

Managing Intravenous Iron in the Oncology Setting

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The prevalence of anemia in patients with cancer is up to 90%,¹ and it is most often associated with the underlying malignancy and/or cancer treatment.



Despite the high prevalence of anemia in this patient population, IV iron supplementation has not been applied rigorously as an adjunct to erythropoietin-stimulating agents (ESA) in oncology practice. In fact, less than 10% of patients with chemotherapy-induced anemia (CIA) are supplemented with IV iron as an adjunct to ESA, which may, in part, contribute to the high rates of ESA

nonresponsiveness in cancer patients (35%-50%).²⁻⁶

Types of Anemia

Two main types of anemia are seen in patients with cancer. The first is functional iron deficiency, which occurs when ESA therapy accelerates the rate of erythropoiesis, increasing the iron demand by the bone marrow. Essentially, the body is unable

to release stored iron fast enough to allow the incorporation of iron into red blood cells during erythropoiesis. The second is absolute iron deficiency. Absolute iron deficiency occurs in the setting of acute blood loss or impaired iron absorption, in which the release of inflammatory cytokines leads to an upregulation of hepcidin, a 25-amino acid polypeptide produced by hepatocytes that is both

an acute phase protein and a major hormone regulator of iron homeostasis; it interferes with both the enteral iron absorption and iron release from macrophages, and it promotes iron degradation. Unlike functional iron deficiency, where iron stores are adequate, absolute iron deficiency is associated with measurable reduction in serum and stored iron.

Erythropoiesis requires close interaction between iron and erythropoietin. Parenteral iron has been shown to improve the efficacy and shorten the duration of ESA therapy, which suggests a synergistic effect between parenteral iron and ESAs.

Main Causes of the Underuse of IV Iron in Cancer Patients

Despite these benefits, IV iron remains underused in this setting in part because a serum ferritin level less than 100 ng/mL often is the only diagnostic tool used to assess the need for iron repletion. Although the benefits of iron supplementation in conjunction with ESA therapy in patients with CIA are well established—even in patients with transferrin saturation (TSAT) up to 35% and a serum ferritin level up to 800 ng/mL—many patients falling within appropriate levels do not receive therapy.

Another barrier to IV iron therapy is the fear of anaphylatic-type reactions. Both high-molecular-weight

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Table. Commercially Available IV Iron Preparations

	High-Molecular-Weight Iron Dextran (Dexferrum, American Regent)	Low-Molecular-Weight Iron Dextran (Infed, Watson)	Ferric Gluconate (Ferrlecit, Sanofi-aventis)	Iron Sucrose (Venofer, American Regent)	Ferumoxytol (Feraheme, Amag)
Molecular weight (Da)	265,000	165,000	289,000-440,000	34,000-60,000	750,000
Test dose required	Yes; 25 mg slow IV push and observe for 1 h	Yes; 25 mg slow IV push and observe for 1 h	No	No	No
Dosage	100 mg IV over 5 min once weekly for 10 doses or total dose infusion over several hours	100 mg IV over 5 min once weekly for 10 doses or total dose infusion over several hours	125 mg IV over 1 h once weekly for 8 doses or 200 mg IV over 3-4 h every 3 wk for 5 doses	200 mg IV over 1 h every 2-3 wk or 200 mg IV over 2-5 min every 1-4 wk	510 mg IV; push once, followed by a second dose 3-8 d later
Black box warning	Yes	Yes	No	No	No

To calculate total dose of elemental iron for iron dextran: total dose of elemental iron (mL) = 0.0442 (desired Hb^a-observed Hb) × LBW (kg) + 0.26 × LBW (kg)

^a Desired Hb=12 g/dL

Hb, hemoglobin; **LBW**, lean body weight

Based on references 9-13, 15, 20.

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iron dextran (Dexferrum, American Regent)^{7,8} and low-molecular weight iron dextran (Infed, Watson)⁹ carry a black box warning on their product labels about the risk for a potentially fatal anaphylactic-type reaction and about the requirement for a test dose prior to the first dose. However, although both products carry these warnings, studies have shown there to be an increased incidence of total and life-threatening adverse events (AEs) with the high-molecular-weight iron dextran product.^{10,11} Additionally, infusion-related reactions associated with low-molecular-weight iron products are usually mild and self-limited.^{12,13} Routine medical interventions (such as histamine-1 blockers and epinephrine) are not needed or recommended in this setting because diphenhydramine and epinephrine can potentially cause a significant vasoactive reaction, mimicking an anaphylactic-type reaction.

There are 5 parenteral iron formulations commercially available in the United States (Table)^{7,9,14-16}; iron dextran (Dexferrum; Infed), sodium ferric gluconate (Ferrlecit, Sanofi-aventis), iron sucrose (Venofer, American Regent), and ferumoxytol (Feraheme, Amag). Iron dextran complexes are indicated for patients with documented iron deficiency when oral iron therapy is not feasible, whereas the indication for other available preparations (sodium ferric gluconate, iron sucrose, and ferumoxytol) is limited to patients with chronic kidney disease and iron deficiency.

Treatment Recommendations/Guidelines

Until recently, no clear recommendation existed on iron repletion in cancer patients. The updated recommendation by American Society of Hematology/American Society of Clinical Oncology was to “institute iron supplementation when indicated”; recommendations on optimal timing or frequency of the iron therapy were inadequate due to lack of available data.¹⁷ The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (v2.2011) recommend that IV iron be considered for the management of functional iron deficiency (defined as serum ferritin ≤ 800 ng/mL and TSAT $< 20\%$) in patients receiving ESAs.¹⁸ The NCCN also notes that most of the reported iron dextran-related AEs are associated with high-molecular-weight iron dextran; therefore, the guideline recommends the use of low-molecular-weight iron dextran over

high-molecular-weight iron dextran.¹⁸

IV vs Oral Iron

IV iron often is a better choice than oral iron in the oncology setting because of factors that can impair enteral absorption of iron in patients with cancer. For example, malignancy and/or chemotherapy can impair gastrointestinal (GI) tract integrity. Also, upregulation of hepcidin can occur as a result of inflammatory cytokine release in these patients and in patients with CIA. In addition to these factors, the poor bioavailability of oral iron products and their undesirable GI adverse effects (ie, emesis, diarrhea, constipation, and dark stool) often contribute to poor patient compliance.

Data also support the use of IV therapy over oral therapy in conjunction with ESAs. In CIA, at least 3 randomized trials have demonstrated superiority of IV iron (low-molecular-weight iron dextran; ferric gluconate; iron sucrose) to oral iron supplementation as an adjunct to ESA therapy. Auerbach et al randomized 157 patients to receive IV iron, oral iron, or no iron as an adjunct to epoetin alpha 40,000 units per week. They observed a significant improvement in hematologic response in the IV iron group compared with the oral or no iron groups (68% vs 35% and 25%, respectively).¹⁹ The mean increases in hemoglobin (Hb) in the IV, oral, and no iron arms were 2.5, 1.5, and 0.9 g/dL, respectively.

In a subsequent study by Henry et al, 187 patients were randomized to receive IV iron, oral iron, or no iron as an adjunct to epoetin alpha 40,000 units per week. The investigators found that there was a significant improvement in hematologic response in the IV iron group compared with the oral or no iron groups (73% vs 46% and 41%, respectively); the mean increases in Hb in the IV, oral, and no iron arms were 2.4, 1.6, and 1.5 g/dL, respectively.²⁰

Bastit and colleagues also investigated the role of IV iron as an adjunct to ESA (darbepoetin alpha 500 mcg every 3 weeks). The investigators randomized 396 patients to either IV iron or no iron arms; there was a significantly improved hematologic response in the IV iron arm (86% vs 73%). Moreover, patients in the IV arm also required fewer red blood cell transfusions (9% vs

20%), the investigators reported.²¹

Pharmacoeconomic Factors

A recent pharmacoeconomic analysis performed in a community practice setting demonstrated a significant improvement in cost-effectiveness of ESA therapy with the addition of IV iron in patients with CIA.²² The pharmacoeconomic analysis included office visits, administration expenses, and pharmacy and drug costs. The yielded cost savings per patient was \$1,300 per 12-week treatment cycle, translating to a weekly cost savings of \$100 per patient. This strategy represents a significant cost-saving potential in oncology practice, as well as for the global health care system.

Conclusion

Determining the need for iron repletion solely based on the serum ferritin level and/or TSAT at the time of initiating ESA therapy can result in suboptimal response to ESA therapy. Mounting evidence indicates that IV iron supplementation should become a routine component of ESA therapy in all patients with CIA whose TSAT is less than 35% and whose serum ferritin is 800 ng/mL or lower. This approach for anemia management has been shown to improve treatment outcomes by reducing the requirement for red blood cell transfusions and to improve the cost-effectiveness of ESA therapy in the oncology setting. Therefore, the use of parenteral iron in the management of anemia in patients with CIA should be expanded to optimize ESA therapy and patient outcomes.

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