



## Weighing the Hazards of Erythropoiesis Stimulation in Patients with Cancer

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On May 10, 2007, the Food and Drug Administration (FDA) convened a meeting of its Oncology Drug Advisory Committee to discuss concerns about risks associated with the erythropoiesis-

stimulating agents (ESAs) used to treat anemia caused by chemotherapy. The principal ESAs under scrutiny were epoetin alfa (Procrit, Eprex, and Epogen) and darbepoetin alfa (Aranesp), and the risks — actual or potential — were thromboembolic disease, promotion of tumor growth, and decreased survival. The actual risk of thromboembolic events was shown in two phase 3 clinical trials, reported in the *Journal* in 2006, that unequivocally showed an increased risk of death or cardiovascular or thromboembolic events among patients with chronic renal failure who were treated with ESAs to drive hemoglobin levels into the normal range (13.5 g per deciliter or higher), as compared with those treated to achieve levels in a subnormal range (10.5 to 11.5 g per deciliter).

In 1993, the FDA approved epoetin alfa for patients with cancer on the basis of pooled data from six randomized, double-blind, placebo-controlled trials that included 131 patients with various types of cancer. The approval focused on the effectiveness of epoetin alfa in reducing the number of transfusions required to treat chemotherapy-induced anemia — not the anemia of cancer. In oncology, ESAs are helpful in supportive care, but the FDA has not approved the use of such agents to alleviate fatigue or weakness or to improve patients' quality of life.

In 2003, concern about a detrimental effect of ESAs in patients with cancer arose with the publication of the results of a multicenter, double-blind trial conducted by Henke et al.<sup>1</sup> involving 351 patients with anemia (hemoglobin

level, <12 g per deciliter in women or <13 g per deciliter in men) who had cancer of the oral cavity, pharynx, or larynx (see table). In this trial, patients were randomly assigned to receive radiotherapy along with either placebo or epoetin beta (Neo-Recormon) at a dose of 300 IU per kilogram of body weight three times weekly, starting 10 to 14 days before radiotherapy and continuing throughout treatment. The epoetin beta group had substantially shorter progression-free survival and overall survival than the placebo group.

In another study, the Breast Cancer Erythropoietin Survival Trial (BEST), 939 patients with metastatic breast cancer receiving first-line chemotherapy were randomly assigned to receive either epoetin alfa (Eprex) at a dose of 40,000 IU once weekly or placebo for 12 months.<sup>2</sup> Treatment with the study drug was initiated if the hemoglobin level was 13 g per deciliter or lower at baseline or if it decreased to that point. Overall survival at 1 year was lower in the

Adverse Outcomes Associated with Erythropoiesis-Stimulating Agents (ESA) Treatment in Patients with Cancer.\*

Study	Type of Cancer	No. of Patients Enrolled (Target Enrollment if Trial Stopped Early)	ESA Treatment	Target Hemoglobin Level g/dl	Adverse Outcome
Henke et al. <sup>1</sup>	Locally advanced head-and-neck cancer	351	Epoetin beta (300 IU/kg 3 times/wk)	≥12 in women; ≥13 in men	Hazard ratio for local–regional progression, 1.69 (P=0.007); hazard ratio for death, 1.39 (P=0.02)
Leyland-Jones et al. <sup>2</sup>	Metastatic breast cancer	939	Epoetin alfa (40,000 U/wk)	≥13	Survival at 12 mo. vs. placebo, 70% vs. 76% (P=0.01)
Wright et al. <sup>3</sup>	Metastatic non–small-cell lung cancer	70 (300)	Epoetin alfa (40,000 U/wk)	12–14	Overall survival vs. placebo, 63 vs. 129 days; hazard ratio for death, 1.84 (P=0.04)
Goldberg <sup>4</sup>	Locally advanced head-and-neck cancer	522 (600)	Darbepoetin alfa (150 µg/wk)	14–15.5	10% increase in local–regional failure (P=0.01); trend toward shorter survival (P=0.08)
Anemia of Cancer Study	Nonmyeloid cancers in patients not receiving chemotherapy or myelosuppressive radiation therapy	989	Darbepoetin alfa (6.75 µg/kg/wk)	≥13	Shorter overall survival; hazard ratio for death, 1.30 (P=0.008)
Lymphoid Cancers Anemia Study	Lymphoproliferative cancers	344	Darbepoetin alfa (2.25 µg/kg/wk)	<15 in women; <14 in men	Shorter overall survival; hazard ratio for death, 1.37 (P=0.04)

\* Data on the Anemia of Cancer Study and the Lymphoid Cancers Anemia Study are from the FDA ([www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-00-index.htm](http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-00-index.htm)).

epoetin alfa group. The study was stopped early by an independent data and safety monitoring committee because of higher mortality in the epoetin alfa group at 4 months. As in the study by Henke et al., the first part of the survival curve in the BEST trial showed an increased risk of death from cancer, which is suggestive of enhanced tumor growth.

In May 2004, the results of such studies prompted the FDA to convene an advisory committee to assess the safety of ESAs in patients with cancer. The committee agreed on the need for additional large, randomized trials to determine the safety of ESAs in patients with several types of tumors, including head and neck, breast, and non–small-cell lung cancer. Accrual was to be completed over a period of 3 to 5 years, but as of May 2007, enrollment was poor.

Two trials involving patients with small-cell lung cancer showed

that the use of an ESA according to approved guidelines resulted in no apparent reduction in survival, and a meta-analysis showed equivalent overall survival and disease control among patients with cancer when ESAs were used within the recommended dose range. Nevertheless, four recent studies showed evidence of harm associated with the use of ESAs in patients with cancer. One of these trials aimed to randomly assign 300 patients with advanced metastatic non–small-cell lung cancer to receive 12 weekly injections of epoetin alfa or placebo, with a target hemoglobin level of 12 to 14 g per deciliter.<sup>3</sup> The trial was stopped early after an unplanned safety analysis involving 70 patients revealed a significant difference in median survival in favor of placebo. In the second study, 522 patients who were scheduled for definitive radiotherapy for head and neck cancer were randomly

assigned to receive darbepoetin alfa or red-cell transfusion.<sup>4</sup> This trial was terminated early after a futility analysis indicated that there was a detrimental effect on local–regional control (the primary end point) and a trend toward shorter survival in the darbepoetin alfa group. The table includes the results of two other unpublished trials in which the outcome was worse in the darbepoetin alfa group than in the control group.

In March 2007, the results of these six trials led the FDA to advise caution in the use of ESAs. The agency mandated the addition of a black-box warning about the potential for tumor promotion and thromboembolic events, and FDA instructions required ESAs to be withheld from patients whose hemoglobin level exceeded 12 g per deciliter until the level fell below 11 g per deciliter.

Given the recent results, the FDA convened another meeting of

## Do Cancer Cells Express Functional Erythropoietin Receptors?

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When erythropoietin won market approval in 1988, it was hailed as a wonder drug because of the selectivity of its action and its resulting relative freedom from untoward effects. This selective action was due largely to the restricted expression of its receptor on erythroid progenitors. As is common with “wonder” drugs, however, things turned out not to be quite so simple. Over the ensuing years, functional erythropoietin receptors have been shown to be present on other types of cells, but these findings have had little effect on the therapeutic uses of erythropoietin — although some of them could be advantageous (for instance, erythropoietin’s cytoprotective effect in the central nervous system).

Meanwhile, accumulating studies have been demonstrating the presence of erythropoietin receptors in various cancer-cell lines and in primary cancer tissue, and recent clinical trials of erythropoietin for treatment of the anemia associated with cancer chemotherapy have indicated adverse outcomes that are thought to be due to tumor progression. It is important to determine whether the adverse outcomes are attributable to erythropoietin treatment, and if so, what the mechanism is. One possibility is a direct effect

of erythropoietin on tumor-cell growth or survival.

If such an effect occurs, then cancer cells must express functional erythropoietin receptors. On this point there is considerable controversy. A functional erythropoietin receptor would be a protein expressed on the cell surface that specifically binds erythropoietin to elicit a cellular response through the activation of erythropoietin-receptor-mediated signaling pathways. Since one would like to be able to detect such receptors in samples of tumor tissue, the availability of an antibody amenable to immunohistochemical analysis would be helpful. There is, at present, no good commercial antibody for this purpose. The one used in many studies (Santa-Cruz C-20, cat # sc-695) lacks specificity, and the approach does not distinguish cell-surface expression from intracellular expression. It would be possible to perform quantitative reverse-transcriptase polymerase chain reaction on clinical tumor samples, but this method is too sensitive, and tumor samples contain endothelial cells, which are known to express erythropoietin receptors. Moreover, this technique measures messenger RNA, which does not necessarily translate into a functional cell-surface erythropoietin receptor.

Are tumor cells responsive to erythropoietin? Again, the answer is not clear. If the effects seen in vitro (often in established cell lines) are real, they are small, and they often become manifest only in the presence of supraphysiologic doses of erythropoietin. Similarly, the few signaling experiments that have been conducted have revealed tyrosine phosphorylation profiles that do not resemble erythropoietin-receptor signaling in other cells known to have functional receptors. The concerns regarding the use of erythropoietin in patients with cancer make the question of whether cancer cells in the patient express functional erythropoietin receptors important to answer unequivocally, using tools permitting the analysis of clinical specimens. Even a finding that erythropoietin receptors present in cancer cells are not functional, however, would not necessarily vindicate erythropoietin, since such receptors might stimulate tumor progression through the effects of erythropoietin on endothelial cells and angiogenesis or through the elaboration of other factors that influence tumor growth.

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the Oncology Drug Advisory Committee to seek guidance in redefining safe guidelines for ESA use in patients with cancer. A clear consensus emerged that product labeling should indicate further restrictions on approved use and that additional trials should be pur-

sued aggressively to clarify whether ESAs are indeed associated with an increased risk of tumor growth. The agency heard recommendations that it consider limiting the use of ESAs in patients with the types of tumors in which clinical trials have demonstrated adverse

outcomes, that it define a hemoglobin level at which ESA treatment should be initiated in asymptomatic patients, and that it restrict the duration of use of ESAs in patients with cancer. The advisory committee did not support a recommendation urging modifica-

tion of the hemoglobin level at which ESA administration should be suspended.

Some meeting participants argued that while awaiting definitive data, oncologists should refrain from using ESAs in patients with squamous-cell cancer of the head and neck for whom curative therapy was intended. Participants also advised caution in the use of ESAs in patients undergoing chemotherapy for breast cancer and non-small-cell lung cancer.

The mechanism underlying the enhanced growth of tumors with higher doses of ESAs remains uncertain. There is good evidence that hypoxic tumors resist chemotherapy and radiotherapy. The biology of tumor hypoxia, with enhanced cell signaling through the Akt-mammalian target of rapamycin (mTOR) axis and subsequent up-regulation of hypoxia-inducible factor 1 $\alpha$ , is what inspired the clinical trials in which ESA treatment was combined with radiotherapy, cytotoxic chemotherapy, or both in an attempt to overcome hypoxia-induced resistance. But another possibility is that certain tumor cells have erythropoietin receptors that stimulate cell

growth when they are bound by erythropoietin or an erythropoietin-like ligand. Squamous-cell lung cancer, squamous-cell tumors of the head and neck, and breast adenocarcinomas seem to express erythropoietin receptors, but such receptors' role, if any, in tumor growth is unclear. Henke et al. showed that erythropoietin receptors were expressed by two thirds of tumors in their study and that expression of such receptors in erythropoietin-treated patients was associated with shorter survival.<sup>5</sup> Conversely, *in vitro* studies have shown that stimulating erythropoietin receptors in cell lines from head and neck cancer and breast cancer causes the death of cells, though the questionable quality of the reagents used to detect erythropoietin receptors must be considered in interpreting these data.

In the face of media attention to the hyperbolic advertising by the companies that make ESAs and the substantial profits accrued by physicians who use such agents aggressively, the FDA has sought guidance in exercising prudent, evidence-based judgment. In order to maintain the public trust, the agency should act transparently

in adopting new guidelines, and medical oncologists should begin using these agents in a compassionate but disciplined fashion, placing patient benefit above all other considerations.

**An interview with James Doroshow, director of the Division of Cancer Treatment and Diagnosis at the National Cancer Institute, can be heard at [www.nejm.org](http://www.nejm.org).**

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## Erythropoietin, the FDA, and Oncology

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As has been the case for patients with chronic renal failure, treatment with erythropoiesis-stimulating agents (ESAs) has substantially raised the hemoglobin concentrations of hundreds of thousands of patients with cancer, diminishing their need for red-cell transfusions during chemotherapy. At the same time, use of these agents has raised safety concerns because they can cause thromboembolic events and increase “the

risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL,” according to the black-box warning that the Food and Drug Administration (FDA) added to the prescribing information in March 2007.<sup>1</sup> Therefore, the FDA warned physicians to “use the lowest dose . . . that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need

for blood transfusion” and to monitor the hemoglobin level regularly until it stabilizes.

Recent clinical trials have also added fuel to a long-standing debate about whether erythropoietins pose additional risks in patients with cancer (see Perspective article by Khuri, pages 2445–2448). One such risk might be an increased likelihood of thrombotic events, given the association between thrombosis and some types