Intravenous Iron and Recombinant Human Erythropoietin in Cancer Patients

TO THE EDITOR: We read with great interest the paper by Auerbach et al.1 In a recent issue of the Journal of Clinical Oncology, the authors observed that intravenous (IV) iron increases the hemoglobin (Hb) and quality-of-life response to recombinant human erythropoietin (rHuEPO) therapy in cancer patients. This study should be hailed as the first paper to address the question of iron supply during rHuEPO therapy in cancer patients. However, the paper falls short of telling physicians the whole story about iron supplementation in this setting. The design of the study is curious. Why did the authors elect to limit the duration of the study to 6 weeks when additional follow-up would have been very easy to implement? This does not correspond to standard practice. This may explain why the no iron group had such a low response rate when compared with virtually all previous studies. Why were patients in the bolus arm followed up longer, and how did this influence the results? Indeed, the authors should have provided the Hb course over time and/or Kaplan-Meier plots of Hb response. One can suspect that longer follow-up could have shown much less difference among the groups, indicating that IV iron accelerates response but does not increase the overall response rate to rHuEPO treatment. If the authors have the data, they must show them. What is the rationale for an Hb level of 140 g/L, again contrary to standard practice and published guidelines? What were the rules for decreasing/discontinuing rHuEPO? What is the basis for the calculated amount of iron (reference to a package insert is not appropriate) to be infused into patients? This calculation led to enormous doses of iron given to patients, much more than needed to increase the Hb (to increase the Hb level by 10 g/L requires 200 mg of iron).

Absolute iron deficiency (ID) is defined by the exhaustion of iron stores in macrophages and hepatocytes, as indicated by serum ferritin values below normal, or values below 40 to 100 μg/L in anemia of chronic disorders, including cancer. The authors did not mention whether such patients were included in the study; the range of ferritin values and the percentage of patients with ferritin below 100 μg/L would be helpful. However, iron deficient erythropoiesis may occur even if iron stores are not exhausted, or are even elevated. This is called functional ID, defined as an imbalance between iron needs in the bone marrow and iron supply by macrophages. This can be encountered when iron release by macrophage is impaired, a typical feature of the anemia of cancer.2 Again, the authors fail to provide the proportion of patients with functional ID, as indicated by transferrin saturation below 20% at baseline. For a study addressing the question of iron supplementation, the paper is reporting poorly on iron data during treatment with rHuEPO. Indeed, functional ID usually worsens when the increased iron needs of an expanding erythroid marrow cannot be matched by sufficient mobilization of iron stores.3 Functional iron deficiency is a major factor limiting the efficacy of erythropoietic agents in iron-replete normal subjects, autologous blood donors, and renal-failure patients.3 As this has not been specifically examined in cancer patients treated with erythropoietic agents, the authors missed the opportunity to clarify this issue. What was the time course of transferrin saturation and ferritin during rHuEPO therapy in the four groups? Was it different in patients who had evidence of absolute or functional ID at baseline and those who did not? In addition, it would have been very helpful, and easy, to monitor better indicators of functional ID, such as the cell Hb content of reticulocytes and the percentage of hypochromic red cells.4 This would have provided insights on the way the four groups of patients handled iron metabolism during rHuEPO therapy.

Compared to no iron, oral iron did not improve the response rate to rHuEPO. This is not surprising, as previous
studies of dialysis patients have clearly indicated that oral iron is not superior to no iron, but that IV iron substantially improves response when rHuEPO therapy is instituted and allows considerable reduction in rHuEPO dose requirements during the maintenance phase. Furthermore, intestinal iron absorption is impaired in cancer patients.

The safety issues also are not fully addressed. Oral iron was extremely well tolerated, with only one patient presenting with a single episode of nausea, and compliance in excess of 90%. This is quite unusual and casts some doubt on how this was monitored. On the other hand, because there is some concern that tumor cells may need iron for optimal growth, routine iron supplementation for all cancer patients receiving erythropoietic agents may not be recommended. Several guidelines have been published to provide treatment schedules with IV iron in patients who have had renal failure. To avoid toxicity from iron excess, IV iron should be withheld when transferrin saturation is above 50% and/or serum ferritin is greater than 1,000 μg/L. Were there such safety guidelines in the Auerbach et al study? In particular, the total amount of iron given to patients is of concern. When a patient receives 3,000 mg and utilizes only 400 mg to increase his Hb by 20 g/L, this means that 2,600 mg of storage iron is added to the normal 1 g of storage iron. This macrophage iron overload may redistribute to parenchymal tissues (where iron is toxic) as well as to tumor cells. What were the mean and range of serum ferritin at the end of the study in each group? Long-term follow-up of serum ferritin as well as clinical data (including survival) must be implemented in these cohorts of patients.

There are three major forms of IV iron on the market (iron dextran, iron gluconate, and iron sucrose or saccharate). All three compounds are primarily taken up by macrophages and then secondarily released to plasma transferrin. Iron is slowly released over a period of weeks from iron dextran complexes, but much more rapidly from iron gluconate complexes, so that their maximum-tolerated doses are much lower. If these doses are respected, the safety profile of iron sucrose or iron gluconate makes them the preferred IV compounds. If too much iron is released too fast, plasma transferrin will become rapidly oversaturated and nontransferrin-bound iron will appear with all its potential toxicities. In particular, this could enhance the toxicity of some chemotherapeutic agents. How did the authors handle this issue?

Yves Beguin
Department of Medicine and Division of Hematology, University of Liège, Liège, Belgium

In Reply: We read Dr Beguin’s letter with considerable interest and appreciate his comments. He raises many useful points, but unfortunately his letter reflects unfamiliarity with the intravenous (IV) iron compounds available in the United States, the availability of laboratory tests during the conduct of our study, and the usefulness of the Fe/total iron binding capacity measurements during therapy with iron dextran. The letter was somewhat unfocused and some of his comments suggest that his reading of the original article was less than thorough. Nevertheless, we will attempt to address his questions in an orderly manner.

The expected time to response to oral iron is 6 weeks. It was our goal to evaluate whether IV iron is superior to no iron and/or oral iron in synergizing with recombinant human erythropoietin. In our study, we showed a response of significantly greater magnitude with IV iron as compared with oral iron and no iron. It is unlikely that a longer follow-up period would have changed this result, since the magnitude of the response with bolus iron was identical to that with total dose infusion, regardless of length of follow-up. Furthermore, at least 74% of oral and of no-iron patients achieved their maximal hemoglobin response in 5 weeks or less. One could easily ask conversely, “would not...