ESAs Further Restricted, but Debate Continues

By Vicki Brower

The best-selling oncology drugs in the United States, erythropoiesis-stimulating agents (ESAs), have been taken by about half of all U.S. cancer patients to treat chemotherapy-induced anemia—more than the number receiving radiation therapy. But that is changing.

This summer, European and American regulatory authorities stringently restricted who should take ESAs, the most recent in a series of steps taken in response to clinical trials and basic research indicating that ESAs may harm cancer patients. Last year, the Centers for Medicare and Medicaid Services began denying coverage for the use of ESAs in cancer patients not undergoing chemotherapy and in those whose hemoglobin level is 10 g/dL or above. The center has further restricted use of darbe- poietin, a second-generation, extended-release version, in patients undergoing chemotherapy.

ESAs include epoetin alfa (Amgen’s Epogen and Procrit, which is manufactured by Amgen but licensed to Johnson & Johnson’s Ortho Biotech), Amgen’s longer-lasting darbe- poietin alfa (Aranesp), and, in Europe, epoetin beta (NeoRecormon). The drugs are recombinant forms of erythropoietin (EPO), a naturally occurring hormone that is produced by the kidneys and controls red blood cell production.

For the past 15 years, oncologists have prescribed ESAs to millions of anemic cancer patients in place of blood transfusions, hoping to improve their quality of life. Amgen scientists also reasoned that increasing anemic patients’ hemoglobin levels would help oxygenate tumors, thereby decreasing resistance to chemotherapy and radiation and improving outcomes.

But a growing body of research on patients with head and neck, lymphoid, breast, cervical, and non–small-cell lung cancers and multiple myeloma indicates that patients taking ESAs have worse overall survival and tumor control when the drugs are given at hemoglobin levels higher than 12 g/dL. These patients are also more likely than patients who did not receive ESAs to have high blood pressure and thrombovascular events (TVEs).

However, a study published in July in the Journal of Clinical Oncology suggested that patients with myelodysplastic syndrome treated long term with ESAs plus a white blood cell growth factor may have a survival advantage if they require few blood transfusions.

But studies also show that ESAs reduce the need for transfusions only minimally, if at all, and that they usually do not improve patients’ quality of life. Ironically, the drugs were approved in 1993 as a safer alternative to blood transfusions just when the blood supply began to be screened for hepatitis B and C and human immunodeficiency virus, rendering blood much safer, while ESAs’ safety is now seriously questioned.

The stakes in this controversy could hardly be higher: a large share of the profits of Amgen and Ortho Biotech; thousands of dollars of income for private practice oncologists who prescribe and administer these drugs; and, most important, the safety of cancer patients.

Labeling Changes Ordered

This summer, the U.S. Food and Drug Administration and European Medicines Agency dealt the latest blow to ESAs, restricting use in patients whose cancer is deemed “curable.” In June, the European Medicines Agency announced that Amgen’s label should read as follows: “Blood transfusions should be preferred in cancer patients with a reasonably long life expectancy,” whereas in July, the FDA ordered Amgen to make similar changes, stating that ESAs should not be taken by patients “whose anticipated outcome is cure.”

Also, the chief of FDA’s Center for Drug Evaluation and Review, Richard Pazdur, M.D., said that the label must indicate that ESAs should not be started in patients whose hemoglobin levels are greater than or equal to 10 g/dL (a change from 12 g/dL) and that they “should not be given if hemoglobin exceeds a level needed to avoid transfusion.” Amgen has not submitted data establishing a favorable risk–benefit ratio in patients receiving chemotherapy for cancers in which cure is anticipated, Pazdur said in a release.

Amgen said that it “is working very closely with the FDA to determine what additional trials it will conduct, in addition to pharmacovigilance studies in a range of cancers previously mandated,” said Roy Baynes, M.D., vice president of global development.

A Troubled History

The FDA began restricting the use of ESAs after a 2004 Oncology Drugs Advisory Committee (ODAC) meeting reviewed data from the ENHANCE head and neck cancer trial and the BEST breast cancer study, both published in 2003 in The Lancet Oncology. The trials showed unexpectedly higher mortality rates in patients taking ESAs. Around that time, a non–small-cell lung cancer study was terminated early because of increased TVEs among patients taking ESAs, as was another head and neck cancer study and four other randomized controlled trials in a variety of cancers.

The FDA asked Amgen for additional double-blind, placebo-controlled trials.
with the primary endpoint of survival and information on TVEs. But by the next ODAC meeting, in May 2007, the trials had not been conducted, according to Vinni Juneja, M.D., an FDA medical officer. In the meantime, six studies had been updated and placed on the meeting agenda. All but one—a small-cell lung cancer study—showed decreased survival in ESA-treated patients, and the lung cancer study showed no survival benefit. ODAC then recommended more restrictions on labeling and more trials. Listening to the update at the 2007 meeting, Otis Brawley, M.D., now chief medical officer of the American Cancer Society, asked, “Is EPO Miracle-Gro for tumors?”

In March 2007, the FDA had required that Amgen add a “black box” warning, based on results of a Danish head and neck cancer trial called the DAHANCA trial, stating that ESAs should be used at the lowest dose to avoid blood clots and transfusions and that they can increase risk of death or serious medical complications if used too aggressively. In November 2007, the FDA revised that warning to state that “increased mortality, serious cardiovascular and thromboembolic events, and tumor progression” may occur with use. Also that month, the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) issued new, restricted guidelines for ESAs, citing a higher risk of TVEs.

In March 2008, the FDA reconvened ODAC for a third time on the basis of updates and reports of two more trials—one in breast cancer and the other in cervical cancer—which showed decreased survival and enhanced tumor progression. This time, ODAC recommended that the drugs continue to be marketed but that the label be changed to reflect that ESAs are not indicated for patients “receiving potentially curative treatments” or for patients with breast and/or head and neck cancers. The agency eventually accepted all but the last recommendation.

While the debate continues as to how harmful ESAs are, the FDA has now mandated that an agency-written informed-consent document be given with each course of ESA treatment, said Leonard Saltz, M.D., attending physician and chairman of the pharmacy and therapeutics committee at New York City’s Memorial Sloan-Kettering Cancer Center.

Responses to Restrictions
Reactions to the latest restrictions vary. “The question of who is ‘curable’ is problematic and troubling,” said David Steensma, M.D., clinical faculty member at the Mayo Clinic in Rochester, Minn. “Now we’ve got to decide who is curable,” he said. “It puts a bit of a burden on us.”

Others feel that the changes are too little, too late. “We don’t understand why, after data from thousands of patients indicating poorer outcomes in patients taking EPO, including studies in patients with metastatic breast cancer, the FDA did not follow the recommendation of the March 2008 ODAC and restrict its use in patients with metastatic breast, and head and neck, cancer, in whom it has shown definitive harm,” said Carolina Hinestrosa, executive vice president of the National Breast Cancer Coalition in Washington, D.C. “If there is evidence of poor outcomes in metastatic breast cancer based on at least two trials, why is the FDA allowing its use in that setting?”

At the March 2008 meeting, Hinestrosa spoke, saying, “We strongly object to, and

ESA Timeline

**July 2008.** FDA orders Amgen to make safety-related labeling changes: ESAs are not indicated for curable cancer patients and should not be used for chemotherapy patients whose hemoglobin levels are greater than or equal to 10 g/dL.

**July 2008.** JCO study by Jidersten et al. indicates that EPO and granulocyte-macrophage colony-stimulating factor may have positive effect on patients with myelodysplastic syndrome.

**June 2008.** European Medicines Agency recommends new warning for ESAs for use in cancer patients, stating that blood transfusions are the preferred method of correcting anemia.

**March 2008.** ODAC recommends that ESAs stay on the market but that labeling should change to indicate that patients who are receiving curative treatment should not take ESAs; but they did not recommend restricting its use to certain cancers.

**March 2008.** JCO study by Smith et al. suggests that ESAs do not statistically significantly reduce transfusions and are associated with an increased incidence of cardiovascular events, thrombovascular events, and death in cancer patients who are anemic and taking darbepoetin but not receiving chemotherapy.

**February 2008.** A meta-analysis in JAMA by Bennett et al. demonstrates that ESAs are associated with greatly increased risks of venous thromboembolism and death in 9,000 patients.

**November 2007.** FDA labeling change warns of increased tumor progression, blood clots, and death in patients with advanced head and neck, breast, lymphoid, and non–small-cell lung cancers.

**November 2007.** ASCO/ASH issue updated guidelines for ESA use.

**July 2007.** CMS limits reimbursement of ESAs to treatment initiated at hemoglobin levels less than 10 g/dL.

**May 2007.** ODAC recommends restrictions on ESAs; asks about limiting use in certain tumor types, setting new hemoglobin levels for starting therapy, and limiting time used after chemotherapy.

**March 2007.** FDA adds “black box” warning to use lowest possible dose of ESAs for anemia.

**December 2006.** DAHANCA head and neck cancer trial is stopped early because of negative results in treated patients.

**November 2006.** FDA issues safety alert, updated in February and March 2007.

**May 2006.** Updated meta-analysis published in JNCI by Bohlius et al. shows that ESA treatment substantially reduced risk for transfusions and risk of thrombovascular events.

**May 2004.** ODAC discusses safety and recommends more double-blind, placebo-controlled trials with survival as primary endpoint.

**2002.** Darbepoetin is approved for cancer patients with anemia.

**1993.** Epoetin alfa is approved for chemotherapy-associated anemia.
quite frankly find offensive and unethical, the suggestion that the use of ESAs should be restricted to patients with metastatic disease. Do we place less value in these patient’s lives as to find it somehow acceptable that in using ESAs we might be speed-up ing up their deaths?”

Richard Klasa, M.D., of the British Columbia Cancer Agency in Vancouver also faulted the FDA for not following other ODAC recommendations for more stringent restrictions and criticized ASH and ASCO for not going far enough in their November 2007 revised guidelines. “Studies show no ‘safe’ level of hemoglobin, and the negative consequences of ESAs were worse when [levels were] pushed higher,” Klasa said. “Megadoses of the drugs that are given—doses purposely not specified in studies—increase hemoglobin levels only slightly while not improving quality of life and not significantly reducing transfusions. Instead they hasten tumor progression, [and they] cause blood clots, hypertension, and death.”

If anything, the bar for adverse effects of ESAs should be higher than that for cancer drugs themselves, said Nevin Murray, M.D., also at the British Columbia Cancer Agency. “The risks of these drugs should be very low, and [they should] help, not hurt, cancer treatment.” Dismayed that it took the U.S. so long to come to its recent decision, Murray noted that ESAs are much less frequently prescribed in Canada and Europe, where they are not reimbursable.

**EPO’s Dark Side**

Scientists had assumed that EPO had no effects outside red blood cell production until a 1990 study showed that it promotes angiogenesis and tumor growth. In defense of ESAs, Amgen cites research showing that the antibodies used to detect the receptors are insufficiently specific and therefore unreliable.

In defense of ESAs, Amgen cites research by Wolfgang Jelkmann, M.D., of the University of Lubeck in Germany that contradicts these findings. The company also emphasizes the poor design of many trials—about which the FDA and ESA critics agree—and problems with reagents used to detect EPO receptors.

“The preclinical hypothesis that some cancer cells have EPO receptors on them and their vasculature is unproven,” said Angus Sinclair, Ph.D., principal scientist at Amgen. “At a December 2007 NCI meeting on this topic, it was agreed that the data in this area are conflicting and confounding and that there are no good preclinical studies,” he said.

But other researchers say that these limitations do not invalidate all receptor studies. Last year, Michael Henke, M.D., professor of medicine at Germany’s Freiburg University Clinic and author of the ENHANCE studies in head and neck cancer, found that patients taking ESAs and experiencing poorer outcomes had tumors bearing EPO receptors. “The whole thing was pretty logical. …The story has come to an end, although the companies are still fighting the battle,” he said.

Another hypothesis is that EPO is part of a multiple growth-factor cascade response that evolved as a response to injury, Murray said. Although good for wound healing, angiogenesis, and epithelial proliferation in normal situations, EPO may not be good for cancer.

Other preclinical studies focus on the angiogenic effects of ESAs in a range of tumor types. Studies in animal models show that blocking EPO or its receptor with an antibody or peptide blocks tumor angiogenesis and tumor growth. And although some studies show that oxygenation of tumors helps them grow, others indicate that it sensitizes them to radiation and chemotherapy.

**Follow the Money**

There are vast historical differences in ESA prescribing practices between the U.S. and Canada and Europe. These can be accounted for largely by economics, Murray said. Until last year, the U.S. government’s reimbursement policies for ESAs were much more liberal than elsewhere, and, hence, the drugs were more commonly prescribed, resulting in $10 billion in sales in 2006.

Another factor that may in part account for the historically greater use of ESAs in the U.S. is the financial benefit reaped by physicians and hospitals that dispense ESAs. They obtain the drugs at a discount from the companies and have had a good deal of freedom to charge what they wish, Klasa said.

“Oncologists are the only physicians who, for the past two decades, have been permitted to act as pharmacists, to sell and dispense drugs. For everyone else, that would be considered a conflict of interest,” Saltz said. Hospitals and academic institutions have also benefited financially by prescribing ESAs, even if individual physicians practicing at them have not, he added.

“I do think that the economics of EPO is a potentially corrupting affair, with an obvious conflict of interest for those prescribing it and getting kickbacks,” Murray said. “There will be many American oncologists that have looked at the evidence and have restricted EPO use, while others will have looked at the evidence and still think it is a good thing to do.”

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Murray noted that there are also EPO supporters in Canada, some of whom are convinced that it helps cancer patients despite the negative evidence. On the other hand, “The marketing of EPO in Canada to physicians and directly to the public was more intense than any drug used for cancer patient in my experience,” he said. Critical of the Canadian system as well, Murray added that Canadian cancer patients must give informed consent when receiving blood transfusions, but not for receiving EPO.

“At the end of the day, two issues got mixed up with ESAs by absolutely ingenious marketing in the media: the message to physicians that the drugs reduced the need for transfusions, and, more importantly, the messages that convinced the public that these drugs would make them feel better,” Saltz said. “Neither was true.”

It is difficult to assess how many physicians have cut down or stopped prescribing ESAs to patients. Over the past 18 months, the use of ESAs at Sloan-Kettering has dropped by about 60%, Saltz said. Amgen recently reported that U.S. sales have dropped by about 25% for both Procrit and Aranesp. Except for Saltz, U.S. oncologists contacted for this article declined to discuss this.

Amgen is not giving up easily, but the tide may be turning. Amgen maintains the drugs are safe; at each ODAC meeting, the company presented its case by describing research that seems to support its continued use and that found fault with the studies already conducted and the reagents used to detect EPO receptors. Whether the FDA will ask for and accept more trials remains unclear.

“Use of ESAs will continue in spite of the fact that the best way to use them is still unknown,” Arcasoy said. “They are very useful drugs, and there are many contexts in which they can be safely used; it is unfortunate that at this time, we still don’t know which they are.”