What Are Cancer Patients Willing to Pay for Prophylactic Epoetin Alfa?—A Cost-Benefit Analysis

The article by Ortega et al. provided further evidence to consider regarding recombinant human erythropoietin (r-HuEPO) use in the treatment of cancer patients.[1] They addressed the economic aspects of r-HuEPO in cancer-related anemia and described the patients' perspective regarding the use of an expensive technology for their treatment.

As the expensive drugs provided by high technologies gain wider areas of application, it seems that this discussion will be more popular among clinicians, patients, and health care providers who are supposed to pay for r-HuEPO. We believe the use of r-HuEPO, which is an expensive drug, will become wider in the near future, as is usually the case with high technology drugs that give the patient more comfort for higher cost. At this point, we have to stress the clinicians' responsibility for defining more clear-cut outlines of the therapeutic aspects of the drug in terms of cost-benefit advantage. In the case of r-HuEPO, this is quite complex. r-HuEPO is not simply a supplementary drug for cancer anemia. It is an endogenously secreted hormone that affects many systems. Chemotherapeutic agents may alter the endogenous secretion of EPO and may cause an EPO-resistant state.[2,3] High EPO levels after a renal injury and enhancement of recovery from cisplatin-induced acute renal failure have been shown, perhaps reflecting the role of EPO as part of the endogenous defense mechanism of the kidney.[4,5] The protective effect of EPO against neuronal damage is also under investigation.[6,7] These points need further investigation and must be considered in determining the potential therapeutic benefits of r-HuEPO therapy (especially for patients receiving cisplatin-based combinations that are potentially nephrotoxic and neurotoxic, because these side effects are being considered as important dose-limiting factors in clinical use).

In this complexity, the clinicians' responsibility starts with investigating the benefits of r-HuEPO and identifying the patient population that will benefit most from the use of this drug. There is no consensus on the administration of this drug to cancer patients for reduction of transfusion requirements or for quality of life, whether the patient is receiving cytotoxic chemotherapy or not, although most studies point out the benefits.[8–12] To determine the patient group that will benefit most from the use of this drug, we must first identify the patients who have the least tolerance of the complications of anemia and blood transfusions (i.e., older patients, who usually have a diminished reserve, and patients with underlying renal, pulmonary, and cardiovascular diseases). A history of previous cytotoxic treatment and frequent transfusions may also be important indicators; and rare blood groups, which are considered less often, must be regarded as important factors in patient selection for treatment with r-HuEPO. After determination of the patient group that is most prone to the complications of anemia and transfusion, we have to identify further the subsets of patients who will benefit from the treatment. These patients have low levels of endogenous EPO and have normal baseline leukocyte and platelet counts, indicating adequate bone marrow reserve. The criteria for the response to treatment have been defined previously and include increases in hemoglobin level more than 0.5 g/dL after 2 weeks, soluble transferrin receptor level after 2 weeks, and reticulocyte count after 4 weeks of r-HuEPO treatment.[8,13,14] Another important issue is the dose: 150 U/kg 3 times a week seems to be an appropriate dose for patients not receiving cytotoxic chemotherapy.[8] Patients treated with cytotoxic agents, especially cisplatin, seem to need higher doses.[8,15] Starting with the dose of 150 U/kg 3 times a week, and then doubling the dose after 2 weeks of therapy if there is not a response, seems to be an appropriate approach; still, dose schedule remains a subject of intensive research.[8,9,11,13,14]

We think this is the clinicians' strategy for extracting and treating the patients who will benefit most from r-HuEPO therapy. However, at this point, what we have learned from Ortega et al is to determine the willingness of the patient to receive a therapy for the correction or prevention of anemia at the expense of frequent injections, side effects such as hypertension, increased frequency of thrombotic events, high cost, and considerable incidence of treatment failure, instead of receiving blood products for the symptomatic management of anemia.

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Bülent Orhan, M.D.
Department of Medical Oncology
Uludag University School of Medicine
Bursa, Turkey
Şuayib Yalçin, M.D.
Department of Medical Oncology
Hacettepe University Institute of Oncology
Bursa, Turkey

Author Reply

In their correspondence, Orhan and Yalçin raised some important issues with respect to the administration of prophylactic epoetin alfa to cancer patients receiving chemotherapy. Our cost-benefit analysis, as well as other economic evaluations using alternative methodology, have concluded that the general prophylactic use of this drug for all cancer patients receiving chemotherapy may not be cost-effective.[1–3] Hence, in our article,[1] we suggested that prophylactic epoetin alfa be considered only for selected patient subgroups who would be at high risk for requiring multiple blood transfusions.

As described by Orhan and Yalçin, some of these subgroups may include patients with underlying renal, pulmonary, or cardiovascular diseases; older patients; those receiving cytotoxic chemotherapy; and patients who required multiple transfusions in the past. Even though risk factors for anemia have been reported in the literature,[4] there has not been a prospective exploratory analysis to predict which cancer patients will likely require blood transfusions.

Our group attempted to address this issue by conducting such an analysis with 100 cancer patients using retrospectively collected data.[5] Using a multiple logistic regression approach with transfusion requirements (no vs. yes) as the outcome variable, baseline hemoglobin (Hb) level and cisplatin dose were identified as risk factors for future transfusions. Specifically, our model suggested that the need for transfusions increases by 28% for every 10 mg/m^2 cisplatin dosage increment. With respect to baseline Hb, patients were 3 times more likely to receive a blood transfusion for every 1 g/dL drop in their prechemotherapy baseline Hb level.[5] With these data, we subsequently developed a simple prediction model that could be applied in the clinic to identify patients likely to require transfusions. Once identified, the drug could also be administered to these patients a few weeks before the first cycle of chemotherapy, because it takes approximately 1 month for the drug's benefit to be realized.[6] Hence, it may be cost-effective to restrict the use of prophylactic epoetin alfa to the high risk patients identified by the model.

The prediction model for transfusion requirements that our group developed has limitations in that retrospective data were used in its development, the sample size was small, the data were obtained from a single center, and it has not been properly validated. Hence, what is required for ensuring that epoetin alfa is used in the most clinically and economically appropriate patient subgroup is the development of a prediction model based on high quality multicenter clinical trial data and with sufficient sample size. A similar instrument for predicting the survival of lymphoma patients has been successfully developed by the Non-Hodgkin's Lymphoma Prognostic Factors Group, which was able to create 4 patient risk groups with 5-year survival as the primary outcome.[7] Through the

application of Generalized Logit regression modeling,[8] we envision a similar categorization of patients receiving cancer chemotherapy, but with need of blood transfusions (i.e., 0 vs. 1–2, 0 vs. >2) as the primary outcome. One practical way of achieving this objective would be to pool the available clinical trial data on epoetin alfa, use the appropriate statistical techniques to create a prediction model, and then validate the final product in the clinic. Our group would fully support such an initiative and would be eager to participate.

In summary, epoetin alfa is an important adjunct therapy for patients receiving cancer chemotherapy, but it is not cost-effective to use it in a broad category of patients. The ability to identify which patients are likely to require blood transfusions would be an important step in ensuring that this high cost drug is used in the most clinically appropriate situations.

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George Dranitsaris, M.Sc.Phm.
Pharmacoeconomic Research Program
Ontario Cancer Institute
Princess Margaret Hospital
Toronto, Ontario, Canada