EDITORIALS

Erythropoiesis Stimulating Agents: A Personal Journey

Brian Leyland-Jones

Correspondence to: Brian Leyland-Jones, MB BS, PhD, Edith Sanford Breast Cancer Research, PO Box 5039, Rte 5031, Sioux Falls, SD 57117-5039 (e-mail: brian.leyland-jones@sanfordhealth.org).

I write this editorial in deference to the many experts who devote their careers to this important field. In this editorial, I simply report the journeyman route of a medical oncologist who is desperately trying to improve the outcomes of women suffering from breast cancer.

At the end of the 1990s, there was much hope that erythropoiesis stimulating agents (ESAs) would improve the survival of cancer patients. It was all so very obvious. Elegant partial oxygen pressure (pO2) histograms showed differential oxygenation between normal and malignant tissues, and patients with higher tumoral pO2 were demonstrated to have improved survival [1,2]. Beverly Teicher had shown the oxygen-dependency of cancer and had published oxygen enhancement ratios for the representative members of the key mechanistic classes of anticancer agents. Preclinical models had shown that erythropoietin restored the anemia-induced reduction in antineoplastic cytotoxicity, eg, cyclophosphamide [3]. Hence, the ESAs, by raising hemoglobin levels, improving oxygenation, and increasing cytotoxicity of our antineoplastics, simply must improve survival!

ESAs even improved antitumor immune response [4] and increased radiosensitity [5,6]. Many of my friends and colleagues will remember slide sets that I showed, listing various references to the beneficial effects of ESAs on tumor regression in a variety of tumor types [7–10].

Then along came the famous Glaser et al. data [11] of epoetin increasing hemoglobin levels and improving prognosis in anemic patients with head and neck cancer and the Littlewood trial [12] that showed an improvement in 12-month survival from 49% to 60% for epoetin vs placebo and even an increase in overall survival from 11 to 17 months.

Put all of this together and one could not have a better background for our own BEST INT76 [13] and Henke trials [14]. Even the names were optimistic: Breast cancer Erythropoietin Survival Trial (BEST), the Breast Cancer-Anemia and the Value of Erythropoietin Trial (BRAVE). The rest is, as they say, history. So where do we stand now?

In August 2003, I wrote a letter to *Lancet Oncology* [15], referencing the imbalance of risk factors between treatment groups and other issues in INT76 and documenting several methodological issues that hindered interpretation of both the BEST and Henke trials, with a conclusion that they "generated more questions than answers."

Ten years later, in my humble opinion, there is no doubt: virtually all of the meta-analyses, including three of the most recent: the Tonelli et al. 2009 meta-analysis [16] of 52 trials that included 12006 patients with a relative risk (RR) for all-cause mortality of 1.15 (95% confidence interval [CI] = 1.03 to 1.29); the Glaspy et al. 2010 meta-analysis [17] of 60 studies that included 15 323 patients with an odds ratio for mortality of 1.05 (95% CI = 0.97 to 1.15); and the Tonia et al. analysis [18] of 78 studies that included 19 003 patients with a hazard ratio (HR) for overall survival of 1.05 (95% CI = 1.00 to 1.11) show worse survival.

One caveat to the above is design flaws, imbalance of risk factors between treatment groups [15] and trial quality ("the 52 trials were generally of poor to moderate quality") [16] affecting much of the data base. Another observation is that adverse odds ratio for survival appears to be driven by eight of the 60 trials [17,19]. Glaspy et al. [17] even notes that simply including the long-term follow-up of our BEST trial (ie, survival data collected beyond the 1-year treatment period) instead of the published data [13,20], reduces the mortality odds ratio in the meta-analysis to 1.02 (95% CI = 0.94 to 1.11; I2 = 0%) using either the random-effects or fixed-effects model.

The Bohlius meta-analysis [21] included studies specifically designed to treat to a high-target hemoglobin concentration (ie, ≥120 g/L) and nonchemotherapy studies. In the analysis of mortality during the active study period for all 53 studies, the hazard ratio was 1.17, and the 95% confidence intervals excluded unity. To assess the effect of individual studies on the combined estimates, the *Lancet* authors excluded one study at a time from the pooled analysis. Of note, when our BEST study was excluded, the hazard ratio for mortality during the active study period decreased to 1.03 from 1.10, and the 95% confidence interval (0.90 to 1.18) included unity. Exclusion of other studies did not substantially affect the results.

Another critical caveat to the above is the target hemoglobin. Pertinent to the above discussion of the 2009 *Lancet* overview, the use of ESA treatment in our BEST study differed substantially from the currently labeled guidance, which states that treatment should be withheld if the hemoglobin concentration exceeds 120 g/L. In our BEST study, the target hemoglobin concentration was high (120–140 g/L), subjects were started on ESA treatment at hemoglobin concentrations above the labeled guidance (130 g/L), and ESA treatment continued for up to 12 months regardless of whether subjects were still receiving chemotherapy. The *Lancet* data for the chemotherapy subset, excluding our BEST study, was consistent with the favorable benefit-risk profile seen when ESAs are used according to labeled guidance. Moreover, the Paladini 2008 [22] meta-analysis of trials performed within label (17 studies, 3788 patients, with baseline hemoglobin <11 g/dL) found no increase in mortality risk (RR = 0.95, 95% CI = 0.88 to 1.03; *P* = .22).

With regard to disease progression, this seems to be the most controversial area. In terms of the two most classical cell lines,

MDA-MB-231 and MCF-7, EpoR expression was localized to a cytosolic distribution and did not transduce a signaling cascade in tumors that leads to tumor growth (19) My own interpretation of the preclinical literature is that there are inconsistent reports of proliferation only seen with epoetin concentrations fivefold to 100-fold greater than achieved clinically. The data from my own BEST trial is consistent with this lack of disease progression (HR = 1.00). With regard to the effect of ESAs on tumor response and disease progression, one of the challenges is that most of the evaluated studies to date were not designed to formally assess this outcome. In general, studies have not rigorously assessed the endpoint of tumor progression to the same standard that would be required to demonstrate the efficacy of a therapeutic agent.

At the combined epoetin alfa (Epogen/PROCRIT) and darbepoietin Oncologic Drugs Advisory Committee meeting in March 2008 (20), a meta-analysis of progression-related endpoints in 24 studies (n = 9197; 4640 ESA, 4557 control) yielded an odds ratio of 1.02 (95% CI = 0.90 to 1.15). The Glaspy et al. 2010 meta-analysis (17) reported an odds ratio for disease progression for each of the eight studies of concern and concluded that use of ESAs does not consistently impact disease progression, with the hazard ratios for disease progression ranging from 0.85 to 1.01. I furthermore refer to our team's article published in the *British Journal of Cancer* last year in which we concluded, "Preclinical data to date suggest that tumor cells either a) do not express EpoR, or, b) express low levels of EpoR molecules that are non-functional and/or are not present at the cell surface. Although assessment and definition of disease progression vary across studies, the current clinical data suggest that ESAs may have little effect on disease progression in chemotherapy patients" (19).

To specifically address the effect of EPREX® (*epoetin alfa*) on tumor progression and mortality within the labeled indication, we are conducting study EPO-ANE-3010, an open-label, randomized and controlled trial in metastatic breast cancer patients specifically designed to measure progression-free survival (primary endpoint) and overall survival (secondary endpoint).

The last critical area is the well-recognized risk of thromboembolic events. The Bohlius et al. 2006 Cochrane (23) and *Journal of the National Cancer Institute* (24) overview observed that treatment with epoetin or darbepoetin increased the risk of thrombo-embolic events (RR = 1.67, 95% CI = 1.35 to 2.06; 35 trials and 6769 patients). The Tonelli et al. (16) overview reported an increased risk of thrombotic events (RR = 1.69, 95% CI = 1.27 to 2.24). The Glaspy et al. 2010 overview (17) reported an increased risk for venous-thromboembolic events (44 studies: OR = 1.48; 95% CI = 1.28 to 1.72). Bennett et al. (25) performed another meta-analysis of VTE associated with ESAs in patients with cancer. There were 334 (7.5%) venous thrombo-embolism events reported for the 4610 subjects in the ESA group vs 173 (4.9%) venous thrombo-embolism events reported for the 3562 subjects in the control group (RR = 1.57, 95% CI = 1.31 to 1.87). Hence, this is one area where there would appear to be great consistency and lack of controversy.

This editorial was invited to accompany the article by Moebus et al. (26) published in this issue of the Journal, which reports that epoetin alfa resulted in improved hemoglobin levels and decreased transfusions without an impact on disease-free survival or overall survival. Epoetin alfa avoided the decrease in hemoglobin level (no decrease in the epoetin alfa group vs –2.20g/dL for the control

group; $P < .001$) and statistically significantly reduced the percentage of subjects requiring red blood cell transfusion (12.8% vs 28.1%; $P < .0001$). After a median follow-up of 62 months, epoetin alfa treatment did not affect overall survival (81% vs 83%; $P = .89$), relapse-free survival (72% vs 71%; $P = .86$), or intramammary relapse (2.4% vs 1.2%; $P = .26$). But epoetin alfa did have a negative effect on patient outcome, resulting in an increased incidence of thrombotic events of 7% in the epoetin alfa arm vs 3% in the control arm. Hence, this article is consistent with the theme of no effect on disease-free survival, an increase in thrombotic events and, here, where the target hemoglobin was 12 to 13g/dL and epoetin was withdrawn at 14g/dL, no adverse effect on overall survival at 5.2 years of follow-up.

So what do I personally conclude, having entered this path with such strong anticipation of positive ESA survival effect based upon the cumulative knowledge 12 years ago? At one of the ESA advisory boards in 2004, my dear friend and colleague George Sledge made the comment, "It takes a fair amount of courage to say that a drug or idea is killed." I now truly believe that the concept of ESAs improving the survival of breast cancer patients is killed. The concept of pushing hemogloblin to 14g/dL was wrong.

I remain to be convinced that ESAs have any negative effect on progression free-survival. In terms of overall survival, the meta-analyses that include all trials trend in the negative direction, but if one limits the analyses to trials where ESAs are prescribed within label, the evidence suggests very little, if any, impact on overall survival. The most convincing and consistently negative effect of the ESAs seen across virtually all datasets is an increased risk of thrombosis, and this adverse effect was also observed the Moebus article published in this issue of the Journal (26).

I have many times commented, in private, that a great athlete can take an ESA and benefit from enhanced performance with little adverse effect; in contrast, if I were to give an ESA to my mother, the risks of adverse effects over the benefits would be high. In an era dominated by personalized medicine, I would beg us all to consider this mantra in every patient. The benefits of ESAs so very clearly demonstrated in the Moebus article (26) and in terms of quality of life are huge. On the other hand, the ESAs are powerful pharmacologic tools and, especially in terms of the elevated risk of thrombosis and other side effects, should be treated with great respect.

References

1. Hockel M, Schlenger K, Aral B, Mitze M, Schaffer U, Vaupel P. Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. *Cancer Res*. 1996;56(19): p. 4509–15.
2. Hockel M, Schlenger K, Hockel S, Aral B, Schaffer U, Vaupel P. Tumor hypoxia in pelvic recurrences of cervical cancer. *Int J Cancer*. 1998;79(4):365–369.
3. Thews O, Kelleher DK, Vaupel P. Erythropoietin restores the anemia-induced reduction in cyclophosphamide cytotoxicity in rat tumors. *Cancer Res*. 2001;61(4)1358–1361.
4. Mittelman M, Neumann D, Peled A, Kanter P, Haran-Ghera N. Erythropoietin induces tumor regression and antitumor immune responses in murine myeloma models. *Proc Natl Acad Sci U S A*. 2001;98(9):5181–5186.
5. Vaupel P, Kelleher DK. *Tumor hypoxia: pathophysiology, clinical significance and therapeutic perspectives*: Wissenschaftliche Verlagsgesellschaft; 1999. (ISBN: 3804717330)
6. Stuben G, Thews O, Pottgen C, Knuhmann K, Vaupel P, Stuschke M. Recombinant human erythropoietin increases the radiosensitivity of xenografted human tumours in anaemic nude mice. *J Cancer Res Clin Oncol*. 2001;127(6):346–350.

7. Kelleher DK, Mattheinsen U, Thews O, Vaupel P. Blood flow, oxygenation, and bioenergetic status of tumors after erythropoietin treatment in normal and anemic rats. *Cancer Res*. 1996;56(20):4728–4734.

8. Rosti V, Pedrazzoli P, Ponchio L, et al. Effect of recombinant human erythropoietin on hematopoietic and non-hematopoietic malignant cell growth in vitro. *Haematologica*. 1993;78(4):208–212.

9. Silver DF, Piver MS. Effects of recombinant human erythropoietin on the antitumor effect of cisplatin in SCID mice bearing human ovarian cancer: A possible oxygen effect. *Gynecol Oncol*. 1999;73(2):280–284.

10. Wollman Y, Westphal G, Blum M, et al. The effect of human recombinant erythropoietin on the growth of a human neuroblastoma cell line. *Life Sci*. 1996;59(4):315–322.

11. Glaser CM, Millesi W, Kornek GV, et al. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. *Int J Radiat Oncol Biol Phys*. 2001;50(3):705–715.

12. Littlewood TJ, Bajetta E, Nortier JWR, Vercamen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: Resuts of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 19(11):2865–2874.

13. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol*. 2005;23(25):5960–5972.

14. Henke M, Laszig R, Rübe C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet*. 362(9392):1255–1260.

15. Leyland-Jones B, BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol*. 2003;4(8):459–460.

16. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ*. 2009;180(11):E62–E71.

17. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer*. 2010;102(2):301–315.

18. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev*. 2012;12:CD003407.

19. Aapro M, Jelkmann W, Constantinescu SN, Leyland-Jones B, et al. Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. *Br J Cancer*. 2012;106(7):1249–1258.

20. Oncologic Drugs Advisory Committee (ODAC) Briefing Document for the 13 March 2008 Meeting: Epoetin alfa (Epogen®/PROCRIT®) and darbepoetin alfa (Aranesp®). Amgen Inc. 7 February 2008. Available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4345b2-00-FDA-index.htm

21. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet*. 2009;373(9674):1532–1542.

22. Paladini L. Meta-analysis of trials performed within label. *Blood*. 2008;112(11):abstract 1305.

23. Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev*. 2006;3:CD003407.

24. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst*. 2006;98(10):708–714.

25. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA*. 2008;299(8):914–924.

26. Moebus V, Jackisch C, Schneeweiss A. Adding epoetin alfa to intense dose-dense adjuvant chemotherapy for breast cancer: randomized clinical trial. *J Natl Cancer Inst*. 2013;105(14):1018–1026.

Note

Affiliation of author: Edith Sanford Breast Cancer Research, Sioux Falls, SD (BLJ).

Epoetin Alfa: To Give or Not to Give

Chau Dang, Clifford Hudis, Larry Norton

Correspondence to: Chau Dang, MD, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, 300 East 66th St, Rm 823, New York, NY 10065 (e-mail: dangc@mskcc.org).

In this issue of the Journal, Moebus et al. (1) reported that an erythropoiesis stimulation agent (ESA) can safely treat chemotherapy-induced anemia in breast cancer patients receiving adjuvant therapy. Earlier evidence of a potentially negative effect on outcomes has made this treatment controversial, and ESAs in general have not been indicated for use in the curative setting. The setting for their report was an Arbeitsgemeinschaft Gynokologische Onkologie (AGO) phase III randomized trial that tested dose intensity and density for 1284 patients with 4 or more positive nodes. Half were randomly assigned to treatment with intense dose-dense (IDD) epirubicin (E at 150mg/m^2) × 3 → paclitaxel (T at 225mg/m^2) × 3 → cyclophosphamide (C at 2500mg/m^2) × 3, all administered every 2 weeks with granulocyte colony stimulating factor and the other half to EC ($90/600 \text{mg/m}^2$) × 4 → P (175mg/m^2) × 4 every 3 weeks (2). At a median follow-up of 5 years, the relapse-free survival (RFS; 70% vs 62%; $P < .001$) and overall survival (OS; 82% vs 77%; $P = .03$) were in favor of IDD chemotherapy. Not surprisingly, there were more nonhematologic and hematologic toxicities with the IDD regimen. With a longer follow-up of 10 years, these benefits were still maintained (3).

To test epoetin alfa (Epo), the authors performed a second randomization among the 643 patients in the IDD ETC arm to receive Epo or not. Epo was given three times a week to maintain a hemoglobin (Hgb) level of 12.5 to 13g/dL, stopped when the Hgb was greater than 14g/dL, and restarted when it was less than 13g/dL. Patients with a Hgb of less than 9.0g/dL were considered for transfusions on both arms of the study. The median duration of Epo administration was 18 weeks. The authors concluded that the use of Epo was beneficial because it prevented the otherwise typical 2.2-g/dL Hgb drop from cycle 1 to cycle 9 of chemotherapy and