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Summary: Of oxygen, hemoglobin, and tumor treatment

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When treating patients with cancer, the clinician's overall goal is to provide a cure. If that is not possible, we look to maximize disease-free survival, improve treatment response, and help patients maintain the best quality of life (QOL) possible. The subject of these symposia—the clinical significance and evolving management of anemia in patients with cancer—is an important factor in optimizing patients' well-being during the period of cancer treatment.

Anemia in cancer is often seen at presentation and is exacerbated by radiotherapy and chemotherapy [1–4]. A reduction in the oxygen-carrying capacity of the blood is one of several interconnected pathogenetic factors that contribute to the development of tumor hypoxia, a condition involving an imbalance between the supply and consumption of oxygen [5]. Hemoglobin (Hb) levels <12 g/dL appear to be a threshold for development of tumor hypoxia [6]. Other major mechanisms contributing to the emergence of hypoxia are structural and functional abnormalities in the tumor microvasculature and an increase in diffusion distances so that cells farther away from the nutritive blood vessel receive too little oxygen [7,8]. Clinically relevant areas of hypoxia are detected in approximately 50% of solid tumors regardless of their size, stage, and histological features.

Numerous clinical and experimental studies have demonstrated that tumor hypoxia can profoundly affect the clinical course of cancer and the response to treatment [5,9–11]. Tumor hypoxia appears to render tumor cells more resistant to sparsely ionizing radiation therapy and some forms of chemotherapy. It also can modulate the proliferation and cell cycle position of tumor cells and, consequently, the number of cells destroyed by therapy [5,7,8]. In addition, through genomic changes and clonal selection, hypoxia can promote aggressive tumor growth and metastatic disease [5].

Studies concerning the relationship between Hb levels and cancer pathophysiology suggest that anemia is correlated with a poor treatment response and prognosis [12]. Uncorrected anemia has been shown to be associated with poor outcome in several hematologic malignancies (non-Hodgkin's lymphoma, mantle cell lymphoma, Hodgkin's disease, acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma) and solid tumors (non-small cell lung cancer, ovarian cancer, renal carcinoma, head and neck cancer). Anemia also appears to independently influence treatment response in patients with acute myeloid leukemia and in those with mantle cell lymphoma, and possibly in those with relapsing ovarian cancer [13]. These findings, although suggestive, must be interpreted with caution, since they are derived almost exclusively from retrospective analyses of medical records.

Hemoglobin levels can also profoundly affect the patient's well-being, regardless of tumor type or prognosis. The development of validated QOL measures (especially the FACT-An) has enabled researchers to explore the impact of anemia on patients' everyday functioning in a number of recent clinical studies [14–16]. Profound, pervasive fatigue, a common symptom of anemia, affects up to 78% of patients with cancer [17]. Fatigue can interfere with every aspect of a patient's well-being—physical, emotional, social, and

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economic—leading to significant functional impairment and a deteriorating QOL. Other symptoms of anemia, such as dyspnea, weakness, and chest pain, can produce an additional impact on patients' lives.

The recently increased appreciation of the impact of anemia-related symptoms has led to a series of clinical trials evaluating the efficacy of recombinant human erythropoietin (rHuEPO, epoetin alfa) in correcting anemia and improving QOL in patients with a variety of solid tumors and nonmyeloid hematologic malignancies. As three of these trials demonstrated, epoetin alfa is effective in increasing Hb levels in approximately 60 to 70% of patients. Further, the hematologic effect of epoetin alfa is achieved rapidly, with Hb levels increasing by ~1 g/dl at 4 weeks and ~2 g/dl at 8 weeks [14–16]. The increase in Hb levels is significantly correlated with less fatigue, as assessed by specific measures of cancer-related fatigue (FACT-An) and improved overall QOL; epoetin alfa therapy has also been associated with a reduced need for transfusions [14–16,18,19]. Longitudinal multivariate regression analysis has demonstrated that these benefits are maintained after controlling for a wide array of patient-, disease-, and treatment-related factors that are also likely to influence QOL [20]. The maximal incremental improvements in QOL scores were observed when Hb levels increased from 11 to 12 g/dl (range 11 to 13 g/dl) [21,22]. The clinical relevance of the statistically significant changes in FACT-An QOL scores among anemic cancer patients treated with epoetin alfa has been confirmed retrospectively by reference to population normative data [23].

Because of the manifold implications of anemia in cancer and the demonstrated benefits of anemia correction, the American Society of Hematology and the American Society of Clinical Oncology (ASH/ASCO), as well as the National Comprehensive Cancer Network (NCCN), have developed recommendations for anemia management. ASH/ASCO recommends therapy with epoetin alfa 150–300 IU/kg TIW for patients with cancer-related anemia who have an Hb level $\leqslant$10 g/dl and, based on clinical circumstance, for patients with Hb $<$12 g/dl [24]. An alternate dosing regimen of 40 000–60 000 IU QW, based on common clinical practice, is also noted. The NCCN recommends therapy with epoetin alfa 150–300 IU/kg TIW or 40 000–60 000 IU QW during radiotherapy or chemotherapy for anemic cancer patients [25]. This approach is particularly recommended for patients whose Hb levels are $<$11 g/dl, since the supporting clinical data are primarily derived from studies involving patients with moderate anemia.

The QW epoetin alfa dose (40 000–60 000 IU) is recommended based on data from prospective clinical trials in which this regimen resulted in an increase in Hb level of ~1.0 g/dL at 4 weeks and ~2 g/dL at 8 weeks [15,26,27]. The magnitude and rapidity of the Hb increase in these studies is similar to that reported in trials involving the TIW regimen [16]. In addition, this QW epoetin alfa dosing regimen is commonly used in the United States with both efficacy and convenience [28]. Encouraging results have also been obtained from small studies evaluating more flexible front-loading dosing regimens to optimize Hb increase and response time while minimizing frequency of administration [29,30].

Although the data supporting use of epoetin alfa therapy are strongest concerning patients with established anemia, there is a growing body of evidence that cancer patients whose Hb level is ~12 g/dl at the start of radiotherapy or chemotherapy may also benefit. Preliminary results of two small studies indicate that early intervention with epoetin alfa in breast cancer patients receiving adjuvant or neoadjuvant chemotherapy effectively maintains normal Hb levels while stabilizing or improving QOL [31,32]. A most intriguing avenue of study remains the effect of improved or maintained Hb levels with epoetin alfa on survival. Studies that evaluated survival differences in anemic patients who were treated versus those not treated with epoetin alfa indicate that higher hemoglobin levels are indicative of longer survival [16,33]. When viewed together with the results of studies demonstrating the negative impact of anemia on treatment outcomes and survival [12,34], there is justification for strongly recommending that effective anemia treatment be an integral part of overall cancer management.

Although the benefits of epoetin alfa have most clearly been demonstrated in the treatment of anemia, recent research in various animal models suggests that the drug's ability to cross the blood-brain barrier may render epoetin alfa neuroprotective under a variety of hypoxic and traumatic conditions [35]. In the rat model of ischemic stroke, for example, tissue damage was significantly reduced when epoetin alfa was administered up to 24 h before ($P<0.01$) or up to 6 h after ($P<0.05$) stroke induction [36]. In experimental transient spinal cord ischemic injury induced in rabbits, epoetin alfa was found to be protective against motor neuron apoptosis and neurological disability [37]. Other studies in rodent models provide a basis for exploring the potential usefulness of epoetin alfa for such CNS-specific illnesses as epilepsy, encephalomyelitis, Parkinson's disease, Alzheimer's disease, and amyotropic lateral sclerosis [36].

In conclusion, the provision of hematopoietic support for patients with cancer has evolved considerably in the past decade and will probably change more in the near term, as the need for it becomes better appreciated and treatment strategies are optimized. Epoetin alfa is known to increase Hb levels, improve QOL, and reduce the need for transfusions in patients with a variety of malignancies. Ongoing research may help to clarify

optimal dosage regimens and identify the best intervention points for the initiation of epoetin alfa therapy in various patient populations. Currently available data indicate the need for additional studies to assess whether the benefits of epoetin alfa extend to improved treatment response and longer survival in patients with cancer, as well as whether epoetin alfa will improve the prognosis for those with a variety of CNS-specific illnesses.

References

1. Mercadante S, Gebbia V, Marrazzo A, Filosto S. Anaemia in cancer: pathophysiology and treatment. *Cancer Treat Rev* 2000, **26**, 303–311.
2. Ludwig H, Birgegard G, Olmi P, Nortier J. European Cancer Anaemia Survey (ECAS): prospective evaluation of anemia in over 15,000 cancer (CA) patients (pts). *Ann Oncol* 2002, **13**(Suppl. 5), 169 (abstr 623PD).
3. Bron D, Meuleman N, Mascaux C. Biological basis of anemia. *Semin Oncol* 2001, **28**(Suppl. 8), 1–6.
4. Harrison L, Shasha D, Shiaova L, *et al*. Prevalence of anemia in cancer patients undergoing radiation therapy. *Semin Oncol* 2001, **28**(Suppl. 8), 54–59.
5. Vaupel P, Kelleher DK, Höckel M. Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. *Semin Oncol* 2001, **28**(Suppl. 8), 29–35.
6. Vaupel P, Thews O, Mayer A, Höckel S, Höckel M. Oxygenation status of gynecologic tumors: what is the optimal hemoglobin level? *Strahlenther Onkol* 2002, **178**, 727–731.
7. Vaupel P, Thews O, Höckel M. Treatment resistance of solid tumors: role of hypoxia and anemia. *Med Oncol* 2001, **18**, 243–259.
8. Vaupel P, Briest S, Höckel M. Hypoxia in breast cancer: pathogenesis, characterization and biological/therapeutic implications. *Wien Med Wschr* 2002, **152**, 334–342.
9. Höckel M, Schlenger K, Aral B, Mitze M, Schäffer U, Vaupel P. Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. *Cancer Res* 1996, **56**, 4509–4515.
10. Sutherland RM. Tumor hypoxia and gene expression—implications for malignant progression and therapy. *Acta Oncol* 1998, **37**, 567–574.
11. Höckel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. *J Natl Cancer Inst* 2001, **93**, 266–276.
12. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer* 2001, **91**, 2214–2221.
13. Van Belle S. Impact of haemoglobin levels on the outcome of cancers treated with chemotherapy. *Crit Rev Oncol Hematol* 2003, In press.
14. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol* 1998, **16**, 3412–3425.
15. 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.
16. Littlewood TJ, Bajetta E, Nortier JWR, 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.
17. Curt GA. The impact of fatigue on patients with cancer: overview of FATIGUE 1 and 2. *Oncologist* 2000, **5**(Suppl. 2), 9–12.
18. Abels RI. Recombinant human erythropoietin in the treatment of the anaemia of cancer. *Acta Haematol* 1992, **87**(Suppl. 1), 4–11.
19. Glaspy J, Bukowski R, Steinberg D, *et al*. Procrit Study Group. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol* 1997, **15**, 1218–1234.
20. Fallowfield L, Gagnon D, Zagari M, *et al*. Multivariate regression analyses of data from a randomised, double-blind, placebo-controlled study confirm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. *Br J Cancer* 2002, **87**, 1341–1353.
21. Nortier JWR, Zagari M, Chen Y. Marginal analysis to identify optimal hemoglobin levels to maximize quality of life improvement in anemic cancer patients receiving epoetin alfa. *Ann Oncol* 2000, **11**(Suppl. 4), 145 (abstr 6660).
22. 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.
23. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz H-J, Nortier JWR. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol* 2003, **21**, 366–373.
24. Rizzo JD, Lichtin AE, Woolf SH, *et al*. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Blood* 2002, **100**, 2303–2320.
25. National Comprehensive Cancer Network. *Practice guidelines in oncology: cancer and treatment-related anemia* v.1.2003. NCCN: Rockledge, PA 2003.
26. Sloan JA, Witzig T, Silberstein P, *et al*. Quality of life, blood transfusions, and toxicity, in anemic patients with advanced cancer receiving weekly erythropoietin while on chemotherapy: results from a phase III randomized double-blind placebo-controlled study. *Blood* 2002, **100**, 287a (abstr 1103).
27. Shasha D, George MJ, Harrison LB. Once-weekly dosing of epoetin alfa increases hemoglobin levels and improves quality of life in anemic cancer patients receiving radiotherapy and chemotherapy. *Cancer* 2003, In press.
28. McKenzie SR, Heifetz LJ, Duh M-S, Piech CT. Effectiveness of epoetin alfa beyond once-weekly dosing schedules in the oncology community practice setting. *Blood* 2002, **100**, 501b (abstr 5591).
29. Chap L, George M, Glaspy JA. Evaluation of epoetin alfa (Procrit®) 60,000 U once weekly in anemia cancer patients receiving chemotherapy. *Proc Am Soc Clin Oncol* 2002, **21**, 264b (abstr 2873).
30. Patton J, Camp M, Kuzur M, *et al*. Epoetin alfa 60,000 U once weekly followed by 120,000 U every 3 weeks maintains hemoglobin levels in anemic cancer patients receiving chemotherapy: final report. *Proc Soc Clin Oncol* 2003, **22**, 754 (abstr 3033).
31. Hudis C, Williams D, Gralow J, for the PROCRIT Study Group. Epoetin alfa maintains hemoglobin and quality of life in breast cancer patients receiving conventional adjuvant chemotherapy: final report. *Proc Soc Clin Oncol* 2003, **22**, 767 (abstr 3084).
32. 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**(Suppl. 1), S138 (abstr 550).

33. 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**, 705–715.
34. Grogan M, Thomas GM, Melamed I, *et al*. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer* 1999, **86**, 1528–1536.
35. Pardridge WM, Eisenberg J, Yang J. Human blood-brain barrier transferrin receptor. *Metabolism* 1987, **36**, 892–895.
36. 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.
37. Celik M, Gökmen N, Erbayraktar S, *et al*. Erythropoietin prevents motor neuron apoptosis and neurologic disability in experimental spinal cord ischemic injury. *Proc Natl Acad Sci USA* 2002, **99**, 2258–2263.