ELSEVIER

EJC Supplements Vol 2 No. 2 (2004) 1–2

EJC Supplements

www.ejconline.com

Introduction: Of oxygen, hemoglobin, and tumor treatment

R. Bugat[a,*], M. Freund[b], J.W.R. Nortier[c], P. Vaupel[d]

[a]*Institut Claudius Regaud, Centre Régional de Lutte Contre Le Cancer, Midi-Pyrénées, 20-24, rue du Pont Saint-Pierre, 31052 Toulouse Cedex, France*

[b]*Department of Oncology/Hematology, Postfach 10088, D-18055 Rostock, Germany*

[c]*Leiden University Medical Center, Medical Oncology, Albinusdreef, Leiden, The Netherlands*

[d]*Institute of Physiology & Pathophysiology, University of Mainz, Duesbergweg 6, D-55099 Mainz, Germany*

Received 19 June 2003; received in revised form 6 October 2003; accepted 17 October 2003

This supplement, "Of Oxygen, Hemoglobin, and Tumor Treatment," combines the presentations and discussions from two successive International Symposia held in conjunction with the European Society for Medical Oncology (ESMO) annual congresses in 2000 and 2002, which assessed the interaction of hemoglobin (Hb) levels with tumor hypoxia and treatment outcomes. The first symposium (Hamburg, Germany, late 2000) provided a detailed overview of the causes of tumor hypoxia and its impact on treatment efficacy and survival. The faculty also explored ongoing research concerning the benefits of reversing anemia with recombinant human erythropoietin (rHuEPO, epoetin alfa) as a means of correcting anemic hypoxia in solid tumors and improving clinical outcome. During the second symposium (Nice, France, October 2002), faculty members discussed advanced strategies for use of epoetin alfa after providing an update on the discussions of the first symposium.

Tumor hypoxia has far-reaching clinical implications, including increased tumor aggressiveness, increased resistance to radiotherapy and chemotherapy, and decreased patient survival, according to research reported by Professor Peter Vaupel [1]. One of the major pathogenetic mechanisms for development of tumor hypoxia is anemia, a common problem associated with cancer as well as its various treatments. Professor Jürgen Dunst summarized the process by which anemia may worsen tumor tissue oxygenation, thereby promoting tumor hypoxia, and reviewed clinical studies demonstrating that a decrease in Hb level during radiotherapy strongly increases the risk of treatment failure. Conversely, administration of epoetin alfa during neoadjuvant radiotherapy rapidly increases Hb levels and may increase the efficacy of treatment [2]. As described by Professor Simon Van Belle, the pretreatment Hb level is an important prognostic factor in both hematologic and solid malignancies. In support of the clinical studies, preclinical data have shown that increasing pretreatment Hb levels can induce an enhanced response to various cytotoxic therapies in models of implanted animal tumors or human cancer xenografts [3–6].

These findings raise the intriguing possibility that correcting anemia may improve survival of cancer patients. Clinical research is beginning to address this issue. Professor Matti Aapro described the results of a recently published placebo-controlled, double-blind study in patients receiving non platinum chemotherapy regimens, which showed that epoetin alfa significantly decreased transfusion requirements, significantly increased Hb levels, and provided significantly greater improvements in cancer- and anemia-specific quality-of-life (QOL) domains [7]. In addition, study results suggested a survival advantage for patients who received epoetin alfa versus placebo. These results must be interpreted with caution, however, because the study was neither designed nor powered to assess survival.

Dr Mathias Freund noted that epoetin alfa possesses biological activities other than erythropoietic effects. For example, epoetin alfa appears to have central nervous system effects according to Dr Anthony Cerami. The erythropoietin receptor is abundantly expressed in brain capillaries, representing a possible route for circulating erythropoietin to enter the brain. Current research suggests that epoetin alfa may have neuroprotective and anti-apoptotic effects in the CNS, perhaps via its apparent ability to cross the blood-brain barrier

* Corresponding author. Tel.: +33-05-6142-4119; fax: +33-05-6142-4620.

E-mail addresses: bugat@icr.fnclcc.fr (R. Bugat), mathias.freund@medizin.uni-rostock.de (M. Freund), j.w.r.nortier@lumc.nl (J.W.R. Nortier), vaupel@uni.mainz.de (P. Vaupel).

1359-6349/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/S1359-6349(03)00101-0

[8,9]. Astrocytes and neurons also express erythropoietin [10]; hence, local erythropoietin production may be even more important than erythropoietin transported through the blood-brain barrier. The CNS-related data are certainly intriguing, and suggest potential therapeutic uses for epoetin alfa in CNS disorders such as ischemic stroke, trauma, and cognitive dysfunction [11].

In addition to evaluating the possible expanded benefits of epoetin alfa treatment, recent research has focused on a once-weekly dosing regimen that improves convenience for patients and physicians while maintaining the established efficacy of thrice-weekly dosing. Clinical data consistently show that the once-weekly epoetin alfa-dosing regimen is effective and safe, according to Dr Paul Sabbatini [12,13]. Moreover, early-intervention studies have demonstrated that institution of once-weekly epoetin alfa before the onset of anemia may help maintain normal Hb levels in breast cancer patients who are undergoing adjuvant or neo-adjuvant chemotherapy, thereby maintaining or improving QOL [14,15]. Other epoetin alfa dosing strategies are under investigation with the ultimate goal of optimizing anemia management and patient convenience.

Professors Bugat and Vaupel reviewed the evidence indicating that higher Hb levels may often lead to better outcomes, as well as the clinical data regarding the benefits of treating cancer patients with epoetin alfa, all of which support revising the current practice to maintain Hb levels of at least 12 g/dl [16].

Overall, the symposia presentations highlighted some of the notable improvements epoetin alfa has made possible in the areas of anemia and oncology, and underscored the need for continued investigation of this agent to allow determination of its full therapeutic potential.

References

1. Vaupel P, Thews O, Hoeckel M. Treatment resistance of solid tumors: role of hypoxia and anemia. *Med Oncol* 2001, **18**, 243–259.
2. Dunst J. The use of epoetin alfa to increase and maintain hemoglobin levels during radiotherapy. *Semin Oncol* 2001, **28**(Suppl. 8), 42–48.
3. 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**, 280–284.
4. Stüben G, Thews O, Pöttgen C, Knühmann K, Vaupel P, Stuschke M. Recombinant human erythropoietin increases the radiosensitivity of xenografted human tumors in anaemic nude mice. *J Cancer Res Clin Oncol* 2001, **127**, 346–350.
5. Thews O, Kelleher DK, Vaupel P. Erythropoietin restores the anemia-induced reduction in cyclophosphamide cytotoxicity in rat tumors. *Cancer Res* 2001, **61**, 1358–1361.
6. Stüben G, Pöttgen C, Knühmann K, *et al*. Erythropoietin restores the anemia-induced reduction in radiosensitivity of experimental human tumors in nude mice. *Int J Radiat Oncol Biol Phys* 2003, **55**, 1358–1362.
7. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, for the Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001, **19**, 2865–2874.
8. Martin LJ, al-Abdulla NA, Brambrink AM, Kirsch JR, Sieber FE, Portera-Cailliau C. Neurodegeneration in excitotoxicity, global cerebral ischemia, and target deprivation: a perspective on the contributions of apoptosis and necrosis. *Brain Res Bull* 1998, **46**, 181–309.
9. Brines ML, Ghezzi P, Keenan S, *et al*. Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. *Proc Natl Acad Sci USA* 2000, **97**, 10526–10531.
10. Buemi M, Cavallaro E, Floccari F, *et al*. The pleiotropic effects of erythropoietin in the central nervous system. *J Neuropathol Exp Neurol* 2003, **62**, 228–236.
11. Cerami A, Brines ML, Ghezzi P, Cerami CJ. Effects of epoetin alfa on the central nervous system. *Semin Oncol* 2001, **28**(Suppl. 8), 66–70.
12. Shasha D, George MJ, Harrison LB. Once-weekly dosing of epoetin-α increases hemoglobin and improves quality of life in anemic cancer patients receiving radiation therapy either concomitantly or sequentially with chemotherapy. *Cancer* 2003, **98**, 1072–1079.
13. Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001, **19**, 2875–2882.
14. Hudis CA, Williams D, Gralow JR, the PROCRIT Study Group. Epoetin alfa maintains hemoglobin and quality of life in breast cancer patients receiving conventional adjuvant chemotherapy: final report. *Proc Clin Soc Oncol* 2003, **22**, 767 (abstr 3084).
15. O'Shaughnessy J, Vukelja S, Savin M, *et al*. Impact of epoetin alfa on cognitive function, asthenia, and quality of life in women with breast cancer receiving adjuvant or neoadjuvant chemotherapy: analysis of 6-month follow-up data. *Breast Cancer Res Treat* 2002, **76**, 138 (abstr 550).
16. Crawford J, Cella D, Cleeland CS, *et al*. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 2002, **95**, 888–895.