

# Is Anemia of Cancer Different From Chemotherapy-Induced Anemia?

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Anemia has myriad causes. In patients with cancer, the chief culprits are direct myelotoxicity from antineoplastic drugs and cytokine-mediated inhibition of erythropoiesis.<sup>1</sup> A host of other malign influences may also be at work, including bleeding, renal injury, nutrient deficiency, and so on. A single patient may suffer from several causes of anemia simultaneously, and it is not always easy to distinguish these. However, it is important to try: although the physiological consequences of a low hemoglobin level are similar regardless of its origin, treatment differs considerably.

In this issue of the *Journal of Clinical Oncology*, Smith et al<sup>2</sup> report results from the Amgen 20010103 clinical trial (Amgen 103). These results suggest that whether or not an anemic patient is receiving myelosuppressive chemotherapy is a clinically relevant distinction, with therapeutic implications. Data from this trial were first presented by John Glaspy in April 2007 at the clinical plenary session of the annual meeting of the American Association for Cancer Research, an event that garnered considerable media attention.<sup>3,4</sup>

The Amgen 103 investigators randomly assigned 989 patients with cancer and hemoglobin  $\leq 11$  g/dL to receive either the erythropoiesis-stimulating agent (ESA) darbepoetin alfa or a placebo. Although 70% of enrolled patients had undergone prior chemotherapy, which finished a median of 9 months before trial participation, patients were not permitted to receive cytotoxic chemotherapy or myelosuppressive radiotherapy during the 16 weeks of study intervention. However, patients were allowed to receive nonmyelosuppressive radiotherapy or hormonal therapy, and many did.

The results of the Amgen 103 trial are negative in two senses. Neither the primary end point—reduction in RBC transfusion needs with darbepoetin—nor a secondary quality of life end point was met. More disturbingly, patients who received darbepoetin did not live as long as those who received placebo (37 weeks *v* 47 weeks median survival;  $P = .022$ ). The trial's sobering findings are included in the new ESA prescribing information approved by the United States Food and Drug Administration (FDA) in November 2007, and the study results have influenced the ongoing debate in the United States about Medicare beneficiaries' access to ESAs.<sup>5,6</sup>

Several of the Amgen 103 study findings are difficult to interpret. Enrolled patients were diverse, with more than 15 different primary tumor sites and all stages of disease; anemia and ESA treatment may have distinct consequences in different cancer settings. Furthermore, survival was not the study's primary end point, so the two study arms were not balanced for known prognostic markers. A retrospective analysis demonstrated that if the groups had been better balanced, the

observed survival difference would no longer have been significant—similar to what happened with the Breast Cancer Erythropoietin Survival Trial (BEST) and ENHANCE studies, which also pointed to potential harm from off-label use of ESAs.<sup>7,8</sup> In another echo of BEST, the Amgen 103 investigators were unable to adjudicate long-term causes of death in trial participants, so we don't know what proportion of the patients died from progressive cancer, thromboembolism, or something else.

The transfusion end point is also murky. The Amgen 103 study was multinational, and 75% of patients enrolled in Europe, including areas of Eastern Europe where blood bank shortages occur.<sup>9</sup> Of the 75 study patients who did not undergo transfusion when their hemoglobin level decreased to less than 8 g/dL, 95% were from Eastern Europe. The trial's primary end point of transfusion reduction with darbepoetin could have been met if these patients had undergone transfusion according to protocol guidelines.

In retrospect, it was probably not a good idea to conduct a study with a transfusion primary end point at sites where access to blood is not assured. United States–based drug companies often pursue clinical trials overseas when they want to accrue patients rapidly, especially when the study question would be difficult to answer in North America because of entrenched clinical practice patterns.<sup>10,11</sup> In the case of the Amgen 103 study, the study sponsor may have had little choice, because placebo-controlled studies of ESAs are notoriously difficult to conduct in the United States. There are many reasons for this, but a major factor is the widespread use of drug purchasing contracts that limit physicians' choice of ESA products in exchange for discounted pricing—an important but controversial revenue source for many oncology practices.<sup>12</sup>

If the results of the Amgen 103 study had appeared several years ago in the golden age of ESAs, they might have been chalked up to limitations of study design and execution. The possibility could still have been left open that in anemic cancer patients who aren't getting chemotherapy, ESAs might modestly reduce transfusion needs and have no impact on survival. Instead, these results arrive at a tumultuous time, when ESAs and their manufacturer, Amgen, are subject to intense scrutiny, after the fallout from a February 2007 exposé in *The Cancer Letter* about poorer survival in head and neck cancer patients treated with darbepoetin in the Danish Head and Neck Cancer study 10 trial.<sup>13,14</sup> Now, ESA safety is on every oncologist's mind, and the Amgen 103 study results only heighten those concerns. We need to take these results seriously, and unless new data emerge, I believe we can't afford to risk testing ESAs in this population again.

The history of ESA use in cancer anemia is important for understanding the context of the Amgen 103 study. Recombinant erythropoietin (epoetin alfa) was initially approved by the FDA in 1989 for use in patients with renal failure or HIV infection. The following year, the first two clinical series describing potential benefits from epoetin in patients with neoplasia (multiple myeloma and lymphoma with bone marrow involvement) were published.<sup>15,16</sup> In April 1993, the FDA allowed expansion of the epoetin label to include a supplemental indication for the treatment of anemia associated with chemotherapy for nonmyeloid cancer. This regulatory approval came after review of pooled results from six small placebo-controlled trials enrolling a total of 131 anemic patients who were receiving chemotherapy, 45% of whom were being treated with cisplatin-containing regimens.<sup>17</sup>

In 1993, the FDA also examined data from small studies of epoetin in patients who were not receiving chemotherapy, but the agency found those results less compelling. Patients who were not receiving anticancer drugs experienced a statistically significant increase in hematocrit with epoetin compared with placebo, but the benefit was less robust than for patients who were receiving cytotoxic chemotherapy, and there was no difference in the RBC transfusion rate.<sup>17,18</sup> Therefore, the package insert for epoetin stated that it was indicated “for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.” When darbepoetin alfa was approved in July 2002 for use in patients with chemotherapy-induced anemia, the label contained similar wording.

Although the Amgen 103 study is the largest ever conducted in an anemia of cancer population, several smaller placebo-controlled ESA trials in this group also failed to show benefit, further validating the FDA’s 1993 decision.<sup>19,20</sup> As a result, even before to this year’s heightened safety concerns, analysts estimated that only approximately 10% to 15% of ESA use in patients with cancer was off-label (ie, outside the chemotherapy setting).<sup>21</sup> A key motivation for the Amgen 103 study must have been to increase that market—a strategy that backfired in a spectacular way, raising concerns among the investment community about the wisdom of sponsoring the trial.<sup>4</sup>

Regulatory and fiscal considerations aside, why might ESAs have different effects on survival in patients with anemia of cancer compared with chemotherapy-induced anemia? There are several possible explanations, but one of the more interesting relates to the different relative risks of transfusion in the two groups of patients. Among patients with chemotherapy-associated anemia, the transfusion rate in those who receive ESAs is typically approximately 20%, compared with 45% for placebo-treated patients.<sup>22,23</sup> In contrast, in the Amgen 103 study, the placebo group’s transfusion rate was only 23.9%, which is similar to other studies in the anemia of cancer. Perhaps transfusions are harmful to patients with cancer by way of transfusion-related immune modulation, which is a real biologic phenomenon but is of uncertain clinical significance.<sup>24</sup> If ESAs are also potentially harmful, but are less risky than transfusions, then benefits from the transfusion-sparing effect of ESA use in chemotherapy-associated anemia would trump any adverse effects from the ESA itself. In contrast, because the transfusion-sparing effect is not significant in patients who are not getting myelosuppressive chemotherapy, negative effects of the ESA dominate. This hypothesis is speculative but warrants further exploration.

The most difficult practical issue in restricting ESA use to patients with chemotherapy-induced anemia is in knowing just when patients

fit into that category. Treatment for cancer often proceeds by fits and starts, with pauses in therapy because of achievement of maximal response or excessive toxicity. When therapy is on hold but anemia persists, it is often ambiguous when anemia is no longer due to the effect of a drug. At the other end of the spectrum, patients with cancer are often anemic at diagnosis; if such patients are still anemic after a month or two of treatment, should that anemia be considered as owing to cancer, its treatment, or both? Published studies of ESAs offer little guidance for clinical decision-making in this area, because investigators have not always carefully defined the patients enrolling in their studies.

Another practical problem faced by clinicians is that cancer treatment is changing. Contemporary chemotherapy is (thankfully!) different from the chemotherapy used 20 years ago when the first clinical studies with epoetin began. Although most patients with advanced cancer are still treated with traditional cytotoxic agents, as in the late 1980s, a growing number of kinase inhibitors, monoclonal antibodies, immunomodulatory agents, hormonal antagonists and partial agonists, epigenetic pattern modifiers, and other biologic therapies have made their way into the clinic, to the great benefit of our patients. These advances bring new dilemmas: is anemia that develops during treatment with these newer agents the same as old-fashioned chemotherapy-induced anemia from cytotoxics? Several of the new biologics do have important effects on erythropoiesis. For instance, almost 90% of patients with gastrointestinal stromal tumors develop anemia during imatinib therapy, and this anemia is classified as grade 3 or 4 in 10% of patients.<sup>25</sup> Likewise, sunitinib monotherapy for metastatic renal cell carcinoma is associated with a 26% rate of clinically significant anemia, whereas the rate of grade 3 or 4 anemia with sirolimus for the same disease is approximately 9%.<sup>26,27</sup> These agents are not cytotoxic or myelosuppressive in the traditional sense, so the safety of ESAs in this setting is not established. Yet neither is there any evidence that ESAs are unsafe when given with newer biologics; there is simply no evidence at all.

If there is one thing that the 2007 *annus horribilis* for ESAs has reminded us, it is that even when therapies are used for a long time in large numbers of patients, there are always plenty of unanswered questions. The need for more clinical trials is endless. For now, the American Society of Hematology/American Society of Clinical Oncology clinical practice guideline for ESA use—which was recently revised, and which I was not involved in developing but support wholeheartedly—is conservative, thoughtful, and based on careful review of complex evidence by experts.<sup>28,29</sup> This guideline should be required reading for all hematologists and oncologists treating patients. Medicare bureaucrats and members of the United States Congress currently reviewing governmental ESA policy might learn something from them as well.

#### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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