The End of the Erythropoiesis-Stimulating Agents Era?

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Erythropoiesis-stimulating agents (ESAs) are widely used in the treatment of anemia associated with cancer chemotherapy. Epoetin alfa was the first agent to be approved for this indication in 1993, followed by the approval of darbepoetin alfa in 2002. Another form of epoetin - epoetin beta - is available outside of the United States. In the oncology setting, these agents were approved based solely on studies that showed a reduction in transfusions during chemotherapy, although "off-label" use in other settings, such as myelodysplastic syndrome and cancer (without chemotherapy), have also become regular uses. Both the Food and Drug Administration (FDA) and the Center for Medicare & Medicaid Services (CMS) consider all of the currently available ESAs to be interchangeable in terms of their safety and efficacy profiles, and thus consider them as one class for purposes of safety, efficacy, and coverage.

In the last 18 months, new clinical data, safety concerns, regulatory agencies involvement, and public interest have forever changed the use of erythropoiesis-stimulating agents in the oncology world (summarized in table).[1,2]

Date	Event
March 2007	**FDA** • Places "black box" warnings on all ESAs due to increased side effects/deaths • Urges use of lowest effective ESA dose
May 2007	**ODAC** • Supports FDA's black box warning • Concurs that data do not support quality of life claims • Votes against lowering hemoglobin Hgb threshold below 12 g/dL **CMS** • Issues a proposed National Coverage Determination (NCD) more restrictive than ODAC recommendations: no ESAs if Hgb above 9 g/dL or above 10 g/dL in symptomatic ischemic patients
July 2007	**CMS** • Issues a revised and somewhat less restrictive NCD o No ESAs if Hgb above 10 g/dL o Maximum 8 weeks treatment after chemotherapy ends o FDA-recommended starting dose o Dose escalation limited to 1 g/dL
Nov 2007	**FDA** • Issues alert discussing additional revisions to ESA package inserts o Discuss potential risks associated with tumor progression and shortened survival when ESAs are dosed for a target Hgb of 12 g/dL or higher o Include a summary of clinical trials that established these risks

July – Aug 2008	**FDA** • Issues a "complete response and safety labeling order" to Amgen requiring ESAs labeling revision to state: o ESAs should not be used in patients "when the anticipated outcome is cure" o ESAs should not be used unless a patient's Hgb < 10 g/dL o Removes language indicating the drug can be safely used until patient's Hgb reaches 12 g/dL • Second labeling revisions on all ESAs o Patients may only receive ESAs when their Hb level is less than 10 g/dL o ESAs is not indicated for patients when the anticipated outcome of their cancer treatment is cure o Per FDA mandate, when patients start ESAs therapy, they must receive a copy of the FDA-approved medication guide.

Although safety signals were first noticed in 2004, major changes in product labeling or reimbursement policies did not occur until March 2007 when the results of several of ESA trials showed a higher risk of serious life-threatening side effects and greater number of deaths in patients treated with these agents. This led the FDA to mandate "black box" warnings on all ESAs and urge physicians to use the lowest dose of ESA that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid blood transfusions. The warning applied to all FDA-approved indications of ESAs. Later that month, CMS announced that it would closely monitor all Medicare policies related to the administration of ESAs in light of the FDA recent issuance of the boxed warning on the agents.

In May 2007, the FDA's Oncology Drug Advisory Committee (ODAC) convened to review safety and efficacy data on ESAs and to redefine safe guidelines for ESA use in patients with cancer. The results of six randomized controlled trials, all conducted in cancer patients, were reviewed by the Committee.[2,3] It is important to note that the hemoglobin target in each of the trials was ≥ 12 g/dL and three of the trials enrolled cancer patients who were not receiving chemotherapy or radiotherapy. And one of the trials evaluated epoetin beta, a product that is not available in the United States. The ODAC upheld the "black box" warning the agency placed on the ESA products and voted that "further marketing restrictions" would be warranted for ESAs. The committee also concurred with the agency that no data existed to support "quality-of-life claims" for the ESAs in oncology or the correlation of ESA doses with responses. ODAC, however, voted against lowering the hemoglobin threshold from the current level of 12 g/dL at that time.

In response to these safety concerns, CMS proposed restricting the ESAs beyond that recommended by ODAC. The proposed National Coverage Determination (NCD) required that no ESAs would be prescribed to patients whose hemoglobin levels were above 9 g/dL or to symptomatic ischemic patients whose hemoglobin levels were above 10 g/dL. This was contrary to the accepted standard of care at the time, which allowed physicians to prescribe ESAs to patients whose hemoglobin dropped below 12 g/dL. The CMS proposal therefore reached beyond the ODAC recommendation. CMS released the final version of its NCD on the use of ESAs in oncology on July 20, 2007. Although the final NCD softened its coverage criteria, it restricted initiation of ESA therapy to hemoglobin values less than 10 g/dL, limited the ESA treatment duration to a maximum of 8 weeks after a chemotherapy session ends, limited the starting dose to the FDA recommended starting dose, and limited dose escalation levels. In October 2007, the FDA issued a statement agreeing with CMS's coverage decision on ESAs. The agency stated that the NCD was generally consistent with the published scientific literature, and the decision to limit reimbursement for ESAs was generally consistent with the FDA's recommendations. The agency concluded that there was no evidence that ESAs are associated with improved survival or quality-of-life in cancer patients undergoing chemotherapy. Current labeling stated that hemoglobin should not exceed 12 g/dL in cancer patients, which is the upper safety limit, not a target for therapy.

On November 8, 2007, the ESA package inserts were revised to include the potential risks associated with tumor progression and shortened survival when ESAs were dosed to a target hemoglobin of ≥ 12 g/dL in cancer patients. The revised labeling also included a summary of the clinical trials that established these risks in cancer patients.

Adverse outcomes continue to be reported in clinical trials of patients receiving ESAs. On November 30, 2007, Amgen notified FDA of the findings of the PREPARE (Preoperative Epirubicin Paclitaxel Aranesp) Study in patients with primary breast cancer receiving chemotherapy prior to surgery and randomly assigned to a group that was to receive Aranesp or no Aranesp. Shortly thereafter, on December 4, 2007, Amgen notified FDA of the findings of study GOG-191 (Gynecologic Oncology Group), a study in which 109 of a planned 460 patients with cervical cancer treated with chemotherapy and radiation were randomly assigned to either receive an ESA or transfusions. Both the PREPARE and GOG-191 studies showed higher rates of death in patients who received an ESA as compared to patients who did not receive an ESA.

In March 2008, ODAC recommended continuing the ESA's indication for treatment of chemotherapy-induced anemia in patients with cancer. But the panel also recommended several changes to the safety labels on ESAs that significantly restrict their use for cancer patients. The ODAC recommended against giving ESAs to patients with potentially curable cancers who are undergoing treatment, or to patients with advanced breast cancer or head and neck cancer. In response to those recommendations, the FDA issued a "complete response and safety labeling order" to Amgen in July 2008, requiring that ESA labeling be revised to state that the medications should not be used in patients "when the anticipated outcome is cure." The FDA ordered the changes using the new authorities granted to the agency last year by Congress that allow it to directly require labeling changes to address emerging safety issues. The revised labels also state that ESAs should not be used unless a patient's hemoglobin level decreases below 10 g/dL and removes language indicating that the drug can be safety used until the hemoglobin reaches 12 g/dL. The FDA did not bar the drugs in patients with breast cancer or head and neck cancer, for which available data suggest the risk of serious adverse events may be greatest. In August 2008, the ESA labeling was revised a second time to clarify the FDA-approved conditions for use in patients with cancer and revised directions for dosing to state the hemoglobin level (≥ 10 g/dL) at which treatment with an ESA should not be initiated. The label states that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. Additional changes include replacing the existing Patient Package Insert with a Medication Guide that contains information that FDA has determined is necessary for patients' safe and effective use of ESAs, and that could affect patients' decision to take the drug. Federal regulations require that the Medication Guide be distributed to patients.

Regulatory bodies in other countries are also considering changes in their recommendations or reimbursement policies. In June 2008, the European Medicines Agency has recommended that the labels for ESAs should warn that blood transfusion should be preferred in cancer patients with a reasonably long life expectancy. The recommendations are based on the agency's advisory group stating that "in cancer patients with a reasonably long life-expectancy, the benefit of using ESAs to avoid blood transfusions does not balance the risks of tumor progression and shorter survival".

Discussion

The mechanisms for how ESAs reduce survival are not clear.[5] Many tumor types express the erythropoietin receptor and it is hypothesized that tumor cells produce erythropoietin and erythropoietin receptors and that stimulation of these receptors can affect cancer cell growth and survival. Other researchers have questioned this hypothesis because of the poor specificity of the methods used to detect the erythropoietin receptor.[6] Another possible mechanism is that ESAs promote tumor growth by stimulating tumor angiogenesis.

The change in CMS reimbursement policy has created ethical dilemmas for treatment centers that administer ESAs. Some, but not all, private insurers have adopted the CMS NCD. Should the treatment center adopt two standards of care: one based on the CMS NCD and the other based on reimbursement policies for private insurers? With the most recent change in product labeling, more private insurers will likely adopt the CMS NCD.

In light of the current restrictions on ESAs use, there is increased interest in the use of iron supplementation with ESAs. Intravenous iron supplementation improves hematologic response to ESA therapy and decreases exposure to ESAs with IV iron supplementation.[7-10] Intravenous iron supplementation also reduces treatment failures to ESA in patients with chemotherapy-related anemia and normal iron status without additional toxicity. Iron supplements should be given intravenously rather then orally because similar improvements were not observed when oral iron was used. Intravenous iron sucrose, ferric gluconate and iron dextran have all been used in chemotherapy-related anemia. Iron dextran has been associated with a higher rate of adverse events. Baseline ferritin, B12, folate, and iron/total iron binding capacity levels should be obtained before initiating iron supplementation in patients with chemotherapy-related anemia.

The recent labeling revisions on ESAs imposed by the FDA suggest that the agency is concerned about the risks, but that the FDA wanted to make ESAs available, at least to certain oncology patients. Additional studies designed to assess overall safety, including progression-free survival, are needed to clarify the risks and benefits of ESAs used in the treatment of cancer patients as currently recommended. Studies designed to assess optimal dose and schedule of iron therapy, and monitoring criteria would provide guidance on how to best utilize iron therapy in patients with chemotherapy-related anemia.

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