



Erythropoietin in Clinical Practice: Current Use, Effect on Survival, and Future Directions

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Abstract

Recombinant human erythropoietin has become an essential part of the management of anemic patients with end-stage renal disease. It is also used to treat the anemia associated with cancer and other diseases, and it improves quality of life. In recent years, studies in animals and humans have focused on the use of rHuEPO for other indications. It has been found to play a role in both cardioprotection and neuroprotection. It has effects on the immune system, and can cause regression in hematologic diseases such as multiple myeloma. It may also improve the response of solid tumors to chemotherapy and radiation therapy. On the other hand, concerns have been raised following two studies of patients with solid tumors in whom those treated with rHuEPO had diminished survival. Criticism of the design of these studies makes it clear that large, well-designed, randomized trials must be performed to determine the role of rHuEPO in the treatment of cancer, and more generally to clarify the full clinical benefits of the drug, while minimizing the harm.

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The use of recombinant human erythropoietin has revolutionized the clinical care of the anemic patient. Initially seen as a replacement for endogenous EPO in patients with end-stage renal failure, its use has broadened to encompass patients with anemia of other causes as well, including cancer-related anemia. Moreover, EPO receptors were found on cells of different organs in the body. Studies have thus examined many other properties of EPO itself and have subsequently expanded its clinical use. This paper reviews the various current clinical uses of rHuEPO in its different forms, and discusses the possible applications of the drug in the future.

EPO production and effect

EPO is an approximately 30 kDa molecule with a peptide core and four carbohydrate chains that are important for its stability in the circulation [1]. During the fetal stage, EPO is produced primarily by hepatocytes, and after birth mostly by peritubular

fibroblast-like cells in the cortex of the kidneys. Smaller amounts are produced in the liver, spleen, lung, testis and brain. The major stimulus for its production is tissue hypoxia where the levels of the hormone can increase exponentially. EPO is removed from the circulation by erythroid cells expressing the EPO receptor. It is also degraded by the liver and the kidney. EPO acts on erythrocyte progenitor cells by preventing apoptosis and by stimulating production and proliferation of erythrocytes. Receptors for EPO have been found on other tissues as well: namely, brain, retina, skeletal muscle, heart, kidney and endothelial cells [1]. This prompted extensive investigation of EPO function in many different areas, both basic and clinical. rHuEPO is available in three forms: epoetin alpha (Procrit® in the United States and Eprex® in Europe), epoetin beta (Neorecormon®) and darbepoietin (Aranesp®). EPO beta is not available in the United States. The differences among these drugs will be discussed below.

Anemia in renal disease

Because EPO is produced primarily in the kidneys, its deficiency in renal disease is a major cause of anemia in these patients. rHuEPO has dramatically improved the care of the patient with end-stage renal disease [2]. The response to rHuEPO is characterized by increasing hemoglobin and hematocrit, reducing the blood transfusion requirements and improving these patients' quality of life.

Anemia in cancer and other chronic diseases

rHuEPO is also used for anemia associated with cancer and other chronic diseases. A recent randomized trial demonstrated improvement of anemia in patients with hematologic malignancies treated with chemotherapy. The response was characterized by an increased hemoglobin level, a reduced transfusion requirement and an improved quality of life [3].

In 2004 the European Organisation for Research and Treatment of Cancer published comprehensive guidelines for the use of rHuEPO in cancer-related anemia caused by chemotherapy, radiotherapy, surgery or by the cancer itself [4]. Similar guidelines were published in 2002 by the American Society of Clinical

rHuEPO = recombinant human erythropoietin
EPO = erythropoietin

Oncology and the American Society of Hematology [5]. rHuEPO was also shown to ameliorate anemia of non-cancerous inflammatory states, such as inflammatory bowel disease [6].

EPO in hematologic malignancies and solid tumors: disease modulation?

In addition to its effect on the anemia of malignancy, the administration of rHuEPO may play a role in the modulation of the disease itself. For example, it was found that when a number of multiple myeloma patients were given rHuEPO for the treatment of anemia in chemotherapy-refractory disease, the patients not only benefited from a rise in their hemoglobin but also lived longer than expected [7]. Studies using a murine model of myeloma demonstrated that EPO treatment induced an immunologic response (T cell-mediated) that could have been responsible for the regression of the disease [8]. In myelodysplastic syndrome, rHuEPO administration in appropriately selected patients improved survival [9], and in patients with B cell chronic lymphocytic leukemia, rHuEPO treatment resulted in a downgrading of the disease stage [10]. Similar results were found in murine experimental models [11].

rHuEPO may confer neuroprotection and cardioprotection and may also serve as an immunomodulatory agent.

There may be benefits in the treatment of solid tumors as well. In a study of mice with either squamous cell carcinoma or fibrosarcoma undergoing radiation therapy, rHuEPO acted as a radiosensitizer and improved the response to radiotherapy [12]. Similarly, in mice injected with cells from a murine lung carcinoma model (Lewis lung carcinoma) and subsequently treated with chemotherapy, the response of the tumor to the chemotherapy treatment was significantly augmented when rHuEPO was also administered [13]. In humans, anemia and its associated hypoxia have a negative impact on the effect of radiation therapy. As such, the administration of epoetin alpha to anemic patients undergoing radiation therapy may improve the response and extend the survival. For example, administration of epoetin alpha to patients with head and neck cancer undergoing chemoradiation improved the response and the survival [14]. Furthermore, there are also case reports of tumor regression following the administration of epoetin in renal cell carcinoma [15].

Despite the impressive results in animal models with solid tumors and in patients with multiple myeloma, recent studies in patients have raised the question of whether treatment with rHuEPO actually prolongs survival. A study that examined the effects of rHuEPO therapy on hematologic parameters and quality of life in cancer patients treated with chemotherapy also noted a tendency toward increased survival in the patients treated with rHuEPO. This improvement was not statistically significant, possibly because the study was not powered to examine survival

[16]. However, some recent studies have shown a decreased survival rate in patients treated with rHuEPO. In a study of patients with head and neck cancer treated with radiation therapy, those who did not receive rHuEPO survived longer [17]. In another study of patients with metastatic breast cancer treated with chemotherapy (BEST trial), those who received rHuEPO survived less than those given the placebo [18]. It is unclear why survival was shorter in the rHuEPO-treated groups. It might be related to the design of these studies [18-20]. In the BEST trial the cause of most of the excess deaths was listed as early disease progression. One possibility for the shorter survival in these patients might be related to the presence of EPO receptors on the surface of the tumor cells. In that case, administration of rHuEPO could potentially enhance the growth of the tumor [21,22]. A study of cancer cells expressing EPO receptors demonstrated resistance to ionizing radiation when exposed to rHuEPO *in vitro* [23], and this may explain the results of Henke and colleagues [17]. Additionally, thromboembolic events and the increased hemoglobin may also play a role, supported by the fact that there were more thromboembolic events in the rHuEPO group in the BEST trial, and that the target hemoglobin level in that trial (12–14 g/dl) was higher than the usual clinically accepted target. Henke et al. [17] also observed in the head and neck cancer trial that in the rHuEPO treatment group there was an increased percentage of “vascular disorders,” including thromboembolic events and a high hemoglobin target. It is possible that at least part of the increased mortality was related to the excessive increase of hemoglobin, similar to the results seen in a study of dialysis patients with congestive heart failure discussed below [24].

If the survival is reduced in patients who have certain cancers, then one may be reluctant to administer rHuEPO even if the goal is to treat their anemia. It is clear that more randomized controlled trials must be designed and performed to determine when to treat cancer patients with rHuEPO. In light of this, a long-term study of patients with multiple myeloma, chronic lymphocytic leukemia and non-Hodgkin's lymphoma demonstrated that rHuEPO administration did not decrease survival, while it did improve the anemia and the quality of life [3].

Cardioprotection

It has been found that the administration of rHuEPO to anemic patients with congestive heart failure can improve their condition. In one study for example, the hemoglobin and the left ventricular ejection fraction improved and the number of hospitalizations fell dramatically [25]. It should be noted that this was a retrospective study, and although the results appeared significant there was no control group receiving blood transfusions. It is therefore unclear whether the improvement was due merely to the rise in hemoglobin or perhaps to another cause, such as a direct effect on the myocardium. Similar results were found in other studies [26]. On the other hand, raising the hemoglobin too much (even to the normal range) can be detrimental. This was seen for example in a study of hemodialysis patients with congestive heart failure receiving rHuEPO [24].

Other evidence supporting the notion that the cardiac protection is likely mediated through other routes, not only those related to increased hemoglobin, comes from a recent study with adult rats found to have EPO receptors on the cardiomyocytes [27]. rHuEPO administration exerts a cardioprotective effect during ischemia-perfusion injury. In tissue studies of the rat heart [28], it was found that treatment with rHuEPO protected the ischemic and infarcted heart by inhibition of apoptosis, thereby limiting the size of the infarct and improving contractile function. This was shown even in the absence of increased red blood cell counts.

Neuroprotection

Similar to the protective effects in cardiovascular disease, a neuroprotective effect of rHuEPO treatment was also reported in animal studies. For example, EPO exerted neuroprotection in rats following spinal cord injury [29] and ischemic injury [30,31]. In one of these studies, Brines and co-authors [30] induced brain infarction in rats by carotid artery ligation, and a single shot of rHuEPO administered 6 hours later resulted in a decrease of the infarcted area by 50–75%. Studies of nerve conduction in mice with induced diabetes mellitus demonstrated that rHuEPO reversed several abnormalities associated with diabetic neuropathy, suggesting another potential future application of rHuEPO [32]. A recent study [33] made the following observations: a) rHuEPO penetrates the brain tissue in rats and humans, b) its presence is enriched in schizophrenic men, c) EPO receptors are more densely expressed in the hippocampus and cortex of schizophrenic patients than in healthy subjects, and d) administered rHuEPO attenuates the haloperidol-induced neuronal death and improves cognitive function in mice. As such, rHuEPO may be a likely candidate for supplemental neuroprotective treatment in schizophrenia.

Different forms and doses of recombinant EPO (alpha, beta, darbpo)

As stated above, there are three commercially available forms of rHuEPO, and while there are some minor differences among them in terms of pharmacokinetics, and perhaps pharmacodynamics, there has never been a head-to-head trial comparing them for any of their indications. The alpha and beta forms are similar in molecular characteristics and pharmacokinetics, but the beta form has a higher molecular weight [34]. Both are synthesized in Chinese hamster ovary cells [35]. Darbepoetin, otherwise known as novel erythropoiesis stimulation protein or AraNESP, was engineered to have two additional glycosylation sites to permit a higher degree of glycosylation [34]. Because the half-life and the biological activity of EPO are directly related to the degree of glycosylation, NESP with its increased glycosylation has both an increased biological activity and a longer half-life [36,37]. As such, it is administered only once weekly or every other week. Efficacy of once-weekly administration of rHuEPO, however, has

also been demonstrated with EPO alpha [38], and similarly with EPO beta [39].

The optimal dose of rHuEPO administration is not yet fully established and only a few studies have addressed this issue. The most common doses range from 20,000 to 40,000 units weekly, although occasionally 60,000–80,000 units per week are required to achieve an erythroid response [40]. It is possible that various indications will require different doses. Moreover, it is difficult to compare various doses of the different rHuEPO preparations. In summary, the difference among the three products and their optimal doses is unclear, and often the decision as to which agent to use takes into account administrative and economic factors as well.

Conclusions

EPO is a hormone that is crucial for the natural production of red blood cells, and because it is produced primarily in the kidney the recombinant form has become a mainstay in the therapy of patients with anemia of end-stage renal disease or even chronic renal failure. Correction of the anemia is associated with a reduced blood transfusion requirement and an

Clinical observations and animal experiments suggest that rHuEPO may cause regression in hematologic diseases like multiple myeloma and may improve the response of solid tumors to chemotherapy and radiotherapy. However, future trials will have to clarify concerns regarding survival of rHuEPO-treated cancer patients

improved quality of life. We have reviewed the many other uses and potential uses of rHuEPO, from cancer-related anemias to protection of the neurologic and cardiovascular systems, to immune related anti-myeloma effects. We have also discussed the potential dangers of the drug where it may impair survival in certain neoplastic diseases. Further studies are underway to explore the nuances of the drug in its various commercial forms, enabling its application to achieve its full potential – maximizing the benefit and minimizing the possible harm.

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NESP = novel erythropoiesis stimulation protein

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