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EDITORIAL

Should Intravenous Iron Be the Standard of Care in Oncology?

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Before 1989, when epoetin was introduced for dialysis-associated anemia, the use of intravenous (IV) iron in the United States was typically avoided. Shortly thereafter, it was shown that responses to epoetin could be improved by IV iron supplementation. By 1998, IV iron had become standard of care in dialysis patients receiving epoetin,[1]and the use of erythropoiesis-stimulating agents (ESAs) in oncology patients was in its infancy. In the ensuing decade, we have witnessed improvements in quality of life and fewer transfusions among patients receiving ESAs for the anemia associated with cancer and cancer chemotherapy. Some studies have shown the maximum improvement in energy, activity, and quality of life occurs when the hemoglobin (Hb) increases from 11 to 13 g/dL.[2] In August 2007, the Committee on Medicare and Medicaid Services issued a Decision Memo restricting ESA usage when patients' Hb levels are ≥10 g/dL. These new regulations were recommended on the basis of data suggesting harm with ESAs when used outside of established guidelines. To date, no study has shown a negative impact on cancer outcomes or survival in patients when ESAs were used in accordance with previously established American Society of Hematology, American Society of Clinical Oncology, or National Comprehensive Cancer Network guidelines. Recent data in the renal literature suggest that it is not the Hb level, but ESA exposure, that is associated with negative outcomes.[3]

The success of IV iron supplementation in improving responses to ESAs in the anemia of end-stage renal disease has yet to be realized by the oncology community. Oncologists spend three times more on ESAs than nephrologists. A 50% reduction in transfusions has been accomplished in oncology patients, whereas transfusions have been virtually eliminated in the dialysis population.[4] Is it possible that it is the suboptimal use of these expensive drugs that played a role in the restrictions recently imposed?

Two articles in this issue of the *Journal of Clinical Oncology* represent the fourth and fifth of five recent publications showing that administration of IV iron to oncology patients receiving ESAs results in significantly greater increments in Hb and hematopoietic response rates compared with ESAs alone or with oral iron[5-9] (Table 1). In all five studies, the benefit was independent of baseline iron parameters. These two studies add unique and useful information to a rapidly growing body of data supporting the routine use of IV iron as an adjunct to ESA therapy in appropriately selected oncology patients.

Bastit et al[5] studied 396 patients with nonmyeloid malignancies receiving chemotherapy, with Hb less than 10.5 g/dL and ferritin more than 10 ng/mL or transferrin saturation (TSAT) more than 15%. Patients were treated with 500 μg of subcutaneous darbepoietin alpha (DA) every 3 weeks alone or with weekly or twice weekly IV iron (iron sucrose or ferric gluconate). Statistically significant improvements in Hb and hematopoietic responses and time to reach the target Hb were seen in the IV iron group. Unlike the other four studies,[6-9] this trial showed a statistically significant reduction in the number of RBC transfusions administered (nine *v* 20) in the IV iron group. Although this trial can be criticized for including overtly or functionally iron deficient patients with ferritin less than 100 ng/mL or TSAT less than 20%, a majority of patients in the trial were iron replete based on iron/total iron binding capacity and ferritin levels. This is the largest study of intravenous iron's synergy with ESAs and the only one to show a significant difference in RBC usage. For both of these trials, a double-blind design (for IV iron) with well-defined transfusion criteria would have been optimal, but this was logistically impractical.

Pedrazzoli et al[6] studied 149 patients with solid tumors receiving chemotherapy who were anemic but iron replete. Patients were treated with 150 μg of subcutaneous DA weekly with or without iron sucrose. The dose of DA was doubled at four weeks if less than a 1-g Hb increment was observed, per the Italian guidelines for ESA usage. The authors correctly point out that, unlike other studies, this trial excluded all patients with absolute or functional iron deficiency. Eligibility for randomization required serum ferritin levels greater than 100 ng/mL and TSATs greater than 20%. There were statistically significant improvements in Hb and hematopoietic responses in the IV iron group. This was the first study to enroll only patients generally considered to have adequate iron stores based on both a high serum ferritin and TSAT.

The results of this study are supported by an earlier trial by Henry et al,[8] in which patients were randomly assigned to weekly epoetin alone or with IV ferric gluconate. There was a significantly higher response rate (73%) for intravenous iron and epoetin, compared with a 41% response rate in the epoetin only group. More than 90% of the study's patients had a ferritin level greater than 100 ng/mL, and the mean TSAT in both groups was greater than 20%, making it unlikely that iron deficiency accounted for the low responder rate in the epoetin only group.

Another interesting observation in the Italian trial is that unresponsive patients at 4 weeks in the DA/iron arm were far more likely ($P = .0199$) to respond to a subsequent doubling of the DA dose (15 [68.2%] of 22) than initial nonresponders in the DA only arm (eight [32%] of 25). As the authors state, "Because of the timing of the DA dose-doubling (nonresponders after 4 weeks), a possible interaction

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Table 1. Overview of Studies Evaluating IV Iron and ESA in Oncology

	Auerbach et al[7] (n = 157)	Henry et al[8] (n = 187)	Hedenus et al[9] (n = 67)	Bastit et al[5] (n = 398)	Pedrazzoli et al[6] (n = 149)
Treatment arms	IV iron (TDI or bolus) *v* oral iron *v* no iron	IV iron *v* oral iron *v* no iron	IV iron *v* no iron	IV iron *v* no/oral iron	IV iron *v* no iron
Inclusion criteria, Hb	≤ 10.5 g/dL	< 11 g/dL	9-11 g/dL	< 11 g/dL	≤ 11 g/dL
Inclusion criteria, TSAT/SF	SF ≤ 200 ng/mL or SF ≤ 300 ng/mL and TSAT ≤ 19%	SF ≥ 100 ng/mL or TSAT ≥ 15%; SF ≤ 900 ng/mL and TSAT ≤ 35%	SF ≤ 800 ng/mL stainable iron in bone marrow	SF ≥ 10 ng/mL and TSAT ≥ 15%; SF ≤ 800 ng/mL	SF ≥ 100 ng/mL and TSAT ≥ 20%; SF ≤ 800 ng/mL and TSAT ≤ 40%
IV iron dosing	Iron dextran TDI or 100 mg to calculated dose	Ferric gluconate 125 mg QW for 8 weeks	Iron sucrose 100 mg QW (week 1-6) 100 mg Q2W (week 8-14)	Ferric gluconate or iron sucrose 200 mg Q3W	Ferric gluconate 125 mg QW for 6 wk
ESA dosing	40,000 U/wk epoetin alpha	40,000 U/wk epoetin alpha	30,000 U/wk epoetin beta	500 mcg Q3W darbepoetin alpha	150 mcg QW darbepoetin alpha for 12 weeks
Hb response	IV iron: 68% Oral iron: 36% No iron: 25%	IV iron: 73% Oral iron: 45% No iron: 41%	IV iron: 93% No iron: 53%	IV iron: 86% No/oral iron: 73%	IV iron: 77% No iron: 62%
% of patients undergoing transfusion	IV iron: 12% Oral iron: 7% No iron: 19%	Week 5 to EOTP: IV iron: 3% Oral iron: 8% No iron: 11%	IV iron: 7% No iron: 3%	Week 5 to EOTP:* IV iron: 9% No/oral iron: 20%	IV iron: 3% No iron: 7%

Abbreviations: IV, intravenous; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TSAT, transferrin saturation; SF, serum ferritin; TDI, total dose infusion; ITT, intent to treat; PP, per protocol; EOTP, end of treatment period; Q, every; W, week.
*Only study powered to detect a difference in transfusion rates.

between DA dose and IV iron supplementation cannot be excluded." A potential explanation for this can be found in the Dialysis Patients' Response to IV Iron with Elevated Fertility (DRIVE) study[10] in which hemodialysis patients with elevated ferritins (500 to 1,200 ng/mL), hyporesponsive to ESAs, received a 25% increase in epoetin dose (to an average of > 40,000 U/wk) at baseline. Patients were then randomly assigned to receive 1 g of IV iron over 2.5 weeks or no iron. At 6 weeks, a 2-g/dL increase in Hb was observed in 46.9% of the IV iron group and 29.2% of the epoetin only group; this difference was statistically significant. However, mean Hb separation between groups did not occur until week 4. In the DRIVE study, reticulocyte Hb content fell steadily and significantly only in the epoetin-only group, strongly suggesting induction of progressive iron-restricted erythropoiesis with high doses of epoetin alone. Similarly, in the Pedrazolli study, the nonresponders in the DA-only group needed iron, not more DA, as they had iron-restricted erythropoiesis. As one might expect, the DA dose increase showed a marginal benefit. Nonresponders in the DA/iron group had adequate iron to allow them to respond to the increased DA after week 4, suggesting the Hb response was due to the IV iron and not the increased DA. In both the DRIVE and Pedrazolli studies, none of the parameters of iron repletion used in clinical practice were predictive of a response. A precise explanation for this phenomenon will require further studies to explain the ability of IV iron to overcome iron-restricted erythropoiesis in iron-replete patients.

Patients with iron-restricted erythropoiesis have iron in their stores that does not get mobilized to the labile iron pool and is subsequently unavailable. This iron restriction is believed to be, at least in part, due to upregulation in many chronic disease states of the hepatic synthesized iron regulatory protein hepcidin. Hepcidin controls the release of absorbed iron into the circulation by inactivating ferroportin, the major exporter of iron. Ferroportin is strongly expressed in duodenal enterocytes and in macrophages. Macrophages are responsible for the recycling of iron from damaged RBCs back into the circulation. One possible explanation for IV iron's success in patients with iron-restricted erythropoiesis could be the direct loading of transferrin and altering the mechanism by which iron is released from macrophages. However, in vitro data to support this hypothesis does not exist.

Currently there are four IV iron preparations available. Three can be given with minimal inconvenience and marginal toxicity: low-molecular-weight iron dextran (INFeD; Watson, Morristown, NJ), iron sucrose (Venofer; American Regent, Shirley, NY), and ferric gluconate (Ferrlecit; Watson). One, high-molecular-weight iron dextran (Dexferrum; American Regent), has been associated with a much higher incidence of serious adverse events and is not recommended.[11-14] When high-molecular-weight iron dextran is excluded, there is no substantially increased risk with the administration of IV iron.

In this era of scarce resources, is the routine use of IV iron with ESAs appropriate? Factoring the cost of IV Fe and the decreased ESA dosage required to reach target Hbs that results from IV iron supplementation, it is estimated that savings of $100 per patient per week can occur. The data for these estimates comes from two sources. In a so-called back-of-the-envelope cost analysis from my practice presented at the 2007 Annual Meeting of the American College of Clinical Pharmacy,[15] the cost of 12 weeks of ESA therapy in cancer chemotherapy patients was compared with the published norm.[16] Total costs of ESA, IV iron, administration, office visits, and associated fees were included in the calculation based on the most common dosing regimen. The routine use of IV iron saved $1,301 per patient per 12-week period over the total cost of anemia therapy. This is consistent with a recently published study of patients with anemic lymphoproliferative disease not undergoing chemotherapy and with positive marrow hemosiderin randomly assigned to epoetin alone or with IV iron sucrose.[9] The decreased epoetin used to reach the target Hb, at that time 12 g/dL, in the IV iron group was estimated to save $100 per patient per week. In the United States, approximately 380,000 oncology

patients receive ESAs for an average of 12 to 24 weeks per year: The potential cost benefit of IV iron is substantial.

The results of these two well-designed clinical trials confirm the utility of IV iron in oncology and support the notion that IV iron supplementation should be considered a component of the management of the anemia of cancer and cancer chemotherapy.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.

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