Intravenous iron: From anathema to standard of care

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A growing body of literature supports the use of intravenous iron as a compliment to erythropoiesis stimulatory therapy and in a significant number of disease states where iron is necessary and oral iron is ineffective or not tolerated. The differences in efficacy, safety, and clinical nature of serious adverse events that occur with the various iron preparations are poorly understood. Misinterpretation of adverse events leads to underutilization of this important treatment modality. Understanding the history of the development and use of intravenous iron is crucial to appreciate its importance in the management of anemias of dialysis, cancer, and cancer chemotherapy and properly assess side effects and toxicity. The benefits seen with intravenous iron therapy are independent of the pretreatment levels of serum ferritin, iron, total iron binding capacity, and percent transferrin saturation. Intravenous iron has been shown to overcome hepcidin induced iron restricted erythropoiesis in iron-replete patients. Available clinical and experimental data suggest that increased utilization of intravenous iron should be considered. Am. J. Hematol. 83:580–588, 2008. © 2008 Wiley-Liss, Inc.

Iron has been used by physicians throughout history. It is believed that Sydenham, in 1681, was the first to recognize the value of iron therapy in chlorosis [1]. This important insight had little impact on medical practice. Although it was well-known at the beginning of the eighteenth century that chlorosis represented a lack of hemoglobin and that iron was present in hemoglobin, it was not until the nineteenth century that a French physician, Pierre Blaud, introduced pills containing ferrous sulfate and reported the cure of chlorosis [2]. Early clinical experience with parenterally administered iron (intramuscularly and subcutaneously) has been summarized by Stockman [1]. Heath et al. [3] injected subcutaneous and intramuscular (IM) iron solutions and noted increases in hemoglobin levels in hypochromic anemias. The increased synthesis of hemoglobin was proportional to the amount of iron delivered.

Parenteral iron usage in the early twentieth century was extremely limited and thought to have prohibitive toxic reactions. To probe the safety issue, Goetsch et al. [4] introduced intravenous (IV) infusions of colloidal ferric hydroxide as therapy for patients with hypochromic anemias. Toxic reactions were severe in most instances and led to the conclusion to “preclude its use for therapeutic purposes except under most unusual circumstances.” Subsequent studies by Nissim [5] utilizing IV solutions of elemental iron as saccharide led to the conclusion that parenteral iron as saccharide could be administered with relative safety and was more suitable than the ferric hydroxide for this purpose. Clinical use of parenteral iron accelerated with the iron saccharides in the 1940’s and shortly thereafter with iron dextran. In 1954, a solution of iron dextran (Imferon, Fisons pharmaceuticals) was introduced by Baird and Padmore [6] for the treatment of selective iron deficiency anemias by the IM route. Used IM and occasionally IV, in divided doses, it soon gained acceptance as it was associated with rapid hematologic responses and a low incidence of adverse events. Since the 1990’s, an upsurge in the clinical use of parenteral iron followed the introduction of recombinant human erythropoietin (EPO) for the correction of anemia in patients with renal failure. Two recent papers validate the safety and efficacy of IV iron in the management of patients who are iron deficient [7,8].

Nonetheless, for over 50 years, recommendations for use of parenteral iron have been supported by little more than folklore. Today, despite numerous publications to the contrary, medical students around the world are routinely taught that oral iron is the method of choice for replenishing iron. Standard texts advise against the use of parenteral iron unless the situation is life threatening or severe malabsorption is present [9]. Until recently IM iron was considered the standard method of administration of parenteral iron, despite excellent data in the Indian literature supporting IV iron’s superiority [10]. IM iron is painful, associated with gluteal sarcomas [11,12], causes permanent discoloration of the skin, and has never been shown to be less toxic or more efficacious than IV iron; therefore, it should be abandoned [13].

Prior to 1992, Imferon, manufactured by Fisons Pharmaceuticals in Homes Chapel England, was the only parenteral product available in the United States. The drug was marketed by Merrill in the United States and was considered a minor product. In 1980, Hamstra et al. [14] published a review of their experience with the usage of IV iron dextran in a cohort of approximately 500 patients with iron deficiency and with no clinical reason to suggest that oral administration would not be adequate. The dose and schedule varied from patient to patient. Virtually all patients achieved clinical benefit. Three serious acute and eight delayed adverse events occurred, none of which were fatal. All acute reactions were classified as anaphylactoid even in

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TABLE I. Currently Available Intravenous Iron Preparations [19]^{a,b,c,d}

	Low-molecular weight iron dextran	High-molecular weight iron dextran	Iron saccharate	Ferric gluconate
Test dose required	Yes	Yes	No	No
Vial volume (mL)	2	1–2	5	5
Mg iron (mg/mL)	50	50	20	12.5
Black-box warning	Yes	Yes	No	No
Total-dose infusion (TDI)	Yes	Yes	No	No
Premedication	TDI only	TDI only	No	No
Preservative	None	None	None	Benzyl alcohol
Molecular weight measured by manufacturer (Da)	165,000	265,000	34–60,000	289–440,000

^a INFeD [prescribing information]. Morristown, NJ: Watson Pharma Inc; 2001.

^b DexFerrum [prescribing information]. Shirley, NY: American Regent Laboratories Inc; 2001.

^c Venofer [prescribing information]. Shirley, NY: American Regent Laboratories Inc; 2001.

^d Ferrlecit [prescribing information]. Morristown, NJ: Watson Pharma Inc; 2001.

the absence of tachycardia, hypotension, or respiratory distress. Hamstra concluded that anaphylactoid reactions are serious and unpredictable and opined that IV iron dextran should be used only when iron deficiency anemia cannot be treated adequately with oral iron. The package insert for Imferon had a black box warning about the potential for anaphylaxis and a test dose was required.

Parenteral iron preparations

The adverse effects of bioactive free iron resulting from parenteral iron administration have been recognized for more than 50 years. This prompted the development of formulations that shielded iron. The currently available IV preparations are all iron–carbohydrate complexes or colloids based on small spheroidal iron–carbohydrate particles. Each particle consists of a core made of an iron–oxyhydroxy gel surrounded by a shell of carbohydrate that stabilizes the gel, slows the release of iron, and maintains the resulting particles in colloidal suspension [13,15]. The currently approved IV irons all share this structure but differ from each other by the size of the core and the identity and density of the surrounding carbohydrate. The characteristics of the four available preparations are listed in Table I. The molecular weight of the iron complex reflects the size of the iron core and the surrounding carbohydrate. Reported molecular weights vary according to method of measurement.

The strengths of the iron complex affect pharmacokinetic characteristics of the IV irons relevant to therapeutic use. The rate of release of bioactive iron is inversely related to the strengths of the complex, the stronger the complex the slower the release of the iron. The toxicological implication of this is that stronger complexes have a lower potential to supersaturate transferrin with subsequent free iron toxicity compared to the weaker complexes [16].

The different preparations all share the same metabolic fate. After IV injections, iron–carbohydrate complexes mix with plasma and are phagocytosed in the reticuloendothelial system. Within phagocytes, iron is released from the iron–carbohydrate complex into a low molecular weight iron pool. This iron is either incorporated by ferritin into intracellular iron stores or is released to the extracellular iron binding protein, transferrin, which delivers iron to the transferrin receptors on the surface of erythroid precursors. The resulting internalization of the iron transferrin complex supplies iron for hemoglobin synthesis.

In summary, IV iron preparations are iron–carbohydrate complexes characterized by specific carbohydrates used for complexing and shielding the iron. The specific carbohy-

drate influences the strength of the iron complex determining the rate of release of bioactive iron.

Clinical use of intravenous iron

In 1988, Auerbach et al. [17] published a study evaluating acute and delayed reactions in anemic patients with absence of bone marrow hemosiderin receiving a total dose infusion (TDI) of high molecular weight iron dextran (HMW ID). Doses ranged from 1,000 to 3,000 mg. The total dose of iron dextran was diluted in 500 ml of normal saline and infused over 4–12 hr after a test dose of the diluted solution. There was no relationship between the infusion rate and adverse event frequency or severity. Subsequently the more rapid rate was recommended. One of 87 patients experienced an acute, nonfatal, anaphylactic reaction. Approximately half of the patients developed arthralgias and myalgias within the first 48 hr following infusion. Premedication with aspirin and diphenhydramine had no effect on the incidence or severity of the arthralgias and myalgias. During the conduct of this study, a case report in *Lancet*, in 1983, of meningism [18] after a dose of IV iron led to a recall of the world's supply of Imferon. A critical review of this article indicated that the patient had a minor arthralgia/myalgia syndrome with headache and neck stiffness and recovered without residua. The subsequent publication [17] recommended parenteral iron be given as a TDI, but generated little interest following the *Lancet* case report and Hamstra's warning about IV iron therapy. Although complete correction of hemoglobin deficit in a subset of seven of these patients with concomitant chronic inflammatory disorders was an exciting and unanticipated finding, the major inference taken from the 1988 paper by the medical community was the 50% incidence of arthralgias and myalgias, a self-limiting harmless reaction that leaves no residua. In 1998, Auerbach et al. [19] reported that 125 mg of methylprednisolone before and after TDI dramatically reduced the frequency and severity of arthralgias and myalgias (Table II). As oral iron was inexpensive and nearly always effective if tolerated, physicians had little need or interest in a product, albeit quite safe and effective, that they had been taught and believed had potentially life threatening complications.

In spite of the admonitions within the medical community regarding the use of IV iron, Fisons continued marketing the product for those clinical situations where iron administration as a TDI was indicated. On June 1, 1989, the FDA approved recombinant human EPO for the correction of anemia in patients with chronic renal failure. Little did anyone realize the role IV iron would play in managing these patients. Amgen, the manufacturer of EPO, and the

TABLE II. Effect of Methylprednisolone on Incidence of Reactions [19]

	No. with reaction (%)	No. with no reaction (%)	Total
Saline	16 (59%)	11 (41%)	27
Methylprednisolone	15 (29%)	36 (71%)	51
Total	31 (40%)	47 (60%)	78

A statistically significant reduction in reactions is noted in the methylprednisolone treated group. Odds ratio = 3.491; 95% confidence interval: 1.315–9.264.

medical community also did not appreciate or anticipate the role of EPO in anemias related to cancer, gastrointestinal disorders, systemic collagen diseases, and a host of other anemias associated with chronic disease states. Hundreds of thousands of dialysis patients world-wide lived with the belief that extreme fatigue and exhaustion from severe anemia due to EPO deficiency could not be ameliorated without chronic transfusions. Dialysis patients had a life expectancy of less than 3½ years. The availability of EPO should have generated enormous hopefulness in the dialysis population, but enthusiasm for its use was far from brisk. In 1991, 2 years after EPO's approval, the mean hemoglobin among US dialysis patients was still less than 10 g/dL, and many patients were not receiving EPO therapy [20]. Causes of EPO's ineffectiveness were not well understood and were thought to be due to bleeding, absolute iron deficiency, or the presence of comorbid conditions (anemias of chronic disease). Functional iron deficiency, a situation where iron stores are present but not readily available for erythropoiesis, became an important area of research interest. Currently there are no satisfactory tools to accurately assess a state of functional iron deficiency. However, measurement of the reticulocyte hemoglobin content appears promising [21].

The nephrology community, lead by the excellent research of Eschbach and others, began to carefully examine the use of IV iron in dialysis patients receiving EPO. In 1987, Eschbach et al. [22] demonstrated the clinical efficacy of 1,000 mg of IV iron dextran in dialysis patients failing to respond to EPO at standard doses of 50 U/kg thrice weekly despite serum ferritin values greater than 500 ng/mL. Prompt increases in hemoglobin levels were seen (Fig. 1). Subsequently, Fishbane et al. [23] showed that the number of patients on dialysis responding suboptimally to EPO administration could be reduced from 30–40% to less than 10% when concomitant IV iron was administered. In 1996, Fishbane et al. [24] published data on the safety and efficacy of low molecular weight iron dextran (LMW ID), a product not commercially available at the time. They showed that significant reductions in dosing and duration of therapy with EPO could be achieved by the addition of IV iron. They concluded that oral iron was not effective in this population due to poor compliance and impaired absorption. They further concluded that IV iron given as 1,000 mg divided over 10 doses during sequential dialysis treatments resulted in a rapid improvement of erythropoiesis and replenishment of depleted stores. In a retrospective chart review, Fishbane noted a serious adverse event (AE) rate of approximately 0.7% following iron dextran administration. Of great interest was a description of what appeared to be an acute arthralgia and myalgia syndrome associated with the test dose. In 0.3% of patients acute onset of chest and back pain without hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema occurred. After a

Figure 1. Functional iron deficiency induced in a patient by 50 U/kg of rHuEPO given three times weekly (Figure adapted from Eschbach et al., 1987).

short delay symptoms routinely abated without treatment and rechallenging did not precipitate recurrence. This harmless reaction was unreported until the publication of a recent review [13]. Unfortunately, this event continues to be misconstrued as an anaphylactoid reaction prompting intervention with drugs such as diphenhydramine and epinephrine, each of which is able to cause severe cardiovascular side effects. Although the National Comprehensive Cancer Network guidelines suggest pretreatment with diphenhydramine and acetaminophen to help reduce the risk of adverse reactions [25], the use of antihistamines can cause vasoactive reactions that may be misinterpreted and are often attributed to the injected iron. Given the lack of efficacy for pretreatment with aspirin and diphenhydramine to reduce the incidence or severity of the arthralgia-myalgia reactions [17], it is reasonable to avoid premedication with these agents [13]. This is corroborated by a study in 135 iron deficient patients receiving LMW ID preceded by premedication with cimetidine, dexamethasone, and diphenhydramine. In this study, most AEs requiring therapy or cessation of treatment were associated with the premedication. No serious events related to LMW ID were seen [26].

Subsequent to the pioneering studies of Hamstra and Fishbane, many investigators studied the role of IV iron as a component of the management of anemia in dialysis patients. The most important impetus to the increased use of IV iron as an adjunct to EPO therapy came from the NKF-KDOQI Clinical Practice Guidelines for the anemia of chronic renal failure [27], which recommended IV iron in preference to oral iron, maintaining serum ferritin >100 ng/mL, and not withholding iron as long as the serum ferritin was <800 ng/mL. Administration of IV iron to patients with this ferritin level, usually considered the lower range for iron overload states, contradicted conventional hematology practice. To prevent iron overload, the guidelines also recommended halting iron therapy if the transferrin saturation exceeded 50%. The recommendation to withhold IV iron when ferritin was >800 ng/mL or transferrin saturation was >50% were opinion-based, and considered a balance between the efficacy of IV iron in these patients and the potential for iron overload. Several studies have failed to identify a specific serum ferritin value in dialysis patients that was predictive of a lack of response to IV iron, but these trials suffered from several design flaws, including lack of a proper control group [28]. IV iron dextran boluses

complementing EPO therapy became the standard of care in dialysis in the 1990's. Because of the perceived 0.3% AE rate, the black box warning remained in the package insert for all iron dextrans and a test dose was required.

Hundreds of thousands of dialysis patients derived enormous clinical benefits and improvements were seen in energy, activity, appetite, cognition, sexual activity, and overall quality of life. For patients receiving EPO therapy the average lifespan on dialysis improved to more than 4 years. Imferon, Fisons' HMW ID was the product routinely utilized until 1991. At the same time it was shown that IV Imferon could be given with equal efficacy as TDI or repeated boluses [29], a contaminated batch of Imferon led to a total US recall of the drug. Serendipitously, the LMW ID used in the Fishbane et al. study (INFeD, Schein Pharmaceuticals—now Watson Pharmaceuticals—and internationally known as Cosmofer, Pharmacosmos, Denmark) was approved for clinical use in the United States. In 1991, Fisons, using molecular blueprinting, compared their product, Imferon, to Schein's INFeD, and discovered that INFeD was a lower molecular weight iron dextran with less variability of the dextran chains (personal communication with Fisons). Subsequently, in 1991, a decision to cease US distribution of Imferon was made, and Imferon was permanently removed from the marketplace in 1992.

In February 1996, Dexferrum (American Regent Pharmaceuticals) a HMW ID similar to Imferon was approved and provided an alternative to INFeD. No randomized trial comparing efficacy and toxicity of any of these three products had been published. INFeD and Dexferrum replaced Imferon in Nephrology, with INFeD being the major product in use. In 1997, INFeD became unavailable for a short period of time, necessitating use of Dexferrum in many dialysis patients. During this time there was an 11-fold increase (Freedom of Information, FDA) in the number of serious AEs reported to the US Food and Drug Administration. In 1998, Case [30] published an article recommending that Dexferrum not be used, noting "in 14 patients receiving Dexferrum 4 patients (28.6%) developed severe reactions consisting of severe back and leg pain, urticaria, and shortness of breath. Subsequently two of the four were given INFeD and had no reactions." Similar conclusions were published by Mamula in children with inflammatory bowel disease [31].

The nondextran IV irons, ferric gluconate and iron sucrose, have been considered to have a markedly lower serious acute event rate than the iron dextrans. In 1999, Faich and Strobos [32] compared the spontaneous reports to the US and European Drug agencies of serious reactions to iron dextrans and non-iron dextrans. They noted a significantly higher rate of reactions and 31 deaths attributed to iron dextrans, while no deaths were attributed to the nondextran irons. In 2002, Michael et al. [33] found a very low reaction rate with ferric gluconate in 2,534 hemodialysis patients in a double-blind, placebo controlled, study in ferric gluconate naïve patients. They also noted that patients having reactions to ferric gluconate did not exhibit an increase in tryptase, a marker of mast cell degranulation [34]. An increase in tryptase would be expected if reactions were true anaphylaxis. They also compared those results to the published reaction rate to iron dextrans, and concluded that ferric gluconate was much safer than iron dextran. None of these papers were able to differentiate the reaction rate of HMW versus LMW iron dextran preparations.

A similarly low reaction rate has been reported in open label studies of iron sucrose. In 1996, Silverberg [35] showed that approximately 20% of dialysis patients could have anemia effectively treated with iron sucrose alone. He recommended administering sufficient iron sucrose to

increase serum ferritin to 200–400 µg/L and/or iron saturation up to 25–35% before considering EPO. Aronoff et al. [36] reported repeated doses of iron sucrose in 665 hemodialysis patients receiving EPO was well tolerated, including 80 patients (12%) considered intolerant to an iron dextran. Black box warnings do not appear in the package inserts of either ferric gluconate or iron sucrose. As a result, these two products have rapidly replaced iron dextran, and TDI because of little interest in nephrology except in patients on peritoneal dialysis. These nondextran irons bind iron less avidly than dextran, and this is believed to account for dose and infusion rate dependent acute vasoactive reactions to iron sucrose and ferric gluconate. Typical reactions include low blood pressure, abdominal discomfort, and back pain, and resolve with cessation of the infusion and time. The current highest recommended dose for ferric gluconate is 125 mg IV push over 5–10 min (Ferrlecit package insert) and for iron sucrose, 200 mg IV push or 300 mg over 2 hr. Doses greater than 300 mg are not recommended [37].

In a review of the US Food and Drug Administration (FDA) database of spontaneous AE reporting, Chertow et al. [38] found no significant differences in life threatening or fatal serious AEs when ferric gluconate and iron sucrose were compared to LMW ID, although these reports are highly insensitive in as much as they reflect only reported events and under-estimate actual reaction rates many-fold. A follow-up analysis [39] examined reactions to iron sucrose, and concluded that the frequency of IV iron related AEs with all products has decreased, and overall the rates were extremely low. The reported incidence of serious AEs among LMW ID, ferric gluconate, and iron sucrose are similar with an estimated incidence of <1:200,000. Similarly, Fletes et al. [40] found an 8-fold higher AE rate associated with the use of HMW ID (Dexferrum) that could not be explained by differences in patient or facility characteristics. McCarthy et al. [41] reported a nearly 3-fold increase in AEs with HMW ID than with LMW ID. This suggests that the incidence of acute reactions for iron dextran believed to be correct (0.3%) is related to the use of HMW ID and the rate with LMW ID is far lower.

Subsequently, three studies [42–44] comparing the efficacy of safety of LMW ID and iron sucrose found no differences in efficacy or toxicity between the two iron preparations. These recent studies conflict with earlier claims of lower reactions rates to nondextran irons based on comparison to historical controls or exposure of patients with prior allergies to these new agents [33,45].

In the last decade three events occurred that would markedly affect the practice of IV iron administration. First, the work of Abels, Glaspy, Henry, Gabrilove, Littlewood, and others [46–50], showed that EPO was of great benefit in correcting anemia in patients with cancer or receiving cancer chemotherapy. Second, ferric gluconate (Ferrlecit, Schein Pharmaceuticals) and iron sucrose (Venofer, American Regent Pharmaceuticals), two products that had been used extensively in Europe and Asia for years, were approved as parenteral iron supplements in the United States. Third, studies [49,52–54] proved that IV iron administered with EPO for the anemia of cancer and cancer chemotherapy more than doubled the response rate compared to EPO alone. All of these trials will be discussed later in the text.

Iron in anemias of chronic disease

Central to the development of the anemia of chronic disease (ACD) is disturbed iron homeostasis characterized by decreased absorption and prevention of recycling of iron from the cells of the reticuloendothelial system. This results

Figure 2. Percentage of responders and nonresponders in each treatment group for the ITT population. Responders were patients who achieved a maximal Hb levels ≥ 120 g/L or an increase in Hb of ≥ 20 g/L during the study. (a) $P < 0.01$ versus no-iron group; (b) $P < 0.01$ versus oral iron group.

in hypoferrremia (low transferrin-bound iron) and resultant iron restricted erythropoiesis. Proinflammatory cytokines are important contributors to the hypoferrremia and anemia seen in chronic diseases. In chronic inflammatory states iron acquisition by macrophages takes place mainly through erythrophagocytosis and the transmembrane transport of ferrous iron by the protein divalent metal transporter 1 (DMT 1) [55]. The proinflammatory cytokines interferon gamma, lipopolysaccharide, and tumor necrosis factor alpha upregulate DMT 1 expression resulting in an increased uptake of iron into activated macrophages and also induces the retention of iron in macrophages by down-regulating the expression of ferroportin. Consequently iron release from macrophages is blocked [56]. Ferroportin, a transmembrane exporter of iron, is believed to be responsible for the transfer of absorbed ferrous iron from duodenal enterocytes into the circulation [57]. Hepcidin, an iron regulatory acute phase protein, has been shown to have an important role in the pathophysiology of ACD. Expression of hepcidin is induced by lipopolysaccharide and interleukin 6 and is inhibited by tumor necrosis factor alpha [58]. Hepcidin is believed to be involved in the diversion of iron traffic by decreasing duodenal iron absorption and blocking iron release from macrophages. A recently identified gene, hemojuvulin, may act in concert with hepcidin to induce these changes [59]. The net effect of these alterations in iron homeostasis is a limitation of the availability of iron for erythroid progenitor cells and impairment of their proliferation by negatively impacting on heme biosynthesis.

In summary, in anemias of chronic diseases, the increase in inflammatory cytokines causes an increase in hepcidin with a subsequent decrease in iron absorption. When inflammatory cytokines are not present, hepcidin levels are much lower and GI absorption of oral iron can more freely occur. This is supported by data in patients with hereditary hemochromatosis, where a mutated HFE gene decreases hepcidin levels and allows unimpeded iron absorption to occur [60].

Iron in the anemia of cancer and cancer chemotherapy

The benefit of EPO in cancer patients is compelling [46–50], yet the transfer of this enthusiasm for EPO usage to the oncology community was slow to evolve. Awareness of the degree of benefit IV iron had on anemia in the nephrology population was generally lacking in the

Figure 3. Change in LASA scores from baseline to end point evaluation for the intent to treat population. QoL, quality of life; TDI, total dose infusion [51].

oncology community. Further, anemias in cancer and cancer chemotherapy patients were not as severe as those in dialysis patients in the pre-EPO days. There was little reason to believe that IV iron would be less beneficial in cancer chemotherapy patients receiving EPO than in dialysis patients, yet IV iron, for all intents and purposes, was not used in oncology patients until published data with iron dextran [51] reported a significant benefit in hemoglobin response, hematopoietic response, time to maximal response, and quality of life variables when IV iron was given to patients receiving EPO for anemia of cancer chemotherapy when compared with oral iron or no iron (Figs. 2 and 3). These responses were independent of type of cancer, intensity of chemotherapy, and baseline iron parameters (percent transferrin saturation and serum ferritin). However, in this study the entry criteria required a serum ferritin of less than 200 ng/mL or less than 300 ng/mL with a percent saturation of transferrin of ≤ 19 . Because of a perception that many of the patients were truly iron deficient this led to a criticism of the conclusions that baseline iron status was not predictive of who would benefit from parenteral iron and that IV iron should be given to all patients receiving EPO for chemotherapy-associated anemia. Subsequently, Henry et al. [61], using ferric gluconate as an adjunct to EPO therapy in cancer chemotherapy patients, corroborated the previously published data. In this study, 187 patients receiving chemotherapy were randomized to receive EPO 40,000 U/wk and either no iron, oral iron as 325 mg ferrous sulfate thrice daily or IV ferric gluconate 125 mg per week. They showed that there was an increase in hemoglobin levels of 2 g or more in significantly more patients treated with IV ferric gluconate (73%) than in those treated with oral iron (46%) and those not treated with iron (41%). These two studies clearly suggest that using IV iron therapy increases the hematopoietic responses to EPO in cancer patients with anemia of cancer chemotherapy. In the Auerbach study the only serious AE occurred in one of two patients receiving HMW ID when LMW ID was not available. In the Henry study there were no serious AE's attributable to iron. The conclusions of these two studies were further supported by a recently published study in patients with lymphoproliferative malignancies, not on chemotherapy, with positive marrow hemosiderin treated with epoetin beta randomized to receive no iron or IV iron sucrose [52]. In the iron treated patients there was a statistically significant improvement in response compared to those not receiving IV iron. In a study presented at the 2007 an-

nual meeting of the American Society of Clinical Oncology, Pinter et al. [50,54] randomized 396 chemotherapy patients receiving darbepoietin every 3 weeks with either 200 mg of IV ferric gluconate or iron sucrose to darbepoietin alone or with oral iron. A statistically significant decreased number of transfusions were reported in the IV iron arm (9 vs. 20). These data are corroborated in a study of 75 anemic patients receiving chemoradiation therapy for carcinoma of the cervix [53]. In this trial, patients were randomized to receive no therapy or 540 mg of IV iron saccharate in 200 mL of normal saline over an unspecified period longer than 30 min. Patients were treated with platinum containing chemotherapy plus radiation therapy to the pelvis. Those anemic at presentation and randomized to the IV iron arm received the IV iron infusion at the beginning of therapy. IV iron was also given to those randomized to the IV iron arm not anemic at onset but developing anemia during therapy. AEs with iron administration were not provided. None of the patients in either arm received an ESA agent. Sixty-four percent of the patients in the control arm and 40% of the patients in the IV iron arm were transfused. Unfortunately, there were significant intragroup differences in this study making interpretation of the results difficult. Nonetheless, this study, albeit underpowered, raises the question of the benefit of IV iron alone in decreasing transfusion requirements in patients receiving chemoradiation therapy.

A soon to be published study lends support to the previously cited studies. Pedrazzoli et al. [62] enrolled 149 patients with solid tumors and at least 12 weeks of planned chemotherapy who were randomized to receive 150 mg of subcutaneously administered darbepoietin weekly alone or with IV ferric saccharate administered as 125 mg per week for the first 6 weeks. This study was unique in its requirement that excluded patients with ferritins < 100 ng/mL and TSATs < 20%. They concluded in patients with chemotherapy related anemia and no iron deficiency IV iron supplementation significantly reduces treatment failures with darbepoietin, without added toxicity. The use of IV iron is increasing in oncology but to date only iron dextran is approved, despite the extensive use and safety record of ferric gluconate and iron sucrose in nephrology. A summary of these studies is listed in Table III.

Potential negative effects of intravenous iron

Iron is a pro-oxidant, an important nutrient for many bacteria, and has been shown to exacerbate sepsis in laboratory animals. Consequently, concerns have been raised that IV iron might increase oxidative stress, infections, mortality, or even tumor growth. Human studies have shown transient increases in markers of oxidative stress with all forms of IV iron [63]; however, use of IV iron in dialysis patients has been associated with comparable or improved survival compared to no iron [64,65] in very large databases. Hoen et al. [66] prospectively examined the risks for infection in 998 hemodialysis patients over 6 months. Central venous catheters, history of bacteremia, arteriovenous grafts, and immunosuppression were associated with increased risk of infections, but not ferritin levels or total dose of IV iron administered. No study to date has contradicted these data. Lastly, in all published trials with IV iron in oncology, there were no differences in tumor outcomes in those who received IV iron compared to ESAs alone. However, as of this review, there are no prospective data with tumor outcome as a primary or secondary endpoint.

There are three studies suggesting that iron sucrose and ferric gluconate may have more nephrotoxicity than iron

dextran in nondialysis settings. Using a rat model, Zager et al. [67] showed increased cellular uptake and subsequent necrosis and decreased recovery of kidney cells in rats receiving iron sucrose > ferric gluconate >> iron dextran (Venofer, Ferlecit, and INFeD respectively) (Fig. 4). Agarwal et al. showed stimulation of proteinuria and lipid peroxidation with iron sucrose in CKD patients [16]. They concluded "our study raises some concerns regarding the use of IV iron preparations in general, and iron sucrose in particular..." A recent comparative crossover study found 100 mg over 10 min of iron sucrose, but not ferric gluconate, induced proteinuria and albuminuria [68]. While transient injury by iron sucrose may be outweighed by the benefits of iron repletion and repair of anemia, these results should question the abandonment of LMW ID as first line therapy. Pai et al. [69] compared nontransferrin bound iron and markers of oxidative stress after single IV doses of iron dextran, ferric gluconate, and iron sucrose. They concluded iron sucrose and ferric gluconate were associated with greater nontransferrin bound iron appearance when compared with iron dextran. However, only ferric gluconate showed significant increases in lipid peroxidation. Long term studies assessing the risks and benefits of different IV iron preparations are needed.

As of this review there exist no clear practice guidelines for IV iron as an adjunct to ESA therapy outside nephrology. Randomized trial data have shown the efficacy of IV iron in epoetin-treated patients, even among patients with elevated ferritin (500–1,200 ng/mL) with TSAT ≤ 25% [70,71]. Among dialysis patients, who frequently have elevated ferritin from inflammation, reliable predictors of a hematological response to IV iron have not been found [71]. The nephrology literature is rife with publications showing IV iron reduces ESA dose even in patients with iron parameters consistent with an iron repletion state [28]. These data are corroborated by publications in the oncology literature [51,52,54,61] in which hemoglobin response occurs in patients with transferrin saturations as high as 50% [61] and in patients with positive marrow hemosiderins [52]. In the absence of formal evidenced based guidelines, and consistent with published data, we believe it is reasonable to recommend that IV iron be added to ESA therapy but avoid iron use if transferrin saturation approaches 50%. The IV iron can be administered either as a TDI of LMW ID or as repeated lower doses of LMW ID, ferric gluconate, or iron sucrose. HMW ID dextran should not be used [13,31,72].

In addition to optimizing efficacy of EPO in anemic dialysis and oncology patients, indications for IV iron as sole anemia therapy are rapidly expanding. In a variety of clinical settings use of IV iron alone is being investigated to reduce or eliminate red blood cell transfusions, or avoid institution of costly EPO therapy. Entities in which IV iron has great potential for treating anemia and ameliorating transfusion need include: inflammatory bowel disease, small bowel malabsorption, gastric bypass surgery, obstetrics and gynecology, surgical blood loss, in those conditions where intestinal blood loss exceeds the ability of the intestines to absorb adequate iron from oral ingestion (Osler-Weber-Rendu), and in patients who are intolerant of or unresponsive to oral iron. With the exception of HMW ID any of the other three available preparations can be utilized safely and effectively. For these conditions, when one considers cost and convenience, TDI of LMW ID is the preferred method of IV iron administration.

Improving anemia in chronically ill patients improves quality of life. Small studies have found IV iron may improve quality of life independent of improvements in anemia [73,74]. Erythropoietic stimulatory agents offer a more

TABLE III. Overview of Studies of IV Iron in Oncology

	Auerbach et al., 2004	Henry et al., 2007	Hedenus et al., 2007	Pinter et al., 2007	Kim et al., 2007
No. of Patients	157	187	67	398	75
Patient population	Nonmyeloid malignancy receiving chemotherapy	Nonmyeloid malignancy starting cycle of chemotherapy	Lymphoproliferative malignancy, no chemotherapy	Nonmyeloid malignancy ≥ 8 weeks of planned chemotherapy	Cervical cancer receiving chemoradiotherapy
Treatment arms	IV iron versus oral iron versus no iron	IV iron versus oral iron versus no iron	IV iron versus no iron	IV iron versus no/oral iron	IV iron versus no iron
Study period	6 weeks or until end bolus treatments	9 weeks	16 weeks	16 weeks	6 weeks
Inclusion criteria Hb	≤ 10.5 g/dL	< 11 g/dL	9–11 g/dL	< 11 g/dL	Hb measured prior to each chemotherapy cycle: Hb 10–12 g/dL: pts in IV iron group received iron; Hb < 10 g/dL: pts in both groups were transfused
Inclusion criteria TSAT/SF	SF ≤ 200 ng/mL or SF ≤ 300 ng/mL and TSAT $\leq 19\%$	SF ≥ 100 ng/mL or TSAT $\geq 15\%$; SF < 900 ng/mL and TSAT $< 35\%$	SF < 800 ng/mL, Stainable iron in bone marrow	SF < 800 ng/mL	N/A
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	Iron sucrose 200 mg if Hb 10–12 g/dL
ESA dosing	40,000 U/wk Procrit no dose adjustments	40,000 U/wk Procrit, dose increase permitted after 4 weeks; dose reduction permitted for safety	30,000 U/wk neoRecomron dose adjustments permitted	500 μ g Q3W Aranesp dose reductions permitted	None
Hb CFB	TDI: 2.4 g/dL, bolus IV iron: 2.5 g/dL, oral iron: 1.5 g/dL, no iron: 0.9 g/dL, ITT population	IV iron: 2.4 g/dL, oral iron: 1.6 g/dL, no iron: 1.5 g/dL, evaluable population	IV iron: 2.91 g/dL, no iron: 1.5 g/dL; PP population	N/A	Similar change between IV iron and control groups
Hb response	TDI: 68%, bolus IV iron: 68%, oral iron: 36%, no iron: 25%, ITT population	IV iron: 73%, oral iron: 45%, no iron: 41%, evaluable population	IV iron: 93%, no iron: 53%, PP population median time to achieve Hb response: 6 weeks	IV iron: 86%, no/oral iron: 73%; Median, time to target Hb: 30 days IV iron versus 43 days No/oral iron	N/A
ESA	No dose adjustment permitted	N/A	At Wk 15, ave difference was $> 10,000$ U or 25% lower in IV iron than no iron group	N/A	N/A
Transfusions	TDI: 5 pts bolus IV iron: 4 pts, oral iron: 3 pts, no iron: 7 pts	IV iron: 11 pts (18%), oral iron: 6 pts (10%), no iron: 14 pts (22%) Tx given after first 4 weeks: IV iron: 2 of 11 pts; oral iron: 5 of 6 pts; no iron: 7 of 14 pts	IV iron: 2 pts, no iron: 1 pt	Pts enrolled in study for at least 29 days: IV iron: 9%; no/oral iron: 20%	IV iron: 40% pts, No iron: 64% pts Mean transfusion volume: IV iron: 1.87 units; No: 3.58 units
Energy/activity QOL	<ul style="list-style-type: none"> IV iron $\uparrow$ LASA scores for energy, activity and QOL Oral iron small $\uparrow$ energy, activity, QOL No iron $\downarrow$ energy, activity, QOL from baseline 	<ul style="list-style-type: none"> Only IV iron group had significant $\uparrow$ in FACT-F score; difference began at 4 weeks while Hb response was still similar between groups 	N/A	% pt achieving FACT-F ≥ 3 points: IV iron: 62%; no/oral iron: 54%	N/A

Figure 4. Cellular injury in cultured human proximal tubule cells after exposure to iron compounds $P < 0.01$ compared with control cells. (Zager et al. Am J Kidney Dis 2002;40:90–103)

physiologic and rational alternative than red blood cell transfusions [75]. IV iron is now the standard of care in nephrology. Antiquated and grossly incorrect notions of severe toxicity associated with formulations of IV iron available world-wide persist in the medical community. Newer IV iron agents are undergoing clinical testing. Given the important role of IV iron in the treatment of various anemias and in synergizing with ESAs, comparative studies of the available preparations are needed to determine their relative safety and efficacy.

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