CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Describe the treatment options for cancer-related anemia
- Explain the risks found in meta-analyses that are associated with treatment with erythropoietin-stimulating agents
- Describe the components of the ESA REMS program used to ensure that the benefits of ESA continue to outweigh the risks

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Using ESAs in patients with cancer-related anemia

Sarah Wenger, PharmD; Lisa A. Thompson, PharmD, BCOP

STATEMENT OF NEED/PROGRAM OVERVIEW

Based on data regarding the risks associated with erythropoietin-stimulating agents (ESAs), the FDA recommended a Risk Evaluation Mitigation Strategy (REMS) program for these agents. Educating patients on the risks and benefits of ESAs is an important component of the REMS program. Oncology nurses are frequently charged with this task. As such, it is important they have a thorough understanding of the data leading to the FDA restrictions. The recommended population for these agents has also drastically changed as a result of these data. Nurses play an important role in ensuring that prescribed treatment plans are appropriate for a particular patient (eg, laboratory parameters are appropriate).

CE INFORMATION

Title: Using ESAs in patients with cancer-related anemia
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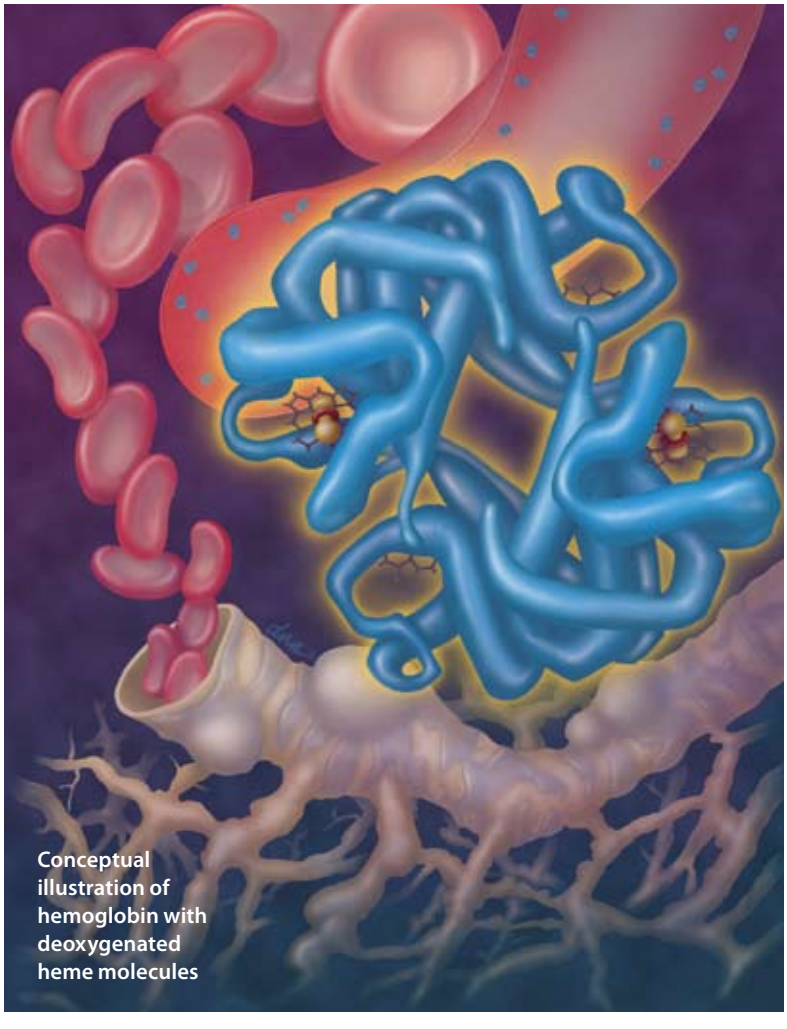
Using ESAs in patients with cancer-related anemia

Although the risks of erythropoietin-stimulating agents can outweigh the benefits, select patients may benefit from these drugs.



Conceptual illustration of hemoglobin with deoxygenated heme molecules

SARAH WENGER, PharmD;
LISA A. THOMPSON, PharmD, BCOP

The pathophysiology of cancer-related anemia is multifactorial.[1] In addition to other potential causes (eg, iron deficiency, gastric ulcer), the myelosuppressive effects of chemotherapy and radiation therapy may cause anemia to develop in patients with cancer. *Anemia* is defined as a deficiency in red blood cells (RBCs).

The presence and severity of anemia symptoms varies depending on the degree of anemia, the rapidity of onset, and the age and physiologic status of the patient. Mild to moderate anemia can cause symptoms such as headache, palpitations, dizziness, tachycardia, and shortness of breath.[2] Fatigue is commonly associated with anemia, and patients report it as the most disturbing symptom affecting their quality of life.[3] Anemia is also associated with worse prognosis in certain cancers.[4]

A full workup to determine the etiology of anemia should be performed, and any potential causes not related to cancer treatment should be

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treated. The goal of anemia treatment is to improve oxygen-carrying capacity, thereby increasing oxygenation to tissues. There is no evidence or strict recommendation for targeting specific hemoglobin (Hgb) values. The treatment options for chemotherapy-related anemia include blood transfusions and erythropoietin-stimulating agents (ESAs) in conjunction with iron supplementation as appropriate. Packed red blood cell (PRBC) transfusion is the fastest method for alleviating symptoms of anemia and increasing Hgb. However, ESAs and PRBC transfusions are not free of risks. Potential complications of PRBC transfusion include transmission of infectious disease, transfusion reactions, iron overload, overtransfusion, and increased morbidity. Treatment with ESAs may incur increased risk of venous thrombotic events (VTEs), decreased survival time, and shortened time to tumor progression.[5]

Currently available erythropoietin-stimulating agents indicated for the treatment of chemotherapy-induced anemia are epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp). Both epoetin alfa and darbepoetin alfa exert the same biologic effects as endogenous erythropoietin. Erythropoetin stimulates the division and differentiation of committed erythroid progenitor cells in the bone marrow, increasing the production and differentiation of red blood cells. The half-life of darbepoetin alfa is approximately three times longer than epoetin alfa, allowing a 3-week administration cycle. Comprehensive reviews have shown there is no difference in safety or efficacy between epoetin alfa and darbepoetin alfa.[6]

BENEFITS AND RISKS ASSOCIATED WITH ESAs

Randomized controlled trials and meta-analyses have consistently shown that ESAs reduce the number of RBC transfusions; however, data showing that ESA use reduces fatigue or improves quality of life are insufficient at this time.[6] Risks versus benefits of ESA use and PRBC transfusion should be individually determined for each patient.

Meta-analyses indicate that ESAs increase mortality, tumor progression, and thromboembolism.[6] In 2007, the FDA issued a black box warning for ESAs regarding the risk of increased mortality and tumor progression based on eight randomized studies that individually demonstrated a decrease in overall survival and/or decreased locoregional disease control in patients with advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers who received an ESA[7-14] (Table 1). Multiple meta-analyses evaluated mortality rates in cancer patients receiving ESAs after the FDA's initial warning. A large meta-analysis that included 53 studies involving 13,933 patients evaluated mortality in all cancer patients in the studies. Results of this meta-analysis showed ESAs increased mortality by a factor of 1.17 and worsened overall survival. A subgroup analysis evaluated data on patients receiving chemotherapy and showed mortality and overall survival outcomes were not statistically significant.[15] Similarly, a second meta-analysis evaluated survival among 13,611 patients with cancer who were treated in 51 phase III trials. These results showed an increased rate of mortality of 1.10 for patients who were treated with an erythropoietin-stimulating agent compared with those treated with a placebo.[16] These findings prompted the FDA mandated black box warning that "ESAs are not indicated for patients receiving myelosuppressive chemotherapy where the outcome is cure."[17-19]

Erythropoietin-stimulating agents have also been associated with an increased risk of VTE, which is due to multiple factors. The presence of the tumor increases baseline risk independently of ESA use. In addition, the classic risks of Virchow triad (circulatory stasis, hypercoagulability, and endothelial injury) associated with thrombosis are typically present in this patient population. However, the risk of thrombosis is heightened when ESAs are administered. This outcome has been evidenced in multiple meta-analyses with an estimated 1.57-fold increased risk of VTE in patients receiving ESAs.[16] Caution should be used when administering ESAs to patients who have additional risk factors for VTE (ie, previous history of VTE; prolonged periods of immobility; surgery; or receiving medications such as thalidomide, lenalidomide, corticosteroids, or doxorubicin).

ESAs were added to the Risk Evaluation and Mitigation Strategy program in 2010 and require all three components of the program.

The studies discussed above targeted higher Hgb levels than currently recommended, which is an important consideration. In these studies, ESA treatment was initiated when Hgb levels were lower than normal for a healthy adult (rather than the recommended less than 10 g/dL). Data do not support initiating ESAs at Hgb levels higher than 10 g/dL, and despite multiple studies on the agents, an optimal target Hgb level cannot be definitively determined.[1,6] Delaying treatment and targeting lower Hgb levels may minimize patient exposure to the risks associated with ESA use and ensure that patients who receive ESAs are those who benefited in studies.

GUIDELINES AND RECOMMENDATIONS FOR USE

The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology/American

TABLE 1. Key studies on ESA safety

Study	Tumor type	Baseline Hgb (g/dL)	Target Hgb (g/dL)	Adverse outcome(s) for treatment arm
Chemoradiation				
GOG-191[7] (n = 113)	Cervical	<12	>14	• Decreased 3-year PFS • Decreased OS • Reduced locoregional control
Chemotherapy				
BEST study[8] (n = 939)	Breast cancer	12.5	12-14	Decreased 12-month OS
PREPARE study[9] (n = 733)	Metastatic breast	Not available	12.5-13	Decreased 3-year RFS and OS
Study 20000161[10] (n = 344)	• Lymphoma • Myeloma	≤11	≥15 (M) ≥14 (W)	Decreased OS
No therapy/palliative radiotherapy				
Amgen 103[11] (n = 989)	Nonmyeloid cancer	≤11	12-13	Decreased OS
EPO-CAN-20[12] (n = 70)	NSCLC	Mean 10.3	12-14	Decreased OS
Radiotherapy				
DAHANCA 10[13] (n = 522)	Head and neck	≤14.5	>15.5	Decreased locoregional disease control
ENHANCE[14] (n = 354)	Head and neck	<13 (M) <12 (W)	≥15 (M) ≥14 (W)	• Decreased 5-year locoregional PFS • Decreased OS

Key: ESA, erythropoietin-stimulating agents; Hgb, hemoglobin; M, men; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; W, women.

Society of Hematology (ASCO/ASH) developed recommendations and guidelines for the ESA use in adult patients with cancer. Evidence-based guidelines recommend that ESAs be reserved for oncology patients undergoing myelosuppressive chemotherapy who have an Hgb level of less than 10 g/dL; in addition, ESAs should not be used until after their potential harms and benefits and a comparison of the potential harms of PRBC transfusions are discussed with the patient.[6]

Erythropoietin-stimulating agents are only indicated for treatment of anemia in oncology patients with nonmyeloid malignancies when anemia is caused by palliative chemotherapy-induced myelosuppression. These agents should not be administered if treatment is of curative intent. ESAs should be discontinued following completion of a chemotherapy course.[5,17-19] Guidelines and product labeling recommend ESAs should be used at the lowest dose possible to avoid transfusions, should be discontinued after 6 to 8 weeks in nonresponders, and should be avoided in patients with cancer who are not receiving concurrent chemotherapy except patients with low-risk myelodysplastic syndromes.[6,11] ESAs may be used to treat patients with low-risk myelodysplastic syndromes when they are not currently receiving chemotherapy; this is the only oncology population to which this recommendation applies.

Hemoglobin levels should be monitored regularly in patients receiving ESAs. If a patient experiences a rapid increase in Hgb (an increase of more than 1 g/dL) or if the patient's Hgb exceeds the level needed to avoid transfusion, the ESA should be held and subsequent doses reduced. ESAs should be discontinued in patients who discontinue chemotherapy as well as those who do not respond after 6 to 8 weeks.

Functional iron deficiency frequently occurs following continued ESA treatment. Rapid RBC production from ESAs increases the rate of iron mobilization from the reticuloendothelial system (RES) to the bone marrow. In addition, release of iron from the RES can be delayed by chemotherapy and the tumor itself. Functional iron deficiency leads to blunted ESA response.[20] Therefore, iron stores (iron, ferritin, total iron-binding capacity, transferrin saturation) should be assessed prior to treatment with an ESA, periodically during treatment, and in patients who are not responding to treatment. Intravenous iron supplementation may be required.

THE REMS AND ESA APPRISE ONCOLOGY PROGRAMS

The FDA instituted the Risk Evaluation and Mitigation Strategy (REMS) program in March 2008. The REMS program was initiated to ensure that the benefits of particular drugs continue to outweigh the risks. Drugs or biologic agents that pose significant toxicity or risk to patients are included in the REMS program, which has three components: (1) a medication guide, (2) a communication plan for health care providers, and (3) elements that assure safe use of the agent. The components that are required for a drug are dependent on the severity of the risks; not all drugs require all three components.[21] ESAs were added to the REMS program in February 2010 and require all three components of the program.

The manufacturers created the ESA Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs (APPRISE) Oncology program to aid health care providers in meeting REMS criteria. Health care providers must enroll in the program and complete training to satisfy the requirements for the REMS program. For each hospital that dispenses ESAs, a hospital designee must enroll in ESA APPRISE. This designee is responsible for establishing and overseeing the measures to promote safe and appropriate ESA use. Prescribers of ESAs must also complete the training and enrollment process. Health care providers and hospitals must re-enroll in the program every 3 years. Repercussions of failing to adhere to training, enrollment, or re-enrollment requirements of the program include suspension of access to the agents.

REMS criteria require providing patients with a medication guide and counseling on the risks versus benefits prior to initiating treatment. Counseling may be performed by nurses or other qualified health care providers.[22] The patient medication guides, as well as enrollment documents and other helpful forms, are available through the ESA APPRISE Web site (www.esa-apprise.com). Although other information may be given to the patient if desired, the ESA APPRISE medication guide must be given to the patient. Patient counseling must be documented via the patient's signature on the Patient Acknowledgement Form, provided through the program. A copy of the signed Acknowledgement form should be faxed or mailed to the ESA APPRISE program. If administered in a hospital, the signed form should be given to the hospital designee. A copy of the signed form may also be given to the patient.

Although ESAs reduce transfusion requirements, they have not been consistently shown to alleviate symptoms associated with anemia.

CONCLUSION

Based on the data on their risks and benefits, ESAs should only be used to treat anemia in oncology patients who are receiving chemotherapy for palliation. Although ESAs reduce transfusion requirements, they have not been consistently shown to alleviate fatigue or symptoms associated with anemia. Multiple meta-analyses have shown that ESAs increase the risk of mortality, tumor progression, and VTEs in oncology patients when used to achieve a target hemoglobin level of 12 to 15 g/dL. The FDA mandates that these risks and benefits be discussed with the patient prior to initiating treatment. The manufacturers support the mandate and developed ESA APPRISE, the REMS program for erythropoietin-stimulating agents. With a thorough understanding of the therapeutic use of ESAs, nurses can play an integral role in counseling patients receiving these agents. ■

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