The presentations at the conference, “Workshop on the Potential Impact of rHuEPO on Prognosis: Modes of Action, Clinical Evidence,” reflected our growing understanding of the role of recombinant human erythropoietin (rHuEPO, epoetin alfa) in the management of cancer patients with anemia and highlighted intriguing aspects of potential therapeutic uses of epoetin alfa yet to be explored.

The core questions asked were whether a low hemoglobin (Hb) level has an impact on treatment outcome in anemic cancer patients and, if so, whether treatment of anemia can improve outcome. The data presented at the workshop and discussed here indicate that a low Hb level, which contributes to conditions of tumor hypoxia and their sequelae, is associated with a poor prognosis and diminished treatment outcomes in cancer patients undergoing therapy.

In this supplement, based on the workshop presentations, Vaupel and Harrison [1] set the stage for succeeding papers with their overview of the prevalence of tumor hypoxia (which can be induced or exacerbated by anemia), issues concerning the measurement of tumor hypoxia, and differential responses of normal and tumor tissue to low oxygen levels. Additionally, they discussed mechanisms by which hypoxia can lead to: A) acute changes in protein expression in tumor cells that promote the cells’ adaptation to and survival in a hypoxic environment; B) tumor cell proliferation, migration, and metastasis; C) long-term effects subsequent to DNA damage and rearrangement in tumor cells, which result in genetic diversity; and D) selection of apoptosis-resistant cells (e.g., cells with mutant p53, which can then become the dominant tumor-cell type). All these effects can potentially contribute to a poorer prognosis. Moreover, as Harrison and Blackwell [2] indicated, hypoxia per se can have a negative impact on the efficacy of radiation therapy and some chemotherapeutic agents by preventing stabilization of free radicals (which cause DNA damage), thus diminishing the ability of tumor cells to undergo apoptosis.

Vaupel [3] and Blackwell et al. [4] discussed hypoxia-inducible factor 1 (HIF-1α) and its role as a key mediator of the effects of hypoxia. This transcription factor, which is upregulated in response to decreasing intracellular oxygen levels, regulates expression of several dozen target genes involved in the physiologic adaptation of cells to hypoxia. Notable among these is the gene that encodes vascular endothelial growth factor (VEGF). This protein is a potent stimulator of angiogenesis, a process that contributes to enhanced tumor growth and metastatic potential. All processes that support tumor growth and propagation contribute to what Vaupel and Harrison [1] referred to as the “vicious circle of hypoxia.” With increasing tumor size, areas of locoregional hypoxia multiply in number, increasing the likelihood of clonal selection and malignant progression—and subsequently, poorer outcome. Whether hypoxia is primarily the cause or effect of these processes remains unclear; however, it is conceivable that hypoxia is both a major cause and a major effect of tumor growth.

The potential contribution of hypoxia to poorer outcome raises the second core question considered at the workshop:
Can rHuEPO management of cancer-related anemia have an impact on tumor growth, and subsequently, on treatment outcomes? In discussing preclinical studies that addressed this issue, Ludwig [5], as well as Harrison and Blackwell [2], cited the finding of Thews and other investigators [6-11] that prevention of anemia in rodent models resulted in improved sensitivity to radiation therapy and chemotherapy. In all these studies, the improvement in treatment sensitivity was attributed to better oxygenation of the tumor as a result of a higher Hb level or an rHuEPO-related increase in oxygen availability.

Hudis and co-authors [12] reviewed the results of a series of clinical studies that collectively examined the prognostic and predictive significance of cancer-related anemia (or low Hb level). Those studies included patients with a broad variety of solid tumors and hematologic malignancies. Results of the majority of the studies suggest that Hb level is a significant independent prognostic factor for overall survival, and in the few cases where it was reported, a predictive factor for outcome of various therapies. Of course, the usual caveats that apply to retrospective data, including lack of a placebo control group and randomization, must be kept in mind when considering the findings of these studies.

Additionally, Hudis et al. [12] reviewed the results of several studies that assessed the influence of epoetin alfa on outcome in patients undergoing cancer treatment. Those results were supportive of a favorable effect of epoetin alfa treatment on survival, locoregional tumor control, and response rates [13-16]. Subsequent to the completion of the workshop, the results of a recently completed randomized, double-blind, placebo-controlled trial of epoetin alfa as an adjunct to chemotherapy in patients with metastatic breast cancer with initially normal Hb levels (>13 g/dl) to evaluate the effects of epoetin alfa on survival were made available. These results, which show a survival advantage at 12 months in the placebo group (76%), versus the epoetin alfa group (70%; \( p = 0.017 \)), are in contrast to the other studies discussed in the workshop. Additionally, a recent study has shown that epoetin beta used beyond the correction of anemia also resulted in poorer locoregional progression-free survival than placebo (adjusted relative risk: 1.62; 95% confidence interval: 1.22-2.14; \( p = 0.0008 \)) [17]. These two prospective studies clearly caution against the noninvestigational use of epoetin alfa to maintain a normal Hb level in nonanemic patients undergoing treatment. Indeed, epoetin alfa was shown to have no adverse safety effects in a third randomized, double-blind trial that assessed the efficacy of high-dose chemotherapy versus conventional chemotherapy in patients with high-risk breast cancer [18]. In that trial, epoetin alfa was administered at usual therapeutic doses.

CONCLUSIONS AND FUTURE DIRECTIONS FOR EPOETIN ALFA

Based on the available preclinical and clinical evidence, it appears that hypoxia does indeed have a negative impact on outcome in anemic patients undergoing cancer treatment. Moreover, the existing data suggest that epoetin alfa can reduce intratumoral hypoxia and, as a result, possibly interrupt one or more hypoxia-driven mechanisms (e.g., HIF-1α-mediated cell adaptation; VEGF upregulation) that lead to treatment resistance and poorer outcome, thereby improving patients’ chances for a better outcome. Also, there are indications that treatment with rHuEPO can increase tumor sensitivity to radiation therapy and the efficacy of certain chemotherapeutic agents, possibly through increased oxygenation of the tumor cells—again portending a better prognosis.

These findings strongly suggest a potential beneficial effect of epoetin alfa on outcomes in anemic patients undergoing cancer therapy—an effect that has been demonstrated in several, but not all, clinical studies, as described above. Many questions remain unanswered regarding epoetin alfa and its clinical use, and it will be the task of future research to address these questions. Most importantly, further research is required to more fully assess the impact of epoetin alfa on survival and locoregional disease control in a variety of cancers, while controlling for all known or suspected confounding demographic and clinical factors as well as quality of life (QOL) end points. Further, future research is required to determine the most effective doses and schedules of epoetin alfa to maximize its therapeutic potential regarding both treatment outcomes and QOL parameters. To this end, eight trials of epoetin alfa are ongoing at the time of this writing; patients selected have a wide range of solid tumors (e.g., cervical, head/neck, gastric/rectal, rectal, breast, and non-small cell lung). In five of the studies, the dosage used is 40,000 IU once weekly, and in two studies, the primary end points are survival and disease-free survival. Information on erythropoietin and erythropoietin receptor expression in cancer tissues should also be expanded to establish definitively whether expression of erythropoietin and its receptor at these sites has a deleterious effect.

Other areas of investigation of epoetin alfa have been suggested by the intriguing findings of several experimental and clinical studies that have demonstrated activity of epoetin alfa unrelated to its hematopoietic function. One study [19], evaluated the biologic effects of epoetin alfa on tumor progression using murine models of multiple myeloma. In that study, treatment of tumor-bearing mice with epoetin alfa resulted in tumor regression that, rather surprisingly, had an immunomodulatory component, suggesting a whole new avenue of research.
Of considerable interest, but not discussed in this supplement, is the work of van Halteren and co-authors [20]. At the 2001 European Cancer Conference, these investigators reported that intervention with epoetin alfa diminished the percentage of weight loss in mice bearing C26-B tumors. A controlled clinical trial of the use of epoetin alfa in cachectic cancer patients showed that patients randomized to receive epoetin alfa (n = 50) at doses of 4,000-10,000 IU three-times weekly when their Hb levels decreased to <12.8 g/dl for men and <12.0 g/dl for women had greater exercise capacity, metabolism, and energy efficiency during a maximum work load than patients in a control group (n = 58) that did not receive epoetin alfa [21]. These findings underscore the postulated relationship between hypoxia and cancer cachexia and support the conduct of additional studies to examine a possible role for epoetin alfa in treating patients experiencing cancer-related cachexia.

In the clinical arena, emerging data suggest that epoetin alfa, in addition to its primary role in treating anemia, may have a place in the management of central nervous system (CNS) disorders. As noted in the papers by Farrell [22] and Hudis et al. [12], both erythropoietin and its receptor have been found in the brain. Their presence there has stimulated questions regarding a possible role for epoetin alfa in protection of the brain cells from hypoxic insult. Pursuing this line of research at the preclinical level, Brines et al. [23] and Cerami et al. [24] demonstrated that epoetin alfa, contrary to previous assumptions, could cross the blood-brain barrier. Subsequent studies by this group in animal models demonstrated that administration of epoetin alfa could reduce injury due to focal ischemic and blunt force injury, mitigate the severity of experimental autoimmune encephalomyelitis symptoms, and delay the onset and reduce the severity of kainate-induced seizures.

The promising CNS results obtained with epoetin alfa in animal models have led to the conduct of several small trials of this agent in humans with CNS disorders. Breast cancer patients, particularly those receiving high-dose chemotherapy, frequently experience impairments of cognitive function, including short- and long-term memory loss, a decrease in attention span, poor concentration, and diminished language skills. Thus, several studies are being conducted to evaluate any potential benefits of epoetin alfa therapy with regard to cognitive function in breast cancer patients receiving adjuvant or neoadjuvant chemotherapy. The recently reported results of O’Shaughnessy and colleagues [25] (as discussed by Hudis et al. [12]) showed that cognitive function, as measured by EXIT25, was improved in more epoetin alfa-treated than placebo-treated patients, and that fatigue and QOL worsened to a lesser extent in epoetin alfa-treated patients. A larger, controlled study of the effects of epoetin alfa on cognitive and executive functions is currently in progress. Also under way is a German multicenter trial of epoetin alfa in approximately 500 ischemic stroke patients. Impetus for this trial came from the results of a small pilot study that showed fewer physical, speech, and memory problems, and lower requirements for daily assistance, in epoetin alfa-treated stroke patients compared with control stroke patients not given epoetin alfa [26].

In summary, the body of preclinical and clinical evidence currently available suggests that hypoxia negatively impacts treatment outcome in anemic patients undergoing cancer treatment, and, further, that administration of epoetin alfa (with the goal of improving QOL parameters and possibly, treatment outcomes) is a rational strategy that should be incorporated into the management of these patients when anemic. Still, many questions regarding the use of epoetin alfa remain with respect to its precise mode(s) of action, its effect on patient survival and other critical outcomes, erythropoietin and erythropoietin receptor expression, its potential immunomodulatory and neuroprotective effects, and potential cognitive benefits of epoetin alfa administration that may translate into better QOL for patients. Thus, while epoetin alfa therapy has a clearly defined profile with respect to its hematopoietic benefits, further research must elucidate the exact nature of its role in other significant arenas, and an explanation for its possible deleterious effect in nonanemic patients is needed.

**REFERENCES**


