ABSTRACT

Recent studies questioning the safety of erythropoiesis-stimulating agent (ESA) therapy and the resultant cautionary US Food and Drug Administration statements and Medicare reimbursement restrictions have impacted transfusion utilization patterns, both in the United States and internationally. This article explores various utilization studies (in Europe, Canada, and in the United States) relating to the complex relationship between ESA regulatory and reimbursement actions, patterns of ESA use, and transfusion practices. In general, ESAs are used more frequently in the United States than in Europe, where the approach has been to administer ESAs or to transfuse red blood cells to patients with chemotherapy-induced anemia (CIA) who were symptomatic, rather than to those who would potentially require a transfusion in the future. However, the European Medicines Agency does note concerns regarding blood transfusions, with the limited supply of blood in Europe being the major issue. Also included in this article, are general trends in CIA management (both in Europe and in the United States) and factors to consider in identifying patients with CIA at risk for blood transfusion. (Adv Stud Med. 2008;8(10):352-356)

In the wake of ongoing controversies regarding the benefits, risks, and costs of alternative supportive care strategies for patients with cancer who have chemotherapy-induced anemia (CIA), the past few years have been tumultuous for healthcare providers, policy makers, patients with cancer, and scientists. These controversies have been played out in a wide range of forums in the United States, Europe, Australia, and Canada. With emerging safety concerns over the use of erythropoiesis-stimulating agents (ESAs) for CIA, critical blood supply questions arise. Specific questions include: How has the demand and utilization of blood products in the setting of CIA changed over the past year? Are there patient- and treatment-related characteristics that can help prospectively identify patients with CIA who are at risk for blood transfusions? Finally, when packed red blood cell (PRBC) transfusions are being considered for supportive care in patients with cancer who have CIA, what is the optimal transfusion trigger?

RBC TRANSFUSIONS IN PATIENTS WITH CIA: UPDATED INTERNATIONAL PERSPECTIVES

Over the years in the United States, ESAs have been used in patients with CIA to a far greater extent than in Europe, Canada, and Australia. However, in the past year, utilization patterns and recommendations relating to the use of transfusions in the treatment of CIA have changed markedly in several countries. These changes are outlined in the following sections.

EUROPE

Conducted in 2001, the European Cancer Anemia Survey was a prospective observational study that evaluated the prevalence, incidence, and treatment of anemia in patients with cancer from 24 countries. Patients (n = 15 367) were evaluated for up to 6 months. Prevalence of anemia at enrollment was 39.3% (hemoglobin [Hb] <10 g/dL, 10%) and 67% during the sur-
vey (Hb <10 g/dL, 39.3%), and incidence of anemia was 53.7% (Hb <10 g/dL, 15.2%). Anemia was treated in 38.9% of patients (ESAs, 17.4%; transfusion, 14.9%; and iron, 6.5%), and the mean Hb level for initiating anemia treatment was 9.7 g/dL. Most patients who were not treated (47.2%) had Hb levels between 10 and 11.9 g/dL; 12.9% who were not treated had Hb levels between 8 g/dL and 9.9 g/dL, and 0.9% had Hb levels lower than 8 g/dL. Patients with anemia who had breast cancer were least likely to receive anemia treatment (73.8%).

In 2007, the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use and its Pharmacovigilance Working Party recommended that labels indicate that ESAs should be used for treatment of symptomatic anemia from chemotherapy or chronic kidney disease, with target Hb ranges of 10 to 12 g/dL. In June 2008, the EMEA Committee recommended that, for patients with cancer who had reasonably long life expectancies, the benefits of ESAs do not outweigh tumor progression/mortality risks and for these patients, transfusions should be used to correct CIA. For other patients with cancer who had CIA, the committee recommended that the decision to prescribe ESAs versus RBC transfusions should be based on benefit-risk assessments of tumor type and stage, anemia severity, life expectancy, and patient preferences.

**Canada**

In April 2007, Health Canada issued a letter to healthcare professionals and to the public outlining recent safety concerns relating to the use of ESAs in the oncology setting. The notification stated that ESAs should no longer be used in patients with non-myeloid malignancies or patients with cancer not receiving radiation or chemotherapy, and that serious cardiovascular adverse events have been observed when Hb is targeted to 12 g/dL or greater. In recognition of concerns regarding blood safety, the most recent (2007) Canadian cancer chemotherapy guidelines supported ESAs (rather than blood transfusions) as a supportive care treatment for patients with cancer who have CIA. Updated guidelines are expected soon, with revisions that will take into consideration the safety concerns for ESAs that have been disseminated throughout late 2007 and into 2008.

**United States**

Erythropoiesis-stimulating agent labels were revised several times in 2007 and 2008. In March 2007, ESA manufacturers added Black Box warnings describing thromboembolic, cardiovascular, and mortality risks associated with ESA administration targeted to Hb levels greater than 12 g/dL. Physicians were advised to use the lowest ESA dosages possible to avoid transfusions. The November 2007 revised Black Box warnings indicate that, in several trials of ESA-treated patients with cancer, shortened survival occurred with ESA administration targeted to Hb levels greater than 12 g/dL; shortened time to tumor progression occurred with ESAs administered to patients with advanced head and neck cancer receiving radiation therapy; shortened survival and increased deaths from disease progression occurred among patients with metastatic breast cancer receiving chemotherapy; and mortality risks developed in patients with cancer not receiving cancer therapy. Additionally, revised ESA labels indicated that 2 trials identified cancer progression and mortality risks among patients with lymphoid and non–small-cell lung cancer receiving ESAs targeted to Hb levels greater than 12 g/dL. The Black Box warning also indicated that mortality and cancer progression risks were not excluded with ESAs targeted to Hb levels lower than 12 g/dL.

In March 2008, the US Food and Drug Administration (FDA) Oncologic Drug Advisory Committee recommended that revised labels warn against administering ESAs to patients with cancer receiving potentially curative treatments or to those with head and neck or metastatic breast cancer. In July 2008, further revisions to the product labels state that, among patients with cancer who have CIA, ESAs should not be administered until Hb levels are lower than 10 g/dL and that ESAs should not be administered if chemotherapy is being given for curative intent. Also, product labels will no longer state that it is safe to continue ESA treatment for CIA until Hb levels reach 12 g/dL. Although ESA manufacturers and the US FDA agreed on most of the revisions for ESA product labels, the ESA manufacturers had requested that revised labels not indicate that Hb levels should be lower than 10 g/dL before ESAs are initiated and that revised labels should continue to indicate that 12 g/dL is the upper limit for discontinuing ESAs. In response, the US FDA ordered ESA manufacturers to change ESA product labels, representing the first time that the agency invoked its newly granted authority to order changes in product labels, rather than to negotiate these changes.
ministration (NCD), restricting ESA reimbursement to treatment of anemia secondary to chemotherapy for solid tumors, multiple myeloma, lymphoma, and chronic lymphocytic leukemia. The NCD limits ESA initiation to Hb levels lower than 10 g/dL, treatment duration to 8 weeks or less after chemotherapy ends, and target Hb levels of 10 g/dL. Following dissemination of the July 2008 product label revisions outlined above (which are generally consistent with the CMS NCD of 2007), it is unlikely that the CMS will further revise the NCD.

Four studies funded by ESA manufacturers addressed RBC transfusion rates before and after the NCD was passed in August 2007. Gilmore et al examined hematologic outcomes of anemia before and after implementation of the NCD and found that, following adoption of NCD guidelines, Medicare patients had lower mean Hb values and higher transfusion rates. The retrospective observational study analyzed 401 Medicare cancer chemotherapy patients who had received 2 or more ESA doses (pre-NCD: n = 243; post-NCD: n = 158) and reported Hb levels that were higher in the pre-NCD cohort compared to the post-NCD cohort at each measured time point (mean Hb, pre- vs post-NCD: baseline, 10.7 vs 9.7 g/dL; 4-week Hb, 11 vs 10.2 g/dL; 8-week Hb, 11.2 vs 10.3 g/dL). A greater proportion of patients required transfusion in the post-NCD cohort (pre-NCD 9.5% vs post-NCD 18.4%).

Two abstracts presented findings from the Dosing and Outcomes Study of Erythropoiesis-Stimulating Therapies Registry. This is a prospective observational registry collecting data on practice patterns and outcomes in 80 community clinics and hospital centers. In a study by Larholt et al, data were analyzed from 323 adult chemotherapy-treated oncology patients who had Hb concentrations lower than 10 g/dL prior to ESA administration and received 2 or more ESA doses. Transfusion rates varied according to mean achieved Hb levels (43% for Hb levels 9.1–10 g/dL, 23% for Hb levels 10.1–11 g/dL, and 19% for Hb levels 11.1–12 g/dL). In another study, Larholt et al evaluated ESA-treated patients with cancer who received care between December 2003 and November 2007, and found that a greater proportion of ESA-treated patients with cancer received a transfusion when baseline Hb levels were lower than 10 g/dL versus when baseline Hb levels were between 10 and 11 g/dL (31% vs 15%, P <.05).

Naeim et al evaluated use of RBC supportive medications and transfusions for Medicare-covered patients with cancer (n = 10 167 patients; 1444 were receiving active chemotherapy) who received care at the University of California, Los Angeles Medical System over a 12-month period, before and after passage of the NCD. Utilization was aggregated into 3 time periods: November 2006 to February 2007 (period 1, baseline), March 2007 to July 2007 (period 2, post-US FDA label changes), and August 2007 to October 2007 (period 3, post-NCD decision). Utilization of RBC transfusions per at-risk patient was 0.24 in period 1, 0.24 in period 2, and 0.28 in period 3. Utilization of ESAs per patient at risk was 0.42 in period 1, 0.2 in period 2 (P <.01), and 0.16 in period 3 (P <.05).

Among Medicare patients, there was an increase in the utilization of transfusions in at-risk patients during period 2 versus period 3 (0.31 vs 0.39; P = .05). Utilization of RBC transfusions and medications was significantly greater in Medicare patients compared to non-Medicare patients across all periods (P = .02). The study concluded that there has been an overall decrease in the use of RBC support medication in patients with cancer undergoing chemotherapy since the US FDA label change in May 2007. In Medicare patients, the use of transfusions increased during the period following the NCD decision in August 2007.

**GENERAL TRENDS IN USE OF TRANSFUSION IN PATIENTS WITH CIA**

In Europe, the United States, and Canada, the treatment approach for CIA has changed dramatically in the past few months. In Europe and Canada, transfusions are used more often than ESAs, although the specific changes vary among various countries. In Europe, where ESA use has always been fairly low, reported changes in actual usage of blood products are generally low, despite the changes in policy statements from the EMEA. A common approach has been to administer ESAs or blood transfusions to patients with CIA who were symptomatic, rather than to those who would potentially require a transfusion in the future. However, the EMEA does note concerns regarding transfusions, with the limited supply of blood in Europe being the major problem. Blood supply in the United States is also an issue, especially in the event of full reliance on transfusion as a treatment for CIA. To this point, a recent analysis indicated that approximately 474,000 additional units of PRBCs would be required to treat patients with CIA if ESA use was completely eliminated. Other potential transfu-
sion-related concerns include allo-immunization after a first blood transfusion, administration of incorrectly matched blood, and risks of introducing serious infections, such as hepatitis C or HIV (although donations are screened to minimize these risks). The immunosuppressive effects of transfusions could also potentially contribute to tumor progression among patients with cancer (see article by Lawrence Tim Goodnough, MD, and Aryeh Shander, MD, FCCM, FCCP).

In the United States, the impact of recent changes regarding the use of transfusions for CIA and revisions to ESA product labels have been more dramatic. As noted in American Society of Clinical Oncology (ASCO) presentations in May 2008, ESA use in the United States had decreased, whereas transfusion use had increased. These changes were initially in response to ESA package label changes and the CMS financing decision (both made in 2007), and are expected to continue in response to the ESA product label revisions in 2008. Overall, the synthesis of statements from the US FDA and CMS decisions generally suggest that regulatory and Medicare officials currently view transfusions as potentially less harmful in 2008 than in 1993 when ESAs were first approved for treatment of CIA. These agencies also view the benefits of ESAs as primarily related to reduced risks of transfusion. However, as noted in ASCO abstracts, recent safety notifications and CMS funding decisions will affect the blood supply.

Going forward, US randomized trials are needed to evaluate tumor progression, venous thromboembolism rates, and survival among patients with CIA who receive transfusions versus ESAs. Although trials of this type have been proposed by ESA manufacturers to the US FDA and to the CMS, decisions to initiate these studies have not been made. Patient recruitment for such trials would certainly be a challenge. In the interim, it is important to identify and monitor oncology patients who have certain risk factors that would predispose them to an increased risk of moderate-to-severe CIA, potentially necessitating transfusion.

IDENTIFYING PATIENTS WITH CIA AT RISK FOR BLOOD TRANSFUSION

Based on retrospective reviews, the incidence of anemia requiring RBC transfusions appears to be highest among patients with lymphomas, lung tumors, and gynecologic (ovarian) or genitourinary tumors.7 Platinum-based therapies, increasing number of chemotherapy cycles, and low prechemotherapy Hb levels are also associated with a particularly high incidence of anemia, placing patients at risk for blood transfusion.16 The Table includes selected single agents and regimens frequently associated with anemia for different types of cancer.18

In assessing patients for development of symptomatic anemia requiring transfusion, risk factors that should be considered include low Hb level, transfusion in the past 6 months, prior myelosuppressive therapy or radiotherapy to more than 20% of the skeleton, and myelosuppressive potential of current therapy (duration, schedule, and agents).16 Various comorbidities (eg, cardiac history, diabetes, and hypertension) should also be taken into account.

The 2008 National Comprehensive Cancer Network (NCCN) guidelines denote transfusion as the only option for patients receiving myelosuppressive chemotherapy who require immediate correction of anemia. However, the evidence for basing decisions on when exactly to transfuse oncology patients with...
anemia is scarce and, as previously discussed, there is wide variation in transfusion practice both internationally and within the United States.\textsuperscript{16} Hb levels (eg, 7–8 g/dL) have historically been used as a trigger for initiation of transfusion, but the updated NCCN guidelines now recommend that identification of patients receiving chemotherapy who require transfusion cannot be made strictly on whether the Hb level has reached a certain threshold. Instead, decisions should be based on an assessment of individual patient characteristics (eg, risk factors and symptoms), comorbidities (may limit patients’ ability to tolerate anemia), and clinical judgment.\textsuperscript{18}

**CONCLUSIONS**

The recent safety concerns related to the use of ESAs appear to have impacted worldwide management of CIA, particularly in regard to transfusion practices. In making therapeutic decisions for patients with CIA, it is important to consider notifications from ESA manufacturers, regulatory authorities, medical societies, emerging data, and patient-specific factors.

**REFERENCES**


