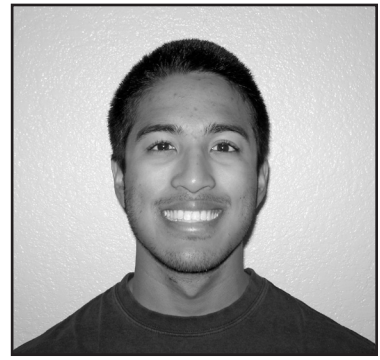
A Review of the Efficacy of Erythropoietin Alfa Treatment for Chemotherapy-Induced Anemia

Tariq Hashmi



Writer's Comment: *Living in Davis, where bicycles abound, a culture centered around competitive cycling isn't difficult to imagine. As with any competitive sport, the pressure to succeed leads some cyclists to experiment with performance-enhancing drugs. Erythropoietin, or "EPO," is a hormone frequently used by cyclists to increase their blood's oxygen-carrying capacity, but it is also notorious for causing stroke in abusers. When I was assigned my first research paper in Pam Demory's UWP 104F class, erythropoietin eventually came to mind. While no one can ethically research EPO's dangerous performance-enhancing effects, I did learn about one of erythropoietin's legitimate uses—treating anemic cancer patients. Initially, navigating scientific journal databases and wading through dense academic prose was frustrating, but with Dr. Demory's encouragement, I eventually became more comfortable with research articles. I hope that this review paper clarifies some of the legitimate benefits of a drug that is popularly associated with athlete doping.*

—Tariq Hashmi

Instructor's Comment: *In Writing in the Health Professions (UWP 104F), students have the option of writing a research report suitable for health professionals or a scientific review article suitable for a scientific journal. Tariq opted for the arguably more difficult task of writing a review article, targeted (ambitiously and appropriately) at the* Journal of the American Medical Association. *One of the challenges of this assignment is finding a suitably narrow yet significant topic. In targeting the performance-enhancing sub-*

stance EPO, Tariq had an automatically interesting start. But in deciding to look not *at its performance-enhancing properties, but at its use in treating chemotherapy-induced anemia, Tariq made the paper even more interesting. Furthermore, Tariq doesn't just summarize or report on the research (that's always the temptation with a paper like this; after all, just reading and analyzing the original research articles is challenge enough); he goes further to help us understand the point of the research done so far by assessing it explicitly. And in so doing he has produced an exemplary scientific review article. And I learned something new—what more could a writing teacher ask for?*

—Pamela Demory, University Writing Program

The National Anemia Action Council states that about 3.4 million Americans are anemic, with causes ranging from serious chronic illnesses to simple dietary insufficiencies (1). Common symptoms include weakness, pallor, tachycardia, shortness of breath, dizziness, headache, chest pain, and numbness in the extremities (1). Since the late 1990s, recombinant erythropoietin has been used to treat anemic patients, including cancer patients whose anemia has been caused by chemotherapy (2).

Recombinant erythropoietin is also known as epoetin alfa, or EPO, a glycoprotein made by transplanting the human erythropoietin gene into the ovary cells of a Chinese hamster species (2). Due to its relative novelty in the research community, older and newer studies are very similar in their findings that erythropoietin effectively raises hemoglobin levels in anemic patients. Current research, however, is focused on quantifying hemoglobin concentration increases from erythropoietin treatment, exploring possible consequences of these increases according to such criteria as patient quality of life, or examining changes in hemoglobin concentration from various starting conditions. This review aims to summarize the major findings of current research on epoetin alfa treatment of chemotherapy-induced anemia.

Increasing Hematocrit

Studies have unanimously shown that epoetin alfa treatment significantly increases patient hematocrit levels, which tends to correct anemia (3-6). As recent research frequently quantifies these changes in hemoglobin levels, scientists are able to agree on what exactly constitutes an

adequate response to epoetin alfa treatment (3-6). Clinical studies typically characterize a hemoglobin response to epoetin alfa as hemoglobin concentration increases ≥ 2g/dL or total patient hemoglobin ≥ 12g/dL, a response usually achieved by half of study participants receiving the standard 40,000 U weekly dosage of EPO (3,5). In dosage protocols that increased weekly dosages in non-responders to 60,000 U, final hemoglobin responses reached as high as 74% (4,6), with 35.8% of patients requiring an increased dosage (4). Compared to controls receiving standard anemia treatment, 10 times more EPO-treated patients showed a significant hemoglobin response (3).

The dosages used are determined by established clinical conventions. The regimen common to most studies is a weekly administration of 40,000 U (6), with increased dosage to 60,000 U weekly for hemoglobin increases < 1 g/dL after about 4 weeks—an increase below the threshold for an adequate hemoglobin response (4,5). For example, a 2001 study by Gabrilove et al. not only found significant hemoglobin response rates but added patient convenience from these once-per-week dosages compared to dosages three times per week of 10,000 U (4). In the particular study protocol that increased epoetin alfa dosage for non-responders, average hemoglobin increases were about 1.9 g/dL, with average final hemoglobin concentration varying around 11.5 g/dL (4,5).

Problems

A common limitation of these studies is the lack of a uniform starting hemoglobin concentration, which potentially skews hemoglobin concentration results. Because studies usually stopped administering epoetin alfa for the sake of patient safety once patients reached hemoglobin concentrations ≥ 13 g/dL (4,6), responses from those with higher starting hematocrit could have been artificially limited by the hematocrit threshold. Thus the results from these patients would not necessarily have reflected epoetin alfa performance alone. Also, patients with higher starting hemoglobin concentrations could have displayed a higher final mean hematocrit, falsely suggesting a better epoetin alfa response. Even so, attempting to correct for these differences by assessing only changes in mean hemoglobin concentration would bias patients with higher baseline hematocrit towards lower increases. Since these patients would be more likely to have their treatment stopped, they would show lower hematocrit

increases, which could be interpreted as a lower epoetin alfa response. Additionally, using patients with higher starting hematocrit would bias hemoglobin response outcomes. These patients would be more likely to fulfill the ≥ 12g/dL total hematocrit criterion, though less likely to achieve an increase in hematocrit ≥ 2g/dL.

Solutions

Some studies have attempted to address these problems by categorizing results based on starting hemoglobin concentrations (6), which has helped to segregate biases in the hemoglobin response data. Still, this strategy does not remove bias entirely, since all results are considered in calculating the total hemoglobin response figures. Even while acknowledging the difficulty of finding subjects for research studies, researchers may want to develop epoetin alfa dosage regimens specific to certain baseline hematocrit ranges, and to modify these dosages to avoid excessive hematocrit increases. Conversely, researchers could retain clinical dosage regimens and instead establish a baseline range from which to conduct epoetin alfa efficacy studies.

Reducing Blood Transfusion Rates

Anemic patients are frequently inconvenienced by their recurring need for blood transfusions, leading to an extensive examination of epoetin alfa's reduction of transfusion requirements (3-5,7-9). Studies cite many disadvantages to blood transfusion, including the scarcity of donated blood, the risk of infection, and the lowered vigor of transfused blood cells (3,4,8). Although research indicates that epoetin alfa patients require fewer blood transfusions (3,8,9), the exact amount of reduction varies among studies. In general, patients with initial hemoglobin levels closer to 12g/dL were less likely to require transfusions (9). Relative reductions in rates of blood transfusions range from 55-65% (3,8), with the average erythropoietin-treated patient requiring one less unit of blood than placebo patients over an 84-day period (8). Absolute reductions in transfusion demands varied from 5.3-14.3% (3,4), with total transfusions per month dropping as much as 42.8% (5).

Potential sources for error include varying study durations, with some studies lasting 12 weeks (3,8,10), and others 16 weeks (4,5,11).

Discrepancies between transfusion rates may also be attributable to different treatment regimens, test subjects, and baseline hemoglobin values. Furthermore, data disparities may not necessarily have been caused by differences in actual treatment. Reducing total blood transfusions per patient would be more difficult over a longer versus a shorter period of time, which would complicate comparison of results from different protocols. Additionally, a longer study would likely show a larger drop in transfusion rates due to the increased time allowed for a hemoglobin response.

Future research might therefore include uniform study durations, and perhaps an assessment of whether different durations make an appreciable difference in transfusion rates. It might also be interesting to compare the cost of epoetin alfa treatment to that of blood transfusions.

Quality of Life

Researchers have developed various ways to assess patient decreases in quality of life due to anemia, including the Functional Assessment of Cancer Therapy anemia, fatigue, and non-fatigue subscales (FACT), the Linear Analog Scale Assessment (LASA), and the Cancer Linear Analog Scale (CLAS) examinations of fatigue and quality of life (3,4,9). Compared to control groups not receiving erythropoietin alfa treatment, all studies have found that epoetin alfa treatment improves quality of life by 20-30% (3,4,9) based on LASA measurements of overall quality of life, energy, and activity, with decreasing respective magnitudes (4,5). Most notably, Gabrilove et al. found the greatest increases in LASA scores in patients with the largest increases in hemoglobin concentration. On the anemia subscale of FACT assessments, Gabrilove et al. also found mean increases of 14% after treatment. Patient fatigue levels and functional ability, as well as assessments of anemia all showed significant improvement with epoetin alfa treatment (3,9). Several studies indicate that quality of life improvements are directly related to increases in hematocrit (5,9).

Depending on the organ system affected, however, patients with different kinds of cancer suffer different degrees of functional impairment. Therefore, independent of epoetin alfa treatment, the type of chemotherapy provided, the exact chemotherapy drugs administered, and the patient's stage of cancer all affect quality of life scores. Conversely,

such factors may also affect patient response to erythropoietin, further interfering with the precision of results. Although several studies have cataloged patient cancer types and the exact chemotherapy drug treatment (3,4,6,7,9), none have yet examined the consequences of such demographic information on patient quality of life during epoetin alfa anemia treatment.

Conclusion

Current research suggests that erythropoietin alfa administration in anemic chemotherapy patients effectively increases patient hematocrit, thus reducing the need for blood transfusions and improving patients' quality of life. While the benefits from erythropoietin alfa treatment for anemic patients are clear, attempts to quantify increases of hematocrit, decreases in required transfusions, and any consequent improvements in quality of life have been impeded by a lack of standardization among studies. Although study results show some agreement, there is not yet enough consensus to apply quantitative results to clinical practice. Therefore, although the scientific community agrees that epoetin alfa helps anemic patients and has established safe dosages, why patients respond to therapy differently remains unknown. Additionally, few studies have compared epoetin alfa treatment to control anemic subjects (3,4,9), instead measuring only patient improvement. The increased use of controls in research would help ensure that patient benefits are due to epoetin alfa treatment rather than chemotherapy, increased immune function, or other variables. Finally, inconsistencies in starting hemoglobin concentrations, varying study durations, and failures to account for differences in cancer and chemotherapy types are all potential sources for error and should be considered when devising new studies.

Consensus on study duration, drug dosages, patient cancer types, patient cancer stages, chemotherapy drugs, and so on would further allow for an easier comparison between studies and therefore a more unified presentation of epoetin alfa treatment as a whole. On the other hand, future studies might devise a method to scale the data from different studies to the same level, allowing for comparisons and speculation on the consequences of any identified similarities and differences. Either of these measures would increase the accuracy of epoetin alfa data, which would translate into increased quality of patient care.

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