CLINICAL VIGNETTE

Are We Harming Cancer Patients When We Use Erythropoiesis Stimulating Agents (Esas)?

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Anemia is common in patients with cancer. Anemia can cause increased fatigue and decreased exercise tolerance impairing functional status. In addition, anemia is associated with poorer outcomes in cancer patients, including decreased survival[1]. Interventions to ameliorate anemia might lead both to improved patient quality of life (QoL) and perhaps better disease outcomes.

Erythropoietin (epo) is the main physiologic growth factor for red blood cell (RBC) production. Since epo is primarily produced by the kidneys, patients with severe chronic kidney disease (CKD) and end stage renal disease (ESRD) almost universally develop moderate to severe anemia. In patients with CKD and ESRD, levels of epo rise significantly as the hemoglobin (Hb) drops below 10[2]. After the cloning of epo and the clinical development of epoetin alfa (epo-A), the first ESA, there was an explosion of pre-clinical and clinical studies. In the laboratory, epo signaling through the erythropoietin receptor (epo-R) has been shown to stimulate gene expression involved in a variety of processes beyond erythropoiesis, including increased angiogenesis and glycolysis[2]. Epo-A was initially used in patients with ESRD. Early success in improving anemia in dialysis patients led to rapid testing in several other patient populations, including patients with CKD and patients with cancer undergoing myelosuppressive chemotherapy (CT) or radiation therapy (RT) treatment. Darbopoietin alfa (darbo), a new molecule with 5 different amino acids than epo and a 3-fold longer in vivo half life which signaled through the epo-R, was developed subsequently and shown to have similar pre-clinical and clinical effects to epo-A[3].

A meta-analysis of 57 studies involving over 9000 patients showed both ESAs reproducibly increased Hb and decreased the number of RBC transfusions in cancer patients receiving CT, with a relative risk (RR) of transfusion of 0.64[4]. An early study of QoL in lung cancer patients demonstrated improved QoL as Hb was increased from less than 10 up to 13[5]. Subsequent studies in cancer patients with CT-induced anemia showed improved QoL, using multiple questionnaires, with Hb increases up to 13[6]. However, the Federal Drug Agency (FDA) approval of both ESAs in cancer patients receiving myelosuppressive CT was only based on reduction in transfusions, since there was no FDA-approved measure of QoL specific to anemia. Given the efficacy of ESAs in ameliorating anemia and preclinical models using either ESA suggesting that increasing Hb might improve cancer outcomes in patients receiving CT or RT[7], several studies were initiated in the late 1990s in cancer patients undergoing CT or RT to determine whether clinical outcomes could be improved by normalizing Hb.

By the late 1990s, approximately 10 years into the rapidly expanding clinical use of ESAs, adverse events had been described in ESRD patients[8]. Specifically, 1231 ESRD patients with either congestive heart failure (CHF) or ischemic heart disease (IHD) were randomized to receive epo targeting either an hct of 30 or 42[8]. The study was stopped early because a trend toward increased death and non-fatal myocardial infarction (MI), with a RR of 1.3 of either outcome, was observed in the high hct group[8]. In addition, ESA treatment was associated with an increased risk of venous thromboembolic events (VTEs), with more recent meta-analyses showing a RR of VTE of 1.57 with ESA treatment[9].

These adverse events did not initially affect the use of ESAs in oncology. However, by the mid-2000s, several studies demonstrated inferior progression free survival (PFS) and overall survival (OS) in cancer patients undergoing CT or RT who received ESA treatment[4, 10, 11]. For example in an RT study with progression free survival (PFS) as the primary endpoint, 351 patients with locally advanced head and neck cancer with any degree of anemia (Hb < 13 in men and Hb < 12 in women) were treated with RT to a standard 60 Gray and were randomized to receive epo or placebo, with epo initiated before and continuing through RT targeting a Hb of 14-15[12]. The epo-treated patients achieved the desired Hb target but, unexpectedly, had a statistically significantly poorer loco-regional PFS, with a RR or 1.62 for progression with epo, and poorer OS, with a

RR of 1.39 of dying with epo[12]. In an early-reporting CT study with overall survival (OS) as the primary outcome, 939 patients with metastatic breast cancer and good performance status were treated with investigator choice of first line CT and were randomized to either weekly epo treatment targeting a Hb of 12 – 14 or placebo[13]. The study was halted early due to an interim analysis showing increased cancer progression and VTEs during the first 4 months of epo treatment[13]. The 1-year survival was 70 % with epo-treated patients and 76 % with placebo patients, representing a RR of dying of 1.37 with epo treatment[13]. While each study can be criticized for some imbalances in pre-treatment patient prognostic factors and the specific RT or CT delivered that may have favored the placebo arms, both studies were relatively large and had pre-specified survival endpoints with statistically significant differences.

Two large meta-analyses of randomized clinical trials (RCT) of ESAs in cancer patients receiving CT or RT have recently been published[10, 11]. In aggregate, the RR of dying with ESA therapy was 1.04 to 1.06, which was not statistically significant in either study[10, 11]. In the most recent study involving 60 clinical trials and 15,323 patients, subset analyses suggested that poorer outcomes were more common if ESAs were initiated with a Hb > 12 or targeted a Hb > 13[11]. A table summarizing the 4 RT and 21 CT trials included in the most recent meta-analysis[11] is available in a 2012 UpToDate summary article[14]. While poorer survival with ESA treatment in cancer patients receiving CT or RT has not been consistently observed, the current data clearly shows an increased risk of VTE and a disturbing trend in tumor progression and survival, particularly when ESAs are initiated at higher Hb or are targeting higher Hb.

As the studies of ESAs in cancer patients undergoing CT or RT were maturing, darbo was being tested in advanced cancer patients off therapy to determine whether anemia would be improved and transfusions decreased by darbo treatment. 989 patients with advanced cancer and anemia (Hb < 11) were randomized to either darbopoietin or placebo for a 16 week treatment with a target Hb of 12 and withholding darbo at a Hb > 13[15]. Unexpectedly, the trend towards higher Hb and lower RBC transfusions was not statistically significant with darbo ((p = 0.07); 15). In contrast, there was a statistically significantly increased cancer progression at 16 weeks (22 vs. 16%) and decreased OS with darbo , resulting in a RR of dying of 1.22 and a median survival of 37 weeks with darbo as opposed to 47 weeks with placebo[15]. Poorer survival was seen despite avoiding higher Hb initiation or Hb targets with ESA treatment, with the mean achieved Hb of 10.5 with darbo[15].

These studies elicited a dramatic response by the FDA and professional cancer specialty societies. Severe restrictions were imposed on the use of ESAs in oncology. A formal Risk Management and Mitigation Strategies (REMS) process was introduced in 2010. Current FDA guidelines include: 1. ESAs could only be used in patients with cancer who are receiving myelosuppressive CT. 2. ESAs should only be started when the Hb < 10. 3. ESA use should target the lowest Hb level to avoid transfusions. 4. ESAs should not be given with a Hb of 12 or higher. 5. ESAs should be avoided if the goal of treatment is cure. 6. All patients must complete a documented informed consent before receiving ESAs, called APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of Erythropoiesis stimulating agents), which describes the poorer cancer outcomes and VTE risks[16]. While the main impetus to the restrictions in ESA use were driven by patient safety concerns, the FDA likely also appreciated that ESAs were a strictly supportive care intervention and that the annual cost of ESA in the United States exceeded $10 billion in 2006[17]. In addition, there is no direct evidence supporting points 2 and 4, since no studies specifically compared different initiation and stopping Hb targets with ESA therapy. Point 3 is nebulous, but allows the oncologist to determine the target Hb, which reliably avoids transfusions. While a few studies in locally advanced but potentially curable cancers demonstrated inferior disease free survival[10, 11], the meta-analyses do not demonstrate a statistically significant inferior survival, so point 5 is also questionable.

No convincing explanation has emerged for the poorer outcomes seen with several ESA studies in cancer patients. The increased risk of VTEs, while consistent across studies, is relatively modest, with a RR of VTE of 1.7[9], and VTEs would not explain increased cancer progression. In vitro studies demonstrate epo-R expression in non-hematopoietic tissues, including cancer cell lines and tumor explants[2]. This suggests possible direct ESA stimulation, through cancer cell epo-Rs, of genes leading to increased cancer cell survival and proliferation. However, the evidence for epo-R on cancer cells is debatable, given the poor specificity of the anti-epo-R antibody used in most studies[17], and biological responses of cancer cells to epo in vitro

require supraphysiologic concentrations of ESAs[2]. ESA treatment might induce endothelial cell and platelet activation and even stimulate angiogenesis and revascularization of cancers, but evidence supporting these mechanisms is limited[2].

Clearly the saga of ESA use in cancer patients presents a cautionary tale for both oncologists and the pharmaceutical industry. Attempts to normalize Hb during RT and CT treatment with ESAs, which could potentially lead to increased usage and sales, appear to have exceeded the Hb level at which patient QoL and ultimate cancer outcomes with therapy are optimized. In addition, less toxicity and risk are acceptable with a purely supportive care intervention, like ESAs, as opposed to CT or RT, which must be shown to improve clinically meaningful cancer outcomes. While the current FDA limits on ESA usage in cancer patients are debatable, a REMS strategy involving both informed consent and restrictions in the use of ESAs, is reasonable.

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