Warning Flags for Erythropoiesis-Stimulating Agents and Cancer-Associated Anemia

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Disclosure of potential conflicts of interest is found at the end of this article.

A recent U.S. Food and Drug Administration (FDA) alert has raised further concerns about potential adverse effects of erythropoiesis-stimulating agents (ESAs) in anemic cancer patients who are not receiving chemotherapy [1]. The warning was issued following interim analysis of an investigator-led phase III trial of 989 patients with head and neck cancers randomized to receive darbepoetin alfa (Aranesp®; Amgen, Thousand Oaks, CA) or placebo (Danish Head and Neck Cancer Group [DAHANCA] 10 study, http://www.dahanca.dk). The enrolled patients were anemic but were not receiving chemotherapy. The trial data showed that darbepoetin alfa was associated with a higher mortality than with placebo (hazard ratio, 1.25; confidence interval [CI], 1.04–1.51) and, furthermore, darbepoetin alfa did not reduce the need for blood transfusion [2]. Hard on the heels of the darbepoetin alfa alert, Roche announced that it had temporarily suspended recruitment into its phase II dose-finding study with Continuous Erythropoietin Receptor Activator (CERA) in anemic patients with advanced nonsmall lung cell cancer (NSCLC) receiving chemotherapy [3]. Very recently, an unplanned safety analysis resulted in closure of a randomized placebo-controlled trial of epoetin alfa in NSCLC patients with disease-related anemia [4]. This analysis suggested poorer overall survival in patients with NSCLC treated with erythropoietin (Epo) [4].

Anemia in cancer patients has a multifactorial etiology. Anemia may develop secondary to impaired production of Epo or a blunted response of erythroid precursors to Epo [5]. Anemia may be exacerbated by chronic blood loss from tumor sites or be secondary to chemotherapy and radiotherapy. Debilitating fatigue, if it is secondary to anemia, can be managed by blood transfusions or ESAs to improve the quality of life (QOL) for anemic cancer patients. Interestingly, the effect of Epo therapy on QOL as a prospective outcome is not entirely consistent [6, 7].

Darbepoetin alfa is a hyperglycosylated Epo analog with an extended serum half-life [8] compared with available recombinant human Epos (epoetin alfa [Procrit®, Ortho Biotech, Bridgewater, NJ; Epogen®, Amgen; or Eprex®, Janssen-Cilag Ltd, High Wycombe, U.K.] and epoetin beta [NeoRecormon®, Roche, Basel, Switzerland]). CERA incorporates methoxy-polyethylene glycol polymers, which increase its mass to 60 kDa, twice that of Epo, and substantially prolong its half-life to about 135 hours. Darbepoetin alfa and CERA therefore have the therapeutic advantage of requiring less frequent administration for anemia management.

Previous reports have suggested that ESA therapy may be harmful to some groups of cancer patients. Henke and colleagues [9] described the outcome of epoetin beta treatment in a randomized trial of 351 anemic head and neck cancer patients undergoing radiotherapy. The therapeutic goal was normalization of hemoglobin to >14 g/dl in men and >13 g/dl in women. Unexpectedly, locoregional progression-free survival was worse in the Epo treatment arm compared with placebo. In the same year, another random-
ized trial, the Breast Cancer Erythropoietin Survival Trial (BEST), reported that overall survival was poorer in the patients assigned to the epoetin alfa arm [10]. The design of both of these trials has been criticized [11], particularly because enrolled patients were treated to higher target hemoglobin levels than the optimal treatment endpoint of 12 g/dl recommended by National Comprehensive Cancer Network guidelines [12].

In 2006, a Cochrane Review collated data on 9,353 cancer patients from 57 trials in which recombinant Epos or darbepoetin alfa was given to prevent or treat anemia [13]. There were significantly lower blood transfusion requirements in ESA-treated patients and suggestive evidence that ESAs may improve QOL. However, there was no significant difference in survival between ESA- and placebo-treated patients, although none of the trials included in the meta-analysis had adequate statistical power to really determine the effects of ESAs on overall survival. Nevertheless, the relative risk for thromboembolic events (such as transient ischemic attacks, stroke, pulmonary emboli, deep vein thrombosis, and myocardial infarction) was much higher in ESA-treated patients compared with controls (relative risk, 1.67; CI, 1.35–2.06) [14]. Overall, these studies have raised concerns that ESAs could, in certain circumstances, adversely affect survival in cancer patients and have led to speculation that these agents may enhance thrombosis, tumor growth, and neovascularization.

Epo was the first hematopoietic growth factor to be identified and for many years was assumed to act exclusively on erythroid progenitor cells. Following the detection of Epo mRNA in several organs and its receptor on multiple cell types, it became clear that Epo has pleiotropic effects extending well beyond the maintenance of red cell mass [5]. Of particular importance, experiments designed to study vascular sequelae (hypertension and thrombosis) of Epo treatment revealed that endothelial cells have large numbers of Epo receptors (EpoRs) and that Epo enhances their proliferation and migration in vitro [15, 16].

In recent years, several investigators have documented the presence of EpoR expression in numerous tumor cell lines and in breast cancer, melanoma, cervical squamous cancer, papillary thyroid cancer, endometrial cancer, NSCLC, and head and neck squamous carcinomata [17]. Several reports used polyclonal anti-EpoR antibodies for the immunohistochemical localization of EpoR in tumor cells within formalin-fixed paraffin-embedded tissue. A pertinent observation by Elliott and colleagues [18] highlighted that the polyclonal antibody C20, commonly used to detect the EpoR, also bound to other proteins, in particular heat shock protein 70 (hsp-70). Binding of this antibody was severely abrogated by two synthetic peptides based on the sequence of hsp-70. Subsequently, our group has demonstrated marked suppression of cytoplasmic staining in NSCLC tissue by the absorbed C20 antibody compared with nonabsorbed antibody [17]. These latter reports call into question the significance of the reported immunohistochemical studies using the C20 antibody and highlight the need for improved tools to study EpoR expression in neoplastic tissues.

Although ESAs bind to and activate EpoRs on the cell surface, it is possible that these agents could trigger multiple nonerythropoietic responses. Recombinant Epo is purified to contain isoforms with 9–14 sialic acid residues (similar to circulating endogenous Epo), but darbepoetin alfa, with its two additional glycosylation sites, contains up to 22 sialic acid residues [19]. In addition to increasing the serum half-life of darbepoetin alfa, the increased net negative charge on the molecule decreases its binding affinity for EpoR, thereby retarding its rate of cellular internalization. This is consistent with the observation that the biological activity of epoetin alfa was estimated to be fourfold greater than that of darbepoetin alfa on a mole-per-mole basis [20]. It is conceivable that darbepoetin alfa, circulating at higher levels and for longer periods than an equivalent dose of epoetin alfa, could increase proliferation of endothelial cells, leading to neovascularization in vivo.

To understand the adverse outcomes of administering ESAs to patients with cancer, it is imperative to examine the functionality of EpoR in neoplasia. Our group has shown that Epo, at pharmacological concentrations, can activate three major signaling cascades, namely, the Janus kinase 2/signal transducer and activator of transcription 5, Ras/extracellular signal–related kinase, and phosphatidylinositol 3’ kinase/Akt pathways in neoplastic cells, such as the NSCLC cell line H838 [21]. Furthermore, we have found impaired downregulation of EpoR in this cell line caused by lack of ubiquitination following Epo stimulation compounded by impaired suppressor of cytokine signaling (SOCS)-3 induction and extremely delayed SOCS-1 response downstream of Epo stimulation [22]. If these findings in vitro are replicated in tumor tissues, then impaired downregulation and degradation of EpoR have clinical implications for patients receiving ESAs for cancer-related anemia.

Continued scrutiny of both clinical trial data and current practice patterns is important to fully understand the risk–benefit ratio of ESA treatment in anemic cancer patients. There may be lessons to be learned from recently published trials (the Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR] and Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin Beta [CREATE] trials) of Epo treatment for the anemia of cancer.
Table 1. Trials showing survival disadvantage in cancer patients not on chemotherapy

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<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Reason for halting</th>
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<tbody>
<tr>
<td>DAHANCA [2]</td>
<td>Darbepoetin alfa</td>
<td>Greater mortality than with placebo</td>
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<tr>
<td>Henke et al. [9]</td>
<td>Epoetin beta</td>
<td>Poorer locoregional progression-free survival</td>
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<tr>
<td>Wright et al. [3]</td>
<td>Epoetin alfa</td>
<td>Shorter overall survival in treated patients</td>
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Abbreviation: DAHANCA, Danish Head and Neck Cancer Group.

chronic kidney disease [23, 24]. These trials have highlighted again that correction of anemia in patients with chronic renal failure to a target hemoglobin level >12 g/dl does not appear to be beneficial. Cardiovascular events were more common in patients with higher hemoglobin levels, a finding consistent with a trend reported almost a decade ago in the controversial Normal Hematocrit Trial in dialysis patients with cardiac disease [25].

Additional research is urgently needed to determine the effects of ESAs on risk of thrombosis, rate of tumor growth, and neovascularization both in vitro and in vivo. Further analyses of patient outcomes in current investigator-led trials of ESAs for cancer-related anemia are eagerly awaited. In the meantime, it would seem prudent not to exceed the current maximum target hemoglobin guideline of 12 g/dl for anemic cancer patients [12].

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

P.G.J. has acted as a consultant to Amgen and Roche.

REFERENCES


22 Dunlop EA, Maxwell AP, Lappin TR. Impaired downregulation following

