interestingly was associated with decreased overall need for the ESA (Chang et al; page 26). This finding raises the possibility that there might be both clinical benefit and cost savings to early administration of erythropoietic drugs.

A meta-analysis of the use of epoetin alfa and darbepoetin alfa in randomized trials and large,

Dr. Burstein is Assistant Professor of Medicine, Harvard Medical School, and a medical oncologist in the Breast Oncology Center, Dana-Farber Cancer Institute, Boston, Massachusetts.

Correspondence to: Harold J. Burstein, MD, PhD, 44 Binney Street, Dana Building D1210, Boston, MA 02115; telephone: (617) 632-3800; fax: (617) 632-1930; e-mail: hburstein@partners.org

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Erythropoiesis-Stimulating Agents

open-label studies demonstrated that both agents are effective for lowering the need for transfusions in cancer patients receiving chemotherapy, with comparable levels of improvement in fatigue symptoms and no clinically important differences between the two agents (Ross et al; page 20). A cost analysis looked at maintenance of hemoglobin with ESAs in the target range of 11–12 g/dL in a series of patients entered onto a clinical registry for treatment (Chen et al; page 12). This study demonstrated modest advantages for epoetin alfa over darbepoetin alfa in maintaining hemoglobin levels in the target range and suggested a 16% overall lower cost with epoetin alfa therapy. If confirmed, this study raises the possibility that carefully performed cost analyses might be valuable for helping clinicians to select specific erythropoietic agents.

Patient Outcomes

One challenge in the field of supportive care is to quantify clinical outcomes in terms of patient experience. Toward that end, investigators proposed a new Functional Capacity Screening Tool, subsequently known as the Brief Functional Capacity Tool (BFCT), which is a short instrument for gauging meaningful changes in quality of life among cancer patients receiving erythropoietic therapy (Cella et al; page 10). Currently, this instrument is being assessed in larger trials and compared with instruments such as the Functional Assessment of Cancer Treatment–Fatigue scales and other surveys of daily function to see how the BFCT will measure up as a research tool.

Although the maintenance of hemoglobin levels clearly improves quality of life and lessens treatment-related fatigue, two potent findings from 2006 remind us that drug therapy is not the only element of health-related quality of life worthy of focus. A survey of over 1,500 cancer patients receiving chemotherapy for solid tumors reported a high incidence of fatigue, and many identified relief of fatigue as a major treatment goal (Henry et al; page 18). In addition, patients with fatigue symptoms frequently reported symptoms of depression and/or anxiety. It is not clear which comes first—does fatigue exacerbate psychosocial distress, or do patients with distress report more fatigue? In either effect, a thorough screening for psychosocial well-being and consideration of interventions beyond maintenance of hemoglobin levels clearly are important parts of the evaluation of cancer patients with fatigue.

Finally, in a provocative study of supportive care, investigators examined whether exercise paired with epoetin alfa might better alleviate symptoms of fatigue in patients with myeloma (Coleman et al; page 26). A cohort of over 100 patients was randomly assigned to receive usual standard care with epoetin alfa or the same with an intensive exercise program during the 15 weeks around an autologous stem cell transplant. Interestingly, patients in the exercise group had fewer red blood cell and platelet transfusions and fewer needed attempts at stem cell collection. If confirmed, this study would suggest that a non-pharmacologic exercise program, paired with erythropoietin support, could substantially improve hematologic endpoints in patients with profound marrow suppression from chemotherapy.

Concerns About Anemia Correction

However, it is possible that 2006 will ultimately be remembered as the year that limits began to emerge to the clinical improvements seen with ESAs. Two studies in patients with renal failure suggested that restoring physiologically normal hemoglobin levels was not clinically beneficial in patients not receiving dialysis. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial was designed to show that use of ESAs for anemia correction in patients with renal insufficiency would lower the incidence of cardiac events.¹ In fact, there was no reduction in cardiac risk for elevating hemoglobin levels to targets greater than 13 g/dL compared with the 10.5–11.5 g/dL range.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study of patients with renal insufficiency who did not need dialysis used epoetin alfa to raise hemoglobin levels to targets of 13.5 g/dL, and in these patients, the study actually demonstrated an increase in death, myocardial infarction, heart failure, and stroke compared with patients whose hemoglobin levels were maintained in the 11–12 g/dL range.² Based on these data, the US Food and Drug Administration issued a public health advisory³ for ESAs in patients with renal insufficiency, reinforcing the current goal of targeting hemoglobin levels to 10–12 g/dL.

The CREATE and CHOIR studies were not focused on patients with cancer; of course, in oncology practice, ESAs are widely used to correct chemotherapy-induced anemia. However, their role in patients who have cancer-related anemia but who

have not been receiving chemotherapy is not well established. A randomized phase II study evaluated darbepoetin alfa given on an every-4-week schedule against placebo among patients with anemia of cancer who did not receive chemotherapy and/or radiotherapy (Gordon et al; page 26). The study demonstrated that darbepoetin alfa could be used to improve hemoglobin levels and was more likely to elevate hemoglobin to levels greater than 13 g/dL than was a placebo. Investigators noted that 2.4% of patients receiving darbepoetin alfa developed deep vein thrombosis, pulmonary embolism, or stroke, compared with none in the placebo group.

In late 2006, Amgen, Inc., made a public statement⁴ about the Anemia of Cancer phase III trial. This randomized, double-blind, placebo-controlled study looked at anemic cancer patients (hemoglobin levels < 11 g/dL) who were not receiving chemotherapy treatment. Through 16 weeks of follow-up, there was no difference in the incidence of transfusion, but there was a significant increased risk of death among patients randomized to receive darbepoetin alfa instead of placebo. Survival follow up on these patients will continue for a minimum of two years.

Shortly thereafter, the US Food and Drug Administration (FDA) received preliminary reports of a similar study for patients with non-small cell lung cancer, randomized to epoetin alfa or placebo, with a goal of maintaining Hgb in the 12–14 g/dL range. In this trial median survival was shorter (68 days versus 131 days; $P = 0.04$) in the patients assigned to receive epoetin alfa. Finally, the preliminary results of the Danish Head and Neck Cancer Study group trial (DAHANCA 10), a randomized study of radiation therapy alone versus radiation therapy plus darbepoetin alfa, with a Hgb level goal of 14–15.5 g/dL, showed worse local-recurrence and overall survival for patients given the ESA.

In response to these data, the FDA issued further updates to clinicians⁵ and initiated a new boxed warning on ESAs. The warning reiterates that the goal of ESA therapy is to reduce the need for transfusions. The use of ESAs to raise Hgb to levels higher than 12 g/dL is not clinically beneficial and may be associated with an increased risk of mortality. As a corollary, patients should have frequent monitoring of Hgb during ESA treatment, and therapy should be held if Hgb rises to levels > 12 g/dL or if Hgb levels rise by more than 1 g/dL in any 2 week period. ESAs are indicated only for use in cancer patients receiving chemotherapy; cancer patients with ane-

mia not related to chemotherapy do not appear to benefit from ESAs. Clinicians and patients should be aware of these issues as they strive to achieve optimal use of these agents.

Conclusion

These experiences underscore the clinical importance of not offering unnecessary therapy in well-intentioned efforts at supportive care—a reminder of the classic medical nostrum *primum non nocere*. ESAs are valuable for maintaining quality of life in cancer patients with chemotherapy-induced anemia when used judiciously and when hemoglobin levels are carefully monitored to a range of 11–12 g/dL, as suggested by multiple guideline panels. Use of ESAs among patients with anemia of cancer, but not from chemotherapy, does not seem to be clinically valuable and may in fact be detrimental to patients. Similarly, there is no rationale aiming to restore “normal” hemoglobin levels greater than 13 g/dL in cancer patients, as such higher hemoglobin levels are not necessarily associated with improved quality of life or clinical outcomes.

Management of fatigue and anemia remains a clinical challenge for oncologists and patients. A remarkable outpouring of data exists to document the utility of ESAs at combating these problems. New strategies that build on the success of ESAs but address other aspects of fatigue and psychosocial function may be needed to further enhance the clinical experience of cancer patients, especially those receiving chemotherapy. This realization is likely to define a new era in supportive care.

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