Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents in Patients with Cancer


Abstract

Purpose: Erythropoiesis-stimulating agents (ESA) are approved for the treatment of anemia in patients with nonmyeloid malignancies whose anemia is due to the effect of concomitantly administered chemotherapy. Since the 1993 approval of epoetin alfa in patients with cancer, the risk of thrombovascular events, decreased survival, and poorer tumor control have been increasingly recognized. The risks of ESAs in patients with cancer and the design of trials to assess these risks have been the topic of discussion at two Oncologic Drugs Advisory Committees in 2004 and 2007.

Experimental Design: Evaluation of randomized clinical trials comparing use of ESAs to transfusion support alone in patients with active cancer.

Results: Six studies (Breast Cancer Erythropoeitin Survival Trial, Evaluation of NeoRecormon on outcome in Head And Neck Cancer in Europe, Danish Head and Neck Cancer, Lymphoid Malignancy, CAN-20, and Anemia of Cancer) investigating ESAs in oncology patients showed decreased survival, decreased duration of locoregional tumor control, and/or increased risk of thrombovascular events. In these six studies, ESA dosing was targeted to achieve and maintain hemoglobin values in excess of current recommendations, and in three of the six studies, ESAs were administered to patients not receiving chemotherapy.

Conclusions: ESAs increase the risk of thrombovascular events and result in decreased survival and poorer tumor control when administered to achieve hemoglobin levels of ≥12 g/dL in patients with nonmyeloid malignancies. No completed or ongoing randomized, controlled trial has addressed safety issues of ESAs in patients with chemotherapy-associated anemia using currently approved dosing regimens in an epidermal tumor type. Additional studies are needed to better characterize these risks.

Erythropoiesis-stimulating agents (ESA) are approved for use in the treatment of anemia in patients with nonmyeloid malignancies whose anemia is due to the effect of concomitantly administered chemotherapy. These approvals were based on the ability to reduce the proportion of patients receiving RBC transfusions. Epoetin alfa [Procrit (Ortho Biotech) and Epogen (Amgen, Inc.)] and darbepoetin alfa (Aranesp; Amgen, Inc.) were approved for this indication in the United States in 1993 and 2002, respectively (Fig. 1). Epoetin alfa (Eprex; Janssen Pharmaceutica) and epoetin β (NeoRecormon; Roche) are marketed in Europe for this use. The Food and Drug Administration (FDA) considers safety information derived from any ESA to be relevant for characterization of risks for the entire class.

Because the 1993 approval of epoetin alfa in patients with cancer, FDA has monitored new data addressing the risks and benefits of ESAs in oncology patients and sought advice regarding relevance of new clinical trial results of ESAs at Oncologic Drug Advisory Committee (ODAC) meetings in May 2004 and May 2007. Recent studies provide evidence for shorter survival and poorer tumor outcomes when ESAs were used to achieve and maintain hemoglobin levels of 12 g/dL or higher, or in trials enrolling patients with cancer not receiving chemotherapy. Recent studies have also better characterized risks of thrombovascular events (TVE) that include myocardial infarction, cerebrovascular accident, angina, cardiac arrest, pulmonary embolism, and deep venous thrombosis. Increased TVEs occur both with recommended and unapproved dosing strategies.

Benefits of ESAs in Trials Supporting Approval for Patients with Cancer

US marketing approval for ESAs is based on demonstration of clinically important, statistically significant reductions in the proportion of patients receiving RBC transfusions (Table 1). Data pooled across 6 randomized, double-blind, placebo-controlled
trials enrolling 131 anemic patients with various solid tumors or lymphoid cancers, receiving either cisplatin-based (45%) or non-cisplatin-based (55%) combination chemotherapy, supported the epoetin alfa approval.1 Darbepoetin alfa approval was based on a single, randomized, double-blind, placebo-controlled trial (Study 980297) enrolling 314 anemic patients with non–small cell lung cancer or small cell lung cancer (SCLC) undergoing initial treatment with a cisplatin-based chemotherapy regimen. Use of ESAs to eliminate the need for transfusions in some patients’ results in avoidance of exposure to transfusions with its attendant risks of serious and fatal viral infections, transfusion-related acute lung injury, and blood group incompatibility. However, since the 1993 US approval of the first ESA for treatment of anemia due to cancer chemotherapy, the risks of transfusion-transmissible infections for hepatitis B virus, hepatitis C virus, and HIV have decreased (Fig. 2;2 ref. 1). Figure 3 illustrates the current risks of RBC transfusion (2–8).

No trial conducted in cancer patients has shown either improved survival or improved tumor outcomes.

### Tumor Promotion Risks of ESAs

The hypothetical risk of tumor promotion via erythropoietin receptors either on tumors or on tumor vasculature was identified during the review of initial studies supporting approval of Epoetin alfa. The initial trials supporting US approval of epoetin alfa were not designed to adequately evaluate or exclude evidence of tumor promotion due to the heterogeneity of the population and small size of the studies. Amgen agreed to conduct a post marketing study (N93-004) to investigate the effects of epoetin alfa on tumor response rates and survival in SCLC. The trial was terminated early due to slow accrual and study results submitted to FDA in Oct 2002. The results are discussed below.

In July 2002, the results of Study 980297 supported a new indication for darbepoetin alfa for treatment of anemia in cancer patients receiving chemotherapy. The data from this study revealed no evidence of adverse effects on progression-free or overall survival (OS); however, the sample size may have precluded the detection of small, yet clinically meaningful, differences.

In October 2002, data from Study N93-004 was submitted to FDA. During review of the N93-004 results, the results of two large, randomized studies were published. Although Study N93-004 did not provide evidence of adverse effects on survival or tumor response rate, the Breast Cancer Erythropoetin Survival Trial (BEST) and Evaluation of NeoRecormon on outcome in Head And Neck Cancer in Europe (ENHANCE) trials reported decreased 12-month survival rates (BEST), and lower locoregional control rates and decreased survival (ENHANCE) in patients randomized to receive ESA (9, 10).

Given the conflicting results, FDA sought advice regarding appropriate actions from the ODAC in May 2004. In addition to the BEST and ENHANCE trials, FDA also presented preliminary information (abstracts or communications) on other trials investigating the benefits of ESAs in patients with cancer, which suggested harmful effects. These included the CAN3-20 trial conducted in patients with non–small cell lung cancer (11), for which an unplanned analysis showed a trend toward increased mortality in ESA arm, and the Radiation Therapy Oncology Group 9903 trial in patients with head and neck cancer, which was terminated after an unplanned analysis revealed a nonsignificant trend to lower locoregional control rates and increased mortality in the ESA arm. In both trials, the unplanned analyses were triggered by the publications of the BEST and ENHANCE trials (9, 10).

FDA also presented available data from randomized controlled trials that terminated early because of evidence of increased rates of TVEs.1

The ODAC recommended the conduct of additional double-blind, placebo-controlled trials, with primary end points of OS and adequate power to detect potential effects on survival. The committee further recommended that such trials be restricted to homogeneous tumor subtypes and stages, contain standardized treatment approaches with prospectively defined, systematic

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3 Trials containing “CAN” in the title were conducted by academic investigators or groups with partial support from Ortho Biotech.
assessments of tumor progression to detect effects on tumor promotion, and include a systematic and prospective schedule of assessments for TVEs. Due to lack of well-characterized assays for erythropoietin receptors, tumor biopsy to assess for the presence of these receptors was deemed optional.

Several studies in Fig. 4 (GBR-7, Radiation Therapy Oncology Group 9903, GER-22, CAN-20, CAN-17, Arbeitsgemeinschaft Gynäkologische Onkologie, EPO-ANE-3010, 2001-0145, PRE-PARE, ARA-03, Danish Head and Neck Cancer, Groupe d’Etude des Lymphomes de l’Adulte) were proposed by Amgen, Inc. and Ortho Biotech to further assess safety concerns. All but one of these trials was ongoing at the time of the 2004 ODAC meeting, and the majority did not fully meet the ODAC study design recommendations for safety signal detection. Study design flaws included infrequent and insensitive baseline tumor measurement assessments, lack of systematic assessment for detection and recording of TVEs, and lack of placebo comparisons. The majority of studies used off-label dosing regimens that permitted or attempted to achieve hemoglobin values of >12 g/dL.

After the May 2004 ODAC, labeling changes as well as a “Dear Health Care Professional” letter were issued in June 2004 to include information from the BEST and ENHANCE trials. Postmarketing commitment status was given for study EPO-ANE-3010 (further described in the Discussion section), a study proposed at the ODAC 2004 meeting, which was designed to address the risks of tumor promotion using the FDA-approved dose of epoetin alfa in patients with metastatic breast cancer.

### Overview of Current Trials Addressing Risks of Tumor Promotion

On May 10, 2007, FDA convened the ODAC to update the committee on the status of the clinical trials assessing the effects of ESAs on tumor promotion and survival and to seek the committee’s advice. An overview of the six studies demonstrating adverse effects are provided in Table 2 and also summarized briefly below.

Postmarketing commitment study N93-004. Study N93-004, a randomized, double-blind, placebo-controlled trial in newly diagnosed, limited or extensive stage SCLC, enrolled 224 of a planned 400 patients and was terminated early for slow accrual. All patients received etoposide and cisplatin chemotherapy, appropriate radiation, and epoetin alfa or placebo for the duration of chemotherapy.

The trial was designed as a noninferiority study to exclude a 15% reduction in overall response rate after 3 chemotherapy cycles. Survival (OS) was a secondary end point. The study met its noninferiority end point, ruling out a potential decrease in response rate of >6% in the ESA-treated arm compared with controls. Survival was not significantly different [Hazard Ratio (HR), 1.17; 95% confidence interval (95% CI), 0.89-1.55] in the epoetin alfa and placebo-treated arms, respectively (12).

**BEST.** The BEST trial enrolled 939 patients receiving first-line treatment for metastatic breast cancer. Patients were randomized to receive either epoetin alfa to achieve and maintain hemoglobin levels of 12 to 14 g/dL or placebo for 12 months. Randomization was stratified by metastatic site but not chemotherapy regimen. The primary objective of the trial was to show superior 12-month survival rates in patients receiving ESAs. Secondary end points included overall response rate and time-to-progression.

The trial was terminated based on the recommendations of the data monitoring committee due to demonstration of a significant decrease in 12-month survival rates in epoetin alfa–treated patients (Table 2). The committee also noted increased mortality rates and shorter time-to-progression at 4 months in ESA-treated patients with no significant difference in overall response rate. Conclusions regarding effects on tumor progression are limited because >25% of patients enrolled had...
incomplete assessment of tumor sites at baseline and/or during treatment (10, 13).

**ENHANCE.** The ENHANCE study enrolled 351 patients receiving definitive radiotherapy for initial treatment of advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients were randomized to receive either epoetin β or placebo during radiotherapy; randomization was stratified by resection status. The primary objective was to show superior locoregional progression-free survival with ESAs; secondary end points included OS and locoregional control.

The trial showed a significantly shorter locoregional progression-free survival and shorter OS in epoetin β–treated patients compared with those receiving placebo (Table 2; ref. 9).

**Amgen study 2001-0145.** Study 2001-0145, a double-blind, placebo-controlled study, enrolled 596 patients with previously untreated, extensive-stage SCLC, and randomized patients to receive either darbepoetin alfa or placebo in conjunction with standard first-line chemotherapy. Demonstration of superior OS and greater increase in hemoglobin from baseline to end of chemotherapy were the primary end points of the trial. The trial failed to show an improvement in OS (HR, 0.93; 95% CI, 0.78-1.11).4

**Amgen study 2001-0103.** Study 2001-0103 enrolled 989 anemic patients with nonmyeloid cancers receiving neither chemotherapy nor myelosuppressive radiotherapy. The trial was intended to support expansion of product labeling for darbepoetin alfa. The primary end point was the proportion of subjects achieving a hemoglobin response of \( \geq 2.0 \) g/dL. Because of the heterogeneity regarding underlying cancer type and treatment, an accurate assessment of tumor promotion could not be made. Analysis in 2004 did not show a difference in survival between the study arms; however, there is presently a statistically significant decrease in OS among patients randomized to receive darbepoetin alfa (Table 2).

**Danish Head and Neck Cancer.** The Danish Head and Neck Cancer trial enrolled 522 patients with head and neck cancer. Demonstration of superior locoregional control rate was the primary end point; OS and disease specific survival were secondary end points. The trial was terminated after a planned interim analysis for futility. Based on summary results, the 3-year locoregional control rate was significantly inferior among patients randomized to darbepoetin alfa treatment, with a trend to shorter OS (Table 2; ref. 14).

**CAN-20.** The CAN-20 trial enrolled 70 of a planned 300 patients with unresectable or recurrent non–small cell lung cancer receiving only palliative care. Improvement in quality of life, the primary end point, was assessed by the Functional Assessment of Cancer Therapy-Anemia score. The trial was terminated prematurely by the steering committee of the trial. Based on the published results in 2007, significantly shorter OS was observed in epoetin alfa arm in an unplanned interim analysis (Table 2). Significant improvement in quality of life in the ESA-treated arm was not shown (11).

**Recent Actions**

The FDA issued three public health advisories (November 2006, January, and February 2007) to disseminate emerging safety information regarding the use of ESAs to achieve hemoglobin levels of >12 g/dL in patients with chronic renal failure or cancer. In March 2007, FDA modified the product labeling for Epogen, Procrit, and Aranesp to include a new black box warning: a summary of recent adverse findings in trials of
ESAs in patients with cancer, chronic renal failure, or undergoing major orthopedic surgery; and clarification of dosing instructions. The new label directs prescribers to “use the lowest ESA dose that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for blood transfusions” and states that ESA dosing should be discontinued for hemoglobin levels above 12 g/dL.

At the May 10, 2007 meeting of the ODAC, the FDA publicly sought advice regarding further regulatory actions concerning ESAs in oncology patients. The ODAC recommended that marketing authorization be contingent upon further restrictions in product labeling and the conduct of additional clinical trials. In addition, labeling should state that ESAs are not indicated for use in the specific tumor types investigated in the trials that showed adverse safety signals. The committee did not specify which tumor types should have restricted use.

Additionally, the ODAC recommended that product labeling should define a hemoglobin level for initiation of ESAs in asymptomatic patients, and that the hemoglobin level at which dosing is to be suspended should remain at 12 g/dL. Product labeling should recommend ESA discontinuation after the completion of a chemotherapy regimen and reevaluation of the need for administration of ESAs based on the degree of anemia observed with subsequent chemotherapy regimen(s).

**Discussion**

The demonstration of efficacy supporting licensure of ESAs in the oncology indication was based on the reduction in the proportion of patients receiving chemotherapy who required RBC transfusions. In the 14 years since the first ESA was approved for this indication, the infectious risks associated with RBC transfusions have decreased.

Six studies have disclosed decreased survival or poorer tumor outcomes with ESA use in oncology patients. In these 6 studies, ESAs were administered per an unapproved dosing regimen (e.g., a strategy to target a hemoglobin, >12 g/dL), and in three of the studies, for an unapproved indication (e.g., after radiation or in anemic patients not receiving chemotherapy). Further clinical investigations will be required to determine if safety signals identified in these studies can be extrapolated to labeled dosing regimens and indications.

Two trials, studies N93-004 and 2001-0145, which enrolled SCLC patients, did not show effects on tumor promotion. Results in trials with SCLC, an aggressive neuroendocrine tumor, may not be generalizable to more common epidermal malignancies. The finding of a non-inferior response rate in Study N93-004 should be viewed cautiously since 17% of patients had missing tumor response data, and the duration of response was not confirmed by repeat evaluation at least 4 weeks after the first assessment.4

Only two studies, Amgen Study 2001-0145 and EPO-ANE-3010, met most of the 2004 ODAC recommendations for adequately designed trials to evaluate ESA safety and tumor growth potential. Although Study 2001-0145 did not meet its coprimary end point of demonstrating that ESA administration resulted in superior OS, this does not exclude the possibility of inferior survival with ESA use. Study EPO-ANE-3010, conducted by Johnson & Johnson, is an ongoing open-label trial in 1,000 women receiving initial treatment for metastatic breast cancer. The trial is designed to exclude a 25% decrement in progression-free survival in the patients randomized to receive ESAs. ESAs are administered to achieve and maintain hemoglobin levels of 12 g/dL, consistent with current labeling. This trial is the only oncology trial assessing ESA effects on tumor promotion that also prospectively collects information on TVEs. Accrual on this trial has been slow, raising concerns about ultimately addressing the safety and tumor promotion potential of the approved dosing regimens.

Further studies are needed to characterize the safety of ESAs when used according to the labeled dose and indication, and to investigate their safety in other clinical settings (e.g., myelodysplastic syndrome) to confirm both the benefits and acceptability of risks of ESAs in oncology patients. These studies should incorporate the design elements recommended by the May 2004
ODAC, and the dose of ESAs as well as the maximum permissible hemoglobin should be consistent with current FDA labeling. The design of such trials must balance clinically meaningful noninferiority margins and timely accrual and completion. Multifactorial trials incorporating secondary ESA-related survival end points may be feasible if the trial is sized and designed appropriately to assess survival. Tumor types that have previously shown adverse outcomes in single trials with target hemoglobin >12 g/dL, as well as tumor types that have not been studied in adequately designed, double-blind, randomized trials are of interest. Additional areas for further study include the characterization of the benefits and risks of ESAs when dosed to different maximum hemoglobin levels, and capturing adverse events and concomitant morbidity associated with RBC transfusions, including the risk of transfusion-related acute lung injury, transfusion-associated graft versus host disease, febrile nonhemolytic transfusion reactions, and acute and delayed hemolytic transfusion reactions.

**Table 2.** Randomized, controlled trials with decreased survival or decreased locoregional control associated with erythropoiesis stimulating agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>ESA dose</th>
<th>Hemoglobin target (g/dL)</th>
<th>No. of enrolled (no. of planned)</th>
<th>Adverse outcome for ESA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST</td>
<td>Metastatic breast cancer, T2, T4, or node positive head/neck cancer</td>
<td>Epoetin alfa 40,000 U/wk</td>
<td>12-14</td>
<td>939 (1600)</td>
<td>12-mo survival (70% vs 68%; P = 0.0117)</td>
</tr>
<tr>
<td>ENHANCE</td>
<td>Non-myeloid malignancies</td>
<td>Epoetin alfa 300 IU/kg thrice/wk</td>
<td>≥15 (men)</td>
<td>351 (522)</td>
<td>Time-to-locoregional progression (HR, 1.69)*</td>
</tr>
<tr>
<td>Lymphoid Malignancy (2000-0161)</td>
<td>Lymphoprolif. malignancies</td>
<td>Darbepoetin alfa 2.25 μg/kg/wk</td>
<td>13-15 (men)</td>
<td>344 (428)</td>
<td>OS (HR, 1.39)†</td>
</tr>
<tr>
<td>Double-blind, placebo controlled trials; patients on chemotherapy or radiotherapy</td>
<td>CAN-20</td>
<td>Epoetin alfa 40,000 U/wk</td>
<td>12-14</td>
<td>70 (300)</td>
<td>OS (HR, 1.84)‡</td>
</tr>
<tr>
<td>Anemia of Cancer (2001-0163)</td>
<td>Non-myeloid malignancies</td>
<td>Darbepoetin alfa 6.75 μg/kg Q4W</td>
<td>12-13</td>
<td>989 (1384)</td>
<td>OS (HR, 1.30)§</td>
</tr>
<tr>
<td>Open-label trial (ESA vs transfusion support); patients on radiotherapy</td>
<td>DAHANCA</td>
<td>Darbepoetin alfa 150 μg/wk</td>
<td>14-15.5</td>
<td>522 (600)</td>
<td>Locoregional failure, P = 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: DAHANCA, Danish Head and Neck Cancer trial; PFS, progression free survival; Q4W, every 4 wk.
