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July 2005 | Issue 2 : Volume 1

HEMATOLOGY eDIGEST

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In this Issue... *Is Therapy with Erythropoietic Agents Safe in Patients with Cancer?*

Recombinant erythropoiesis stimulating proteins (ESPs), including epoetin alfa, epoetin beta and darbepoetin alfa have been applied with rapidly increasing frequency to the treatment of anemic cancer patients in the United States and Europe with the widening recognition that this treatment is associated not only with a decreased transfusion risk, but also with improvements in functional status and quality of life.(1-6) There is no longer controversy regarding these benefits of successful treatment of anemia in patients receiving chemotherapy.

However, the effects, if any, of ESP therapy on the natural history of malignancy and ultimately on the survival of patients with cancer remain less well documented. In this issue, we focus on the growing body of research that has been exploring the positive and negative results of using ESP agents in patients with various cancers.

Commentary & Reviews

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John Glaspy, MD

+ **Guest Editor of the Month:**
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Faculty Disclosure: Dr. Glaspy has indicated research support with Amgen, Roche and Johnson & Johnson.

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Commentary

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Anemia correlates with an unfavorable outcome for a variety of malignancies. More importantly, in preclinical models, tissue hypoxia associated with anemia decreases the responsiveness of tumors to radiotherapy and chemotherapy; conversely, increases in hemoglobin are associated with increased responsiveness. These data suggest that the correction of anemia in cancer patients undergoing chemotherapy or radiotherapy might improve therapeutic efficacy and, therefore, survival.(7) In a randomized, placebo-controlled trial of epoetin alfa in anemic cancer patients undergoing chemotherapy, carried out with QOL as the primary endpoint, a trend toward improved survival was observed in patients receiving epoetin alfa.(4) A similar finding was reported for patients with small cell lung cancer randomized to darbepoetin alfa compared to those randomized to placebo.(5) While these observations are not definitive, they are consistent with pre-clinical models and the hypotheses generated.

In 2003, the results of two randomized, placebo-controlled trials of epoetin alfa (8) and epoetin beta (9) for the prevention of anemia during chemotherapy for breast cancer or radiotherapy for head and neck cancer, respectively, were reported. These studies suggested that ESP therapy may be associated with a reduced survival and/or loco-regional disease control. These reports led to a meeting of the Food and Drug Administration's Oncology Drug Advisory Committee (ODAC) in May, 2004. The briefing documents submitted by the sponsors of each of the three ESPs in clinical use in the United States and Europe as well as the FDA's analysis are available [online](#) and remain an excellent resource for the interested reader. Summary statistical approaches to inferring tumor effects of each ESP on tumor progression or survival showed no significant effects, and no trends suggesting a deleterious effect. A recently published meta-analysis of data from randomized trials of epoetin alfa and epoetin beta by the Cochrane group shows a marginally significant trend toward improved survival in ESP treated patients.(10) Although these reviews are reassuring, they are limited to trials of ESPs for the treatment, rather than the prevention of anemia, and leave unaddressed the concern raised by the two prevention trials.

Over the last two years, most of the work on potential deleterious effects of ESPs on survival have focused on the hypothesis that there are functional erythropoietin receptors (EPO-R) on tumor cells, and that pharmacologic doses of ESPs act on these receptors to inhibit apoptosis or promote proliferation of tumor cells. Some studies of human tumors have reported the identification of EPO-R, supporting this hypothesis.(11-14) However, there are profound technical difficulties in reliably detecting EPO-R, in demonstrating that the receptors are expressed on the membrane of tumor cells, as opposed to stroma cells, and are functional. There are corresponding shortcomings in the available literature. It is a mistake to assume that any negative effects of ESPs on survival are mediated by tumor cell EPO-R, as opposed to effects on other EPO-R bearing cells (endothelial cells in tumor vasculature or other vascular endothelial cells promoting increased thrombosis risk), or independent of EPO-R through some effect of supra-normal hemoglobin levels. The clinical data to date suggest that if there is any negative effect of ESPs on tumor progression or survival,

this effect is limited to situations in which ESPs are administered to patients who are not anemic. The most plausible theory for a potential mechanism of decreasing survival by ESPs should explain that for anemic cancer patients there appears to be no effect or a benefit from ESPs. There are several large, well designed, randomized trials of ESPs for the prevention of anemia in several tumor types during chemotherapy or radiotherapy currently in progress. Until these results are available, ESP therapy should be restricted to the treatment of anemia, with a target hemoglobin concentration of 12 g/dL.

In the meantime, the following questions will remain:

- Does therapy with erythropoietic agents change the survival rate of cancer patients?
- How does the effect on survival depend upon hemoglobin level (anemic vs. non-anemic), tumor type, treatment modality (chemotherapy vs. radiotherapy), or stage of disease?
- If the effect on survival is a positive one, what is the mechanism and how can this effect be maximized?
- If the effect on survival is a negative one, what is the mechanism (tumor EPO-R, tumor vessel EPO-R, blood viscosity, hemoglobin level) and how can this effect be eliminated?

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NEGATIVE SAFETY SIGNALS - ESPS TO PREVENT ANEMIA

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Henke et al randomized 351 patients with squamous cell cancer of the head and neck scheduled to undergo radiotherapy to receive epoetin beta or placebo prior to and during RT if the hemoglobin level was <12 g/dL (women) or <13 g/dL (men). The primary endpoint was an event-time analysis of locoregional progression. On an intent-to-treat based analysis, a statistically significant decrease in locoregional progression free survival and in overall survival was observed (for survival, the observed relative risk was 1.39, confidence intervals 1.05-1.84, $p=.02$). Of note, 82% of patients treated with epoetin beta experienced supra-normal hemoglobin levels.

This trial had two deficiencies that make assessing its meaning difficult: 1) there were important imbalances in baseline prognostic factors that biased toward improved local control and/or survival in the placebo group, including less tumor relapse before treatment, fewer current smokers, fewer T4 and N2 tumors, and fewer patients with inoperable tumors; and 2) a large number of protocol violations including variations in radiotherapy, failure to assess local control (the primary endpoint of the study), and study medication errors. When the survival analysis is limited to patients who received protocol-specified radiation, the local control and overall survival differences are not significant; when the analysis is restricted to patients who received the specified radiation, had the primary endpoint assessed, and received the correct study medication, the differences in outcome in the two study groups are eliminated. In addition, the difference in locoregional progression and survival was limited to the subset of patients with hypopharyngeal tumors.

Obviously, the observation of an apparent negative survival impact is very important, and needs to be further investigated via further trials. A larger randomized trial of an ESP in patients with head and neck cancers receiving radiotherapy is in progress, and the results should be available within two years.

The Leyland-Jones trial has not been published in full, but reported as a brief communication; additional information is available on the [FDA website](#).

In this trial, 939 patients with metastatic breast cancer at 139 sites in 20 countries were randomized to receive either epoetin alfa or placebo in conjunction with what was supposed to have been first-line chemotherapy. The objective of the trial was to determine the effects of the prevention of anemia on survival in breast cancer, following upon the Littlewood trial (reviewed elsewhere in this issue) that suggested that survival in breast cancer may be increased by epoetin treatment. There was a statistically significant observed decrease in one year survival associated with epoetin alfa treatment, due to an excess in very early deaths. (The early death rates were actually higher than expected in both groups, increasing concern that ineligible, low performance status and/or heavily pre-treated patients were being enrolled.) Twelve month survival (the primary endpoint) was 76% in the placebo group and 70% in the epoetin group ($p=.01$).

There were several deficiencies in the conduct of this trial, some of which are detailed in the [ODAC Johnson and Johnson briefing document](#), including: a failure to collect and stratify for known prognostic factors in breast cancer (HER-2/neu status, extent and sites of disease involvement, disease free interval), enrollment of ineligible patients, and insufficient documentation of the causes of these early deaths (thrombosis vs disease progression vs other). As with the Henke study, these results are of concern, but their significance is unclear.

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☰ POSITIVE SAFETY DATA - ESPS TO TREAT ANEMIA

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Bohlius et al report on the results of the Cochrane meta-analysis of the placebo-controlled trials of epoetin alfa and epoetin beta as it relates to the effects of these agents on the overall survival of cancer patients. This publication is a follow up on the prior report of this group's meta-analysis of multiple endpoints for recombinant EPO in this setting. The comprehensive literature review included 27 trials involving 3,287 patients. The authors found that there was a trend suggesting improved survival associated with rhuEPO treatment (hazard ratio .81, 95% CI 0.69 to 0.99).

While these findings are very important and reassuring, there are limitations. First, meta-analyses are well

known to have limitations due to publication bias and other factors, and they are no substitute for large, well designed and adequately powered trials. Second, the studies reviewed by this group were limited to those that enrolled anemic patients, and did not include the two trials published to date (Henke et al and Leyland-Jones, reviewed herein) with negative survival findings. Finally, darbepoetin alfa trials were not included in this analysis. Limitations notwithstanding, the findings of this meta-analysis provide an important counter-balance to the Henke and Leyland Jones trials, particularly with respect to any hypothesis that rhuEPO acting through EPO-R leads to growth and/or survival of human cancers.

Publishing their results in 2001, Littlewood et al randomized 375 anemic (hb <10.5 g/dL) patients with non-myeloid malignancies undergoing chemotherapy to receive epoetin alfa or placebo. The primary endpoints were transfusion rates and quality of life change, but survival data were also collected. There was a clear trend in the data suggesting improved survival in the epoetin arm for both the subset with non-myeloid hematologic malignancy and with solid tumors, most of which were breast cancers. The observed death hazard ratio for the placebo group was 1.3. This observation formed the rationale for the development of the Leyland-Jones trial summarized this issue.

While appropriate as a hypothesis generating study, the Littlewood trial was not powered for the survival endpoint, and no provisions were made to assure that patients in the two treatment groups were balanced for baseline predicted survival or received standardized, equivalent anti-cancer therapy. Another important difference between this trial and that reported by Leyland-Jones is that patients in the Littlewood study were anemic, in accord with the consistent observation to date that negative effects on survival have not been observed when anemic cancer patients have been treated with ESPs. In the setting of treatment (as opposed to prevention) of anemia, the observed effect has been either no impact or a favorable effect on survival.

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☰ TUMOR EPO-R AS A POTENTIAL MEDIATOR OF ESP EFFECTS ON SURVIVAL

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Acs et al studied 184 invasive breast cancer specimens and 158 samples of intraductal breast cancer and benign mammary epithelium using immunohistochemical (IHC) techniques to determine EPO-R and EPO protein expression. The hypothesis they were addressing was that, because tumors frequently develop hypoxia due to inadequate perfusion in areas most distant from vascular structures, hypoxic tumor cells may adapt through the expression of EPO and EPO-R, with resultant diminished apoptotic potential and consequent resistance to therapy. The EPO-R IHC reagent employed was the C20 rabbit polyclonal antibody. The authors observed "weak" EPO-R expression by benign mammary cells with increased relative expression in carcinomas, especially those of high histologic grade. The authors conclude that EPO-r expression may play an important role in breast carcinogenesis.

These data are of interest, especially in light of the results of the Leyland-Jones trial of rhuEPO therapy for patients with breast cancer. However, there are serious methodological issues remaining to be addressed before it can be concluded that EPO-R is expressed during breast oncogenesis. As noted, the IHC demonstration of EPO-R protein in tumor samples is not sufficient to demonstrate that the protein is either expressed on the cell surface or is functional. Much more importantly, there is mounting evidence that several of the EPO-R IHC reagents, including the one utilized in this study, are not specific for EPO-R and also bind to other cancer-related proteins containing the peptide sequence utilized to generate the anti-sera. This evidence includes the observation that these reagents stain tissues from EPO-R knockout mouse embryos.

Based upon a hypothesis similar to that of Acs and following up on the clinical trial report by Henke regarding rhuEPO and patients with head and neck cancer, Arcasoy et al studied a marker of tissue hypoxia as well as EPO-R and EPO protein expression in tumors from patients with head and neck cancer. After injection of the hypoxia marker pimonidazole, 74 biopsies were obtained from tumors in 21 patients. EPO-R was studied with IHC using the same C20 polyclonal antibody used in the Acs study. Results included the detection of EPO-R protein in 97% of biopsy specimens (with EPO co-expression in 905 of the samples). Co-localization of pimonidazole and EPO staining was inconsistent.

This work has obvious relevance to the Henke study, suggesting a mechanism — enhancement of a constitutive molecular adaptation to hypoxia by human tumors — for rhuEPO therapy increasing radio-resistance of head and neck cancers. As with the Acs study, the most serious limitation to this work is the absence of data demonstrating that the protein being detected in these tissues with the C20 IHC is EPO-R, as opposed to other proteins reactive with this polyclonal anti-sera. The majority of studies have not detected increased EPO-R protein on tumor cells when more specific techniques, such as competitive EPO binding are used, and have failed to find EPO-R gene amplification or increased levels of EPO-R transcript in tumor cells. Further work using more rigorous techniques and better characterized reagents are clearly needed.

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At the conclusion of this activity, participants should be able to:

- Discuss the existing data suggesting that in anemic cancer patients, treatment with erythropoietic agents does not adversely impact survival.
- Evaluate the clinical trial data associating decreased survival with erythropoietic therapy for cancer patients who are not anemic.
- Describe the limitations of current data regarding the putative presence of functional erythropoietin receptors on human cancer cells.

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