Intravenous Iron in Oncology

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Key Words

Anemia, intravenous iron, erythropoiesis-stimulatory agents, chemotherapy-induced anemia

Abstract

Intravenous iron (IV Fe) as an adjunct to therapy with erythropoiesis-stimulatory agents (ESAs) is standard care in dialysis-associated anemia, adding huge increments in hemoglobin and hematopoietic responses and decreased transfusions without significant toxicity. Cost savings, decreased exposure to ESAs, and decreased times to reach target hemoglobins are realized. Although similar benefits have been seen in all studies performed in patients with chemotherapy-induced anemia (CIA), experts are reluctant to incorporate routine use of IV Fe into treatment, largely because of misinterpretation and misunderstanding of the clinical nature of adverse events reportedly associated with its administration. IV Fe is therefore underused in oncology patients with anemia. Published experience with more than 1000 patients in clinical trials involving the use of IV Fe suggests minimal toxicity and substantial benefit are experienced when high molecular weight iron dextran is avoided. This article presents evidence recommending routine incorporation of IV Fe into treatment for CIA. (*JNCCN* 2008;6:585–592)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Identify erythropoiesis stimulatory agents (ESAs) approved and licensed for use in the United States for oncology patients
- Describe the most likely mechanisms accounting for anemia among patients with cancer
- Define characteristics of functional iron deficiency in oncology patients
- Provide the most likely explanation for a suboptimal response to ESAs in oncology patients
- Describe the recommendations of the authors for the use of intravenous iron in oncology patients

In August 2007, the Committee on Medicare and Medicaid Services issued a Decision Memo restricting the use of erythropoiesis-stimulatory agents (ESAs) in patients with cancer- and chemotherapy-related anemia. The use of ESAs has been proscribed in all patients with cancer-related anemia not undergoing chemotherapy and patients with chemotherapy-induced anemia (CIA) with hemoglobin levels greater than 10 g/dL. The National Institute for Health and Clinical Excellence in the United Kingdom recommends ESAs not be used unless clinically significant anemia is present and transfusions are unavailable.¹ These decisions were based on 3 randomized, placebo-controlled studies showing negative cancer outcomes in patients receiving ESAs compared with placebo.^{2–4} In 2 of these studies, nonanemic oncology patients were treated to supratherapeutic

hemoglobin levels.^{2,3} All 3 studies had imbalances in pretreatment prognostic indicators favoring the placebo group.

In the United States and worldwide, \$4 and \$6 billion, respectively, are spent per year on ESAs. Oncologists spend 3 times as much per patient for half the transfusion decrement seen in dialysis patients.⁵ Although virtually 100% of patients undergoing dialysis receive intravenous iron (IV Fe) as an adjunct to ESA therapy, fewer than 10% of oncology patients are estimated to receive IV Fe when appropriate.⁶ In dialysis-associated anemia, the target hemoglobin level remains 12 to 13 g/dL. No restriction of ESA use in dialysis-associated anemia or anemia associated with chronic kidney disease has yet been issued. No clear guidelines have been published recommending parameters for initiating IV Fe in oncology. The NCCN and American Society of Hematology/American Society of Clinical Oncology recommend using IV Fe when iron supplementation is indicated.

This article summarizes numerous recent publications showing the efficacy and safety of IV Fe alone and as a component of ESA therapy and proposes a new treatment paradigm incorporating its routine use for treating anemia in oncology patients.

Currently Available Iron Preparations

Four agents are licensed for use in the United States (Table 1). The first 2 approved were low molecular weight iron dextran (LMW ID) and high molecular weight iron dextran (HMW ID). Both iron dextrans can be given as intravenous boluses in doses up to 400 mg or as a single infusion of the total calculated iron

deficit. Reported safety differences in these compounds are discussed in detail later.

The third and fourth agents approved were ferric gluconate and iron sucrose. These agents can be given as short intravenous infusions at doses up to 200 mg for ferric gluconate and 300 mg for iron sucrose, but higher doses have been proscribed.⁷ Both dextrans are approved for use in nephrology and oncology patients, whereas the 2 iron salts are only approved for nephrology patients.

Why IV Fe Works

Anemia in patients with cancer is believed to reflect a reduction of red cell production by the bone marrow and the interplay of several factors, including a relative decrease in erythropoietin, impaired release of iron from macrophages in the reticuloendothelial system, and diminished or hyporesistance to endogenous erythropoietin by erythroid precursors in the marrow.

In a large subset of patients with cancer-related anemia, an important response-limiting factor is the presence of functional iron deficiency (FID), characterized by an imbalance between iron needs in the erythropoietic marrow and iron supply, which depends on adequacy of iron stores and its rate of mobilization. When supraphysiologic doses of erythropoietin are administered, red cells are produced at a rate that outstrips labile iron availability, causing FID. FID is characterized by hypoferremia, normal or decreased transferrin, and a low transferrin saturation (TSAT) in the presence of adequate storage iron. FID may account for the lack of response in patients who do not experience an adequate response to ESAs.

Table 1 Currently Available Intravenous Iron Preparations

	LMW ID	Iron Saccharate	Ferric Gluconate	HMW ID
Test dose required	Yes	No	No	Yes
Vial volume	2 mL	5 mL	5 mL	1–2 mL
Mg iron per mL	50 mg/mL	20 mg/mL	12.5 mg/mL	50 mg/mL
Black-box warning	Yes	No	No	Yes
Total-dose infusion	Yes	No	No	Yes
Premedication	TDI only	No	No	TDI only
Preservative	None	None	Benzyl alcohol	None
Molecular weight measured by manufacturer	165,000 Da	34,000–60,000 Da	289,000–440,000 Da	265,000 Da

Abbreviation: HMW ID, high molecular weight iron dextran; LMW ID, low molecular weight iron dextran; TDI, total dose infusion.

The distribution of body iron stores underscores the importance of iron in red cell production. Normally, most iron available for erythropoiesis comes from catabolism of red blood cells by macrophages in the reticuloendothelial system. Approximately 70% of total body iron is found in circulating erythrocytes and approximately 20% is stored as tissue ferritin, primarily in the liver. Smaller amounts are coupled with enzymes, such as myoglobin.⁸ Iron is absorbed from the duodenum and proximal jejunum. On entering circulation, iron is rapidly transferred to the carrier protein transferrin, which delivers it to all cells in the body. Approximately 80% of absorbed iron is delivered to the bone marrow.

Erythropoiesis involves close interaction between iron and erythropoietin. Essentially, erythropoietin is the hormone that drives erythropoiesis, providing fuel for the production of red blood cells. When iron and erythropoietin are appropriately coupled, red cell production occurs briskly and efficiently; when one component is deficient, anemia results. Even when both components are present in adequate quantities, they must be coordinately delivered to the bone marrow for proper action.

After the erythropoietin gene was cloned in the 1980s, the product became available for clinical use in 1989. The hematocrit of patients with chronic renal failure rose dramatically when erythropoietin was administered. Enhanced red cell production manifested as a rise in the plasma iron turnover and a decrease in the half-life of iron in the plasma. The plasma ferritin level of patients dropped substantially despite adequate iron stores. This was the first indication that erythropoietin used in high doses could drive red cell production more rapidly than iron could be delivered.⁹

Rutherford et al.⁸ dramatically showed the interplay between iron and erythropoietin. In a study to determine whether erythropoietin could raise baseline hemoglobin to a level that would enhance autologous blood donation, they administered oral iron supplementation during erythropoietin treatment. Baseline hemoglobin levels increased by 1 g/dL, reflecting enhanced erythropoiesis. Subjects were unable to maintain adequate serum iron levels despite oral iron supplementation. TSAT at onset was 40%, but decreased to 10% within 2 weeks of erythropoietin treatment. These results showed that developing red blood cells removed iron from circulating transferrin at a

rate faster than it could be replaced by either the iron stores or orally absorbed iron.

Hepcidin has emerged as a primary regulator of iron homeostasis. It is a 25-amino acid polypeptide produced by hepatocytes that is an acute-phase protein and the major hormone regulator of iron balance. It inhibits iron release from macrophages in storage sites, diminishing its recycling, and plays a major role in enteral iron absorption through interaction with the transmembrane exporter, ferroportin, accelerating its degradation and resulting in decreased entrance of iron into circulating blood plasma.¹⁰ In a substantial number of patients with cancer- and chemotherapy-related anemia, inflammatory cytokines are released, causing upregulation of hepcidin with resulting hypoferremia. In these clinical settings, oral administration is inadequate. However, when inflammatory cytokines are not present, oral iron absorption occurs more freely.

Although ESAs have provided a safe and effective option for treating cancer- and chemotherapy-related anemia, not all patients experience adequate response. A lack of available labile iron is the most frequently encountered cause of suboptimal response to ESAs, and unbalanced iron metabolism is a major factor. Control of iron balance requires coordination among sites of uptake, use, and storage. The hepcidin–ferroportin interaction is critical for normal iron homeostasis.

In patients with chronic renal failure, FID is the most common cause of inadequate response to ESAs. Studies in renal failure have shown that IV Fe can correct FID more effectively than oral iron and is now standard care. An understanding of FID and the importance of maintaining an adequate supply of labile iron to meet the needs of the ESA-stimulated erythroid precursors is fundamental. Oral formulations of iron have been shown to be suboptimal and therefore cannot provide labile iron rapidly enough to supply the accelerated erythropoiesis that occurs when ESAs are administered. In contrast, IV Fe provides sufficient quantities at a rate that optimizes efficacy.

Studies of IV Fe in Oncology

The first study to show the benefit of IV Fe in oncology was published in 2004.¹¹ In this study, 155 patients with chemotherapy-related anemia received erythropoietin, 40,000 U subcutaneously per week and either no iron; ferrous sulfate, 325 mg twice daily; 100-mg boluses of iron dextran weekly to the calculated total dose;

or a single total dose infusion of iron dextran given over 4 hours. Patients randomized to total dose infusion received 125 mg of methylprednisolone pre- and post-infusion to prevent the arthralgias and myalgias¹² associated with this method of IV Fe administration.¹³ No differences were seen in baseline serum ferritin levels (294, 290, 207, and 240 ng/mL, respectively) or TSATs (15%, 18%, 19%, and 14%, respectively) among the 4 groups.

Although no differences in response rates were observed between the IV Fe arms, statistically significant improvements in hemoglobin and hematopoietic responses occurred in individuals who received IV Fe compared with those who did not. The time to reach the target hemoglobin was 60% shorter in the IV Fe groups, and the total ESA exposure was lower.

In this study, 81 patients received IV Fe, 79 received LMW ID, and 2 received HWM ID when LMW ID was unavailable for a short time. One individual who received HMW ID experienced anaphylactic shock requiring intubation. Months later, off-study, this patient received LMW ID uneventfully. Entry criteria included a serum ferritin of 200 ng/mL or less or 300 ng/mL or less, and a TSAT of less than 19%. Although the mean serum ferritin was greater than 200 ng/mL and the responses were independent of baseline ferritins and TSAT, this study has been criticized for treating mainly patients with iron deficiency.

Recently, reports of 4 clinical trials corroborating the results of this earlier study were published. In the first, Henry et al.¹⁴ published results of 187 patients with chemotherapy-related anemia and serum ferritins between 100 and 900 ng/mL or TSAT between 15% and 35% who were scheduled to be treated with epoetin, 40,000 U subcutaneously per week. The investigators randomized these patients to treatment with 8 weeks of 125 mg of intravenous ferric gluconate weekly, 325 mg of oral ferrous sulfate 3 times daily, or no iron. No differences were seen in baseline serum ferritin levels (321.5, 373.9, and 388.2 ng/mL, respectively) or TSATs (29.4%, 29.1%, and 36.3%, respectively) among the 3 groups, although statistically significantly greater hemoglobin and hematopoietic responses were seen in the group receiving IV Fe.

Although patients with TSAT less than 20% receiving IV Fe showed a greater magnitude of hemoglobin rise and response rates, significantly greater hemoglobin and hematopoietic responses were seen in patients with TSAT greater than 20% compared with

those receiving oral ferrous sulfate or no iron. A recent reanalysis of the data, presented at the 2007 American Society of Hematology meeting, showed a significant decrease in thromboembolic events in the ferric gluconate arm compared with the epoetin alone arm.¹⁵ No significant toxicity attributable to ferric gluconate was seen.

In the second corroborating trial, Hedenus et al.¹⁶ performed a multicenter randomized trial in 60 patients with lymphoproliferative malignancies and anemia not on chemotherapy. This study was unique in its entry requirements of serum ferritin less than 800 ng/mL and positive stain for bone marrow hemosiderin before randomization. The mean serum ferritin among the groups was 128 ng/mL (range, 22–794 ng/mL) and the mean TSAT was 21.5% (range, 5%–45%). Patients were then randomized into 2 treatment groups receiving epoetin beta 30,000 U subcutaneously per week alone or with iron sucrose administered as 100 mg intravenously on alternate weeks from weeks 8 to 14.

Significantly greater increases in mean hemoglobin levels were seen from week 8 onward in the iron group. The number of patients experiencing at least a 2-g increment in hemoglobin was nearly doubled in the iron group (53% vs. 93%; $P = .001$). Despite more missed doses in the no-iron group, the mean weekly epoetin dose after 15 weeks of therapy was 25% lower in the iron group. Using Swedish pharmacy pricing at the time of the study, the decrement in ESA dosing translated to a savings of \$100 per patient per week. No significant toxicity was seen in the patients receiving iron sucrose.

In the third trial, Bastit et al.¹⁷ studied 396 patients with nonmyeloid malignancies and CIA. Unlike the prior 2 studies, patients in this study received darbepoetin, 500 mcg, subcutaneously every 3 weeks alone or with intravenous iron sucrose or ferric gluconate weekly for 16 weeks. No differences were seen in baseline serum ferritin levels (279.9 and 278.9 ng/mL) or TSAT (21.2% and 23.7%) between the groups. Only 4 patients in both groups were truly iron deficient, defined as having a TSAT less than 20% and serum ferritin less than 15 ng/mL. This study corroborated the results of previous trials, with significantly higher hemoglobin and hematopoietic responses in the IV Fe group. However, unlike the other studies, this study showed a significantly decreased number of transfusions in the IV Fe group compared with the no iron group (Figure 1).¹⁸ No significant toxicities were seen with IV Fe.

In the fourth trial, Pedrazzoli et al.¹⁹ studied 149 patients with CIA who received either 150 mcg of darbepoetin subcutaneously per week alone, or 125 mg of ferric gluconate intravenously for the first 6 weeks. The darbepoetin dose was doubled one time to 300 mcg/wk if a 1-g/dL increment in hemoglobin was not attained in 4 weeks.

This trial was unique because it excluded patients with absolute or functional iron deficiency by requiring a serum ferritin level of 100 ng/mL or more and a TSAT of 20% or more. Exclusion criteria were serum ferritins greater than 800 ng/mL and a TSAT greater than 40%. No differences were seen in baseline serum ferritin levels (350.7 and 333 ng/mL) or TSATs (30.6% and 27.6%) between the groups. The IV Fe group had statistically significantly more hematopoietic responses compared with the no-iron group (92.5% vs. 70%). No significant toxicity was associated with ferric gluconate. These results were also corroborated by a study presented by Bellet et al.¹⁹ at the 2006 American Society of Clinical Oncology Meeting.

These 5 trials included 920 patients; all showed significant improvement in hemoglobin and hematopoietic responses in patients randomized to receive IV Fe compared with oral iron or none. One study showed a statistically significantly lowered number of transfusions.¹⁷ All responses to IV Fe in the CIA trials were independent of baseline iron parameters. No significant toxicity related to IV Fe was seen in any of the

studies, except for 1 of 2 patients who received HMW ID when LMW ID was unavailable. The studies with concomitant ESA therapy all showed significantly decreased exposure to ESAs and considerable cost savings. Results of a recently completed trial comparing 5 treatments of either 300 or 500 mcg of subcutaneous darbepoetin every 3 weeks alone or with 400 mg of LMW ID administered over 30 to 60 minutes are eagerly awaited.

Toxicities of Currently Available Iron Preparations

The most serious toxicity associated with IV Fe is anaphylactic shock. The authors believe that fear of anaphylaxis is why IV Fe is underused, despite 5 recent publications showing its safety and efficacy in synergizing with ESAs. The overwhelming number of anaphylactic reactions reported are caused by the HMW ID products Imferon (Fisons Pharmaceuticals, Hones Chapel, England), which is no longer available, and Dexferrum (American Regent Labs, Shirley, NY), which is not recommended.²¹⁻²⁴

The first paper to indicate this was published by Chertow et al.²⁵ in 2004 and updated in 2006.²⁶ This study, a retrospective analysis of 50 million doses of IV Fe based on adverse events reported to regulatory agencies, showed that when severe adverse reactions were stratified by iron product, virtually all were caused by HMW ID, with an estimated incidence of serious adverse events less than 1:200,000 with LMW ID, iron sucrose, and ferric gluconate.

Unfortunately, a general lack of knowledge about the currently available preparations exists outside the nephrology community. Hospital pharmacists may purchase the less-expensive HMW ID as a generic equivalent, despite different J-codes assigned by the FDA in 2005 and numerous publications showing a drastically higher serious adverse event rate with HMW ID.

Not all reactions to IV Fe are severe; LMW ID, iron sucrose, and ferric gluconate may be associated with minor, self-limiting, infusion-related reactions. Chest and back pain may occur without hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema in approximately 1 of 200 patients receiving LMW ID. This reaction subsides without treatment and does not occur with rechallenge.²⁷

However, medical personnel unfamiliar with this reaction can often administer diphenhydramine or

Figure 1 Percentage of patients who received transfusions.

*For patients enrolled in the study for at least 29 days

Abbreviations: CI, confidence interval; IV, intravenous.

Source: Bastit L, Vandebroek A, Altintas S. A randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alfa administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *J Clin Oncol* 2008;26:1616; with permission.

epinephrine inappropriately, which cause significant vasoactive reactions that may mimic anaphylaxis and be incorrectly attributed to the iron preparation. Premedication with diphenhydramine before the IV Fe test dose, which may cause the same misinterpretation of adverse events, has been shown to be ineffective¹³ and therefore should be abandoned.²⁷ Premedication is only appropriate using methylprednisolone before and after total dose infusion of LMW ID.¹² This premedication has been shown to ameliorate the arthralgias and myalgias that occur frequently with this method of IV Fe administration.

Ferric gluconate and iron sucrose can be safely administered as bolus injections or short intravenous infusions in doses up to 300 mg. However, higher doses are associated with frequent, annoying, dose-dependent gastrointestinal and vasoactive reactions in up to 30% of patients, and therefore should be avoided.⁷ Based on numerous publications in large series of nephrology and oncology patients, when HMW ID is avoided, IV Fe can be administered with minimal toxicity.

Until 2007, no prospective comparison study of LMW ID, iron sucrose, or ferric gluconate had been performed. Monheim and Bhandari²⁸ compared 144 patients undergoing hemodialysis receiving LMW ID with 110 receiving iron sucrose. Patients were treated with one agent for 6 months and then crossed over to the other for an additional 6 months. No anaphylaxis was seen in either group. The 2 forms of IV Fe were equally effective and safe. The use of LMW ID resulted in a savings of £77 per patient per 6-month period.

In a study of 60 patients equally divided between LMW ID and iron sucrose, Sav et al.²⁹ saw no serious reactions in either group and showed that the 2 therapies were equally effective and safe. These data were confirmed by a systematic review of 60 studies.³⁰ Long-term toxicity of IV Fe may be a concern; however, in 14 years of experience with the routine use of IV Fe in nephrology, Kalantar-Zadeh et al.³¹ showed none associated with serum ferritins up to 1200 ng/mL and TSATs of 40%.

Economic Analysis of IV Fe

Approximately 380,000 patients are currently receiving ESAs for CIA. The cost of 1 complete course of IV Fe adds little to the cost of ESA therapy. A recent cost analysis in 60 patients in a community oncology prac-

tice that routinely administers IV Fe to patients receiving ESAs for CIA was presented at the 2007 meeting of the American College of Clinical Pharmacy.³² The cost analysis for ESA and ESA plus iron included office visits, administration expenses, and pharmacy and drug costs. The cost of ESA therapy plus IV Fe was compared with the average cost of ESA therapy in the published norms for patients with CIA. The addition of IV Fe resulted in a cost savings of \$1300 per patient. However, in the subset of patients with non-small cell lung cancer, the addition of IV Fe saved \$5300 per patient (Figure 2). Overall, this translates to a cost savings of \$100 per patient per week, which is consistent with the data from Hedenus et al.¹⁶ based on the value of the Norwegian krona at the end of 2006.

Conclusions

In all published studies, IV Fe significantly improved the hemoglobin and hematopoietic responses of patients with CIA receiving ESAs, without substantially increasing toxicity. In approximately 1000 patients receiving thousands of doses of IV Fe, only 1 serious adverse event was recorded, and this event occurred in 1 of 2 patients who received HMW ID. In every study, IV Fe decreased ESA exposure and time to reach target hemoglobin. Large cost savings are realized with routine use of IV Fe with ESAs. A trend is occurring toward a decreased transfusion requirement with IV Fe.¹⁷ In all studies, the results were independent of the

Figure 2 Cost of anemia management. Cost savings overall were \$1301 per 12-week cycle for unspecified cancer and \$5235 per patient with lung cancer.

Source: Auerbach M, Pappadakis J, Doherty E. Therapeutic and financial optimization of anemia management in cancer patients with chemotherapy-related anemia through low molecular weight (LMW) iron dextran administration. Presented at the Annual Meeting of the American College of Clinical Pharmacy; Denver, Colorado; October 14–17, 2007. Abstract 188.

baseline iron parameters serum ferritin and TSAT. In oncology, the safety data exists up to ferritins of 1000 ng/mL and TSATs of 40%.

Considering the great improvement in efficacy and cost without increased toxicity, the authors believe sufficient data recommend the use of IV Fe in patients receiving ESAs for CIA who are unresponsive after 4 weeks. For patients receiving frequent doses of ESAs during chemotherapy, LMW ID, iron sucrose, and ferric gluconate can be given over short periods in doses up to 300 mg with equal safety and efficacy. For total dose infusion, only LMW ID should be used. For patients with absolute iron deficiency, full IV Fe replacement should be given before ESAs. Currently, IV Fe is underused in oncology.

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Iron Replacement in Oncology

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1.

Which of the following agents is *most likely* to be approved for use in both oncology and nephrology patients with anemia?

A. Low-molecular-weight dextran

B. Iron sucrose

C. Ferric gluconate

D. None of the above
2.

Anemia occurring in oncology patients is *most likely* to reflect which of the following processes?

A. Decrease in erythropoietin

B. Impaired release of iron from macrophages

C. Hyporesistance to endogenous erythropoietin by erythroid precursors

D. All of the above
3.

Which of the following is *least likely* to be a characteristic of functional iron deficiency (FID)?

A. Hyperferremia

B. Normal transferrin

C. Low transferrin saturation

D. Adequate storage iron
4.

Which of the following is the *most* frequently encountered cause of suboptimal response to ESAs in the treatment of cancer- and chemotherapy-related anemia in the absence of chronic renal failure?

A. Lack of available labile iron

B. Interaction with other therapies

C. Presence of metastases

D. None of the above
5.

All trials of intravenous iron in patients with cancer-induced anemia have shown which of the following effects?

A. Improved mortality

B. Improved hemoglobin after ESA use

C. No effect on hemoglobin

D. Anaphylaxis as a common adverse effect

Activity Evaluation									
1. The activity supported the learning objectives.					3. The content learned from this activity will impact my practice.				
Strongly Disagree		Strongly Agree			Strongly Disagree		Strongly Agree		
1	2	3	4	5	1	2	3	4	5
2. The material was organized clearly for learning to occur.					4. The activity was presented objectively and free of commercial bias.				
Strongly Disagree		Strongly Agree			Strongly Disagree		Strongly Agree		
1	2	3	4	5	1	2	3	4	5

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