The Role of Intravenous Iron in the Treatment of Anemia Associated with Cancer and Chemotherapy

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Abstract

Cancer-related anemia (CRA) is a commonly occurring problem for patients with cancer regardless of whether they are receiving treatment with chemotherapy or immunotherapy. It may result from one or more processes (decreased production, increased destruction, or increased loss of red blood cells, RBC). Perturbations in iron availability form the primary basis for anemia in many patients with cancer-related anemia. Functional iron deficiency (FID) anemia is a condition in which the patient has adequate or increased iron stores, but this iron pool is not available for erythropoiesis. Erythropoiesis-stimulating agents (ESAs) were the original treatment for FID; over time, however, if the supply of iron cannot keep pace with increased RBC synthesis driven by ESAs, FID may eventually lead to the lack or loss of ESA responsiveness. Subsequent clinical trials reported that intravenous (IV) iron could enhance the erythropoietic response to ESAs. This chapter reviews the pathogenesis of FID and summarizes the literature on the treatment of cancer- and chemotherapy-induced anemia. Clinical trials using IV iron with or without ESAs are reviewed in addition to the currently available

IV iron products. The consensus conclusions from these trials, as well as guideline recommendations, support the use of IV iron in these patients to enhance ESA responsiveness, decrease ESA dosage, and reduce RBC transfusions. Little data have been published on the long-term safety of IV iron or its impact on tumor growth. This paper also briefly explores novel approaches for the treatment of FID anemia, which has relevance in treating not only cancer patients but also patients with benign inflammatory disorders.

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Introduction

Despite the increasing use of targeted therapies in cancer patients, chemotherapy remains a mainstay of cancer treatment. Consequently, anemia remains a common, expected complication in patients receiving chemotherapy [1]. In addition to the myelosuppressive effects of chemotherapy, other cancer-associated conditions that contribute to the decreased production of red blood cells (RBCs) and lead to anemia include: renal disease associated with erythropoietin deficiency, tumor involvement within the bone marrow, possible vitamin deficiencies, and, perhaps most importantly, functional iron deficiency (FID) [1]. Synonyms for FID include “anemia of chronic disease” and “anemia of

inflammation.” FID is an important contributor to anemia not only in cancer patients but also in those with infectious or inflammatory disorders, such as inflammatory bowel disease and rheumatoid arthritis, for example.

Understanding the pathogenesis of FID is crucial to understanding the basis of anemia in cancer patients as well as in patients with benign inflammatory disorders. This paper summarizes the role of FID in cancer- and chemotherapy-associated anemia and reviews clinical trial results on treating chemotherapy-induced anemia (CIA) with a focus on the use of intravenous (IV) iron.

Pathogenesis of FID

Although the pathogenesis of FID has been elucidated over the past 10–20 years, it is still not fully understood [2]. Two key cells involved in the process of iron movement into and throughout the body are enterocytes of the gastrointestinal tract (responsible for absorbing dietary or supplemental oral iron) and macrophages of the reticuloendothelial system in the bone marrow (responsible for mobilization of iron stores used primarily for erythropoiesis). Two key proteins in this mechanism are ferroportin, an iron transport protein present in enterocytes and macrophages that controls cellular iron export, and hepcidin, an inflammatory response protein that regulates the ability of ferroportin to export iron. Figure 1 summarizes aspects of iron metabolism that relate to normal iron utilization and erythropoiesis, as well as the consequences of inflammation (due to benign or malignant conditions) that lead to FID. Known ligands, receptors, intracellular signaling pathways, and hormones regulate iron mobilization are included. Known constituents of the iron life cycle are listed in Figure 1.

In the normal, noninflamed state (low hepcidin concentrations), dietary or supplemental oral iron is ingested; enterocytes in the proximal small bowel absorb iron, and that iron is transported via enterocyte ferroportin to blood vessels where iron then becomes bound to serum transferrin and carried either to erythroblasts, bone marrow macrophages, or other tissues in the body such as the brain [2]. Iron is stored in spleen and marrow macrophages until needed for erythropoiesis, at which time iron is transported via macrophage ferroportin to serum transferrin and then to RBC precursors, where it is utilized to synthesize hemoglobin (Hb) (Fig. 1).

In the “inflamed” state of cancer or other inflammatory disorders, hepcidin synthesis by the liver is increased in response to cytokines such as interleukin (IL)-6. Ele-

vated hepcidin levels result in inhibition of ferroportin-mediated iron transport in both enterocytes and macrophages. Hepcidin binding to ferroportin leads to internalization and lysosomal destruction of the hepcidin-ferroportin complex with subsequent sequestration of iron within both enterocytes and macrophages (Fig. 1). The result of this hepcidin upregulation is decreased serum iron, decreased transferrin-bound iron, and a lack of available iron for erythropoiesis, despite adequate (or increased) iron stores, hence the name FID. The recently discovered hormone erythroferrone (nicknamed ERFE) is secreted by erythroblasts to decrease hepcidin and increase iron bioavailability when erythropoiesis is under stress (Fig. 1) [3].

Two important conclusions that can be drawn from this information are (a) oral iron may be ineffective in treating FID from any cause, since ingested iron may be sequestered in the enterocyte and not available for erythropoiesis, and (b) IV iron should be effective in overcoming the gastrointestinal and macrophage “iron block” of FID.

Based on the above pathogenesis information on FID, numerous clinical trials have been conducted that reported clinically useful information on how FID patients should be managed. We will first review the IV iron products that have been studied in CIA clinical trials; then, results of clinical trials using IV iron, with and without erythropoiesis-stimulating agents (ESAs), will be summarized.

IV Iron Products with Efficacy in CIA

Six IV products have been studied in CIA clinical trials and reported to be efficacious: low-molecular-weight iron dextran, iron sucrose, ferric gluconate, ferric carboxymaltose, ferumoxytol, and iron isomaltoside. Table 1 summarizes these products and their recommended dosing regimens. Fewer reported CIA patients have been treated with ferumoxytol or iron isomaltoside in clinical trials compared to those treated with the other products.

Summary of CIA Clinical Trials Using IV Iron with ESAs

Seven clinical trials in CIA patients using IV iron with ESAs versus ESA alone have been published as of February 2019. Table 2 summarizes these trials, IV iron prod-

Fig. 1. Normal iron metabolism, erythropoiesis, and pathogenesis of functional iron deficiency. In the normal (noninflamed) state, dietary iron (or an oral iron supplement) is ingested. Iron is absorbed by enterocytes in the proximal small intestine via the divalent metal transporter 1 and transported to blood vessels via ferroportin, then to the bone marrow via transferrin. In the bone marrow, iron is taken up by macrophages where it is stored as ferritin until needed for erythropoiesis. At that time, stored iron is transferred via ferroportin to red blood cell (RBC) precursors for hemoglobin synthesis. Erythropoietin (EPO) is the physiologic regulator of RBC production. EPO is produced by fibroblasts in the kidney in response to hypoxia. In the “inflamed state” (lower

portion of Fig. 1), interleukin (IL)-6 is produced, inducing hepatic release of hepcidin. Hepcidin binds both enterocyte and macrophage ferroportin; the hepcidin-ferroportin complexes are internalized and degraded in lysosomes, resulting in an “iron block” – inability of enterocyte- and macrophage-stored iron to be exported. (For figure simplicity, only hepcidin inhibition of macrophage ferroportin is shown.) This leads to reduced serum iron levels, increased storage of iron in bone marrow macrophages (i.e., ferritin), and the condition of functional iron deficiency. Erythroferrone (ERFE) is a negative regulator of hepcidin production. ERFE is produced by erythroblasts in response to EPO. REPC, renal EPO-producing cells.

ucts used, numbers of CIA patients studied, and key responses. Of note, only clinical trials published as full articles, but not abstracts, are included in this analysis. At the time of original publication, 6 of 7 trials reported positive results, including improving the ESA response rate, allowance of a lower ESA dose, and decreased RBC transfusion requirement. Reanalysis of the data in the negative

trial subsequently demonstrated a positive result when patients intolerant to doses above those that are routinely recommended were censored. Thus, all clinical trials utilizing a variety of IV iron products demonstrated positive results. The benefits of IV iron used for FIDA anemia (FIDA) were largely independent of baseline serum iron parameters.

Table 1. Intravenous iron products studied in clinical trials on chemotherapy-induced anemia (CIA)

Product	Trade name	Dose, mg	Infusion	
			time, min	frequency
LMW iron dextran	INFeD®	100–2,000	60–240	Single or divided doses to achieve 1–2 g
Iron sucrose	Venofer®	200–300	5–60	Divided doses to achieve 1 g
Ferric gluconate	Ferrlecit®	125	60	Divided doses to achieve 1 g
Ferric carboxymaltose	Injectafer®	750	7.5–15	Single infusion
Ferumoxytol	Feraheme®	510	≥15	Two doses within 1 week
Iron isomaltoside	Monofer®	500–1,000	2–15	Single or divided doses to achieve 1–2 g

Drug doses listed were those described in CIA clinical trials. LMW, low molecular weight. Ferric carboxymaltose is available as a 750-mg vial. Therefore, some clinicians may choose to start with 750 mg and assess response before administering another dose to patients with cancer.

Table 2. Summary of clinical trials on chemotherapy-induced anemia (CIA) using intravenous (IV) iron with erythropoiesis-stimulating agents (ESAs)

First author, year	Patients, <i>n</i>	IV iron product	ESA	Results
Auerbach [9], 2004	157	LMW iron dextran	Epoetin	IV iron enhanced ESA response Oral iron ineffective
Hedenus [10], 2007	67	Iron sucrose	Epoetin	IV iron enhanced ESA response and permitted lower ESA dose
Henry [11], 2007	187	Ferric gluconate	Epoetin	IV iron enhanced ESA response
Bastit [12], 2008	396	Ferric gluconate/ iron sucrose	Darbepoetin	IV iron enhanced ESA response and decreased transfusion
Pedrazzoli [13], 2008	149	Ferric gluconate	Darbepoetin	IV iron enhanced ESA response
Auerbach [14], 2010	243	LMW iron dextran	Darbepoetin	IV iron enhanced ESA response
Steensma [15], 2011	502	Ferric gluconate	Darbepoetin	–
Steinmetz [17], 2013	73	Ferric carboxymaltose	Not specified	IV iron enhanced ESA response

The original publication by Steensma et al. [15] reported no benefit of IV iron in this study. However, a reanalysis of trial data indicated that trial participants who received at least 80% of the planned IV iron dosage had hematologic responses similar to participants in the other IV iron trials [16]. LMW, low-molecular weight.

Summary of CIA Clinical Trials Using IV Iron Monotherapy

Although ESAs are useful in treating FID of CIA, their use is associated with potential adverse events and come with myriad restrictions dictated by insurers such as Medicare. For example, ESAs are only approved for cancer patients with incurable diseases, receiving palliative myelosuppressive chemotherapy only, and with Hb <10 g/dL. Moreover, the most recent label update states that ESAs are “not indicated for patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.” As a result of this amendment, it could be argued that ESAs such as darbepoetin

alfa and epoetin alfa are no longer indicated for any patient with cancer, or that they are only indicated for a small subset of patients receiving chemotherapy with noncurative intent whose Hb falls below 10 g/dL but remains above any trigger for RBC transfusion. Because few patients with cancer qualify for an ESA, clinicians are in need of alternative therapies to manage anemia beyond RBC transfusion. As of February 2019, 7 CIA clinical trials have investigated IV iron monotherapy; these are summarized in Table 3. Overall, every trial with IV iron monotherapy yielded positive results, which either leads to increased Hb levels, decreased RBC transfusion requirement, or both. Using IV iron monotherapy has the advantage of treating both absolute iron deficiency and

Table 3. Summary of clinical trials on chemotherapy-induced anemia (CIA) using intravenous (IV) iron monotherapy

First author, year	Patients, <i>n</i>	IV iron product	Results
Kim [18], 2007	75	Iron sucrose	IV iron improved Hb and decreased transfusions
Dangsuwan [19], 2010	44	Iron sucrose	IV iron improved Hb and decreased transfusions
Abdel-Razeq [20], 2013	25	Iron sucrose	IV iron improved Hb
Athibovonsuk [21], 2013	64	Iron sucrose	IV iron decreased transfusions
Steinmetz [17], 2013	577	Ferric carboxymaltose	IV iron improved Hb
Hedenus [22], 2014	17	Ferric carboxymaltose	IV iron improved Hb
Birgegård [23], 2016	229	Iron isomaltoside	IV iron improved Hb
Vadhan-Raj [24], 2017	75	Ferumoxytol	IV iron improved Hb

Hb, hemoglobin.

FID; also, the patient's cancer status (curable vs. incurable), type of cancer treatment (chemotherapy vs. biologic therapy vs. hormonal therapy), and baseline Hb level are not part of required criteria for using IV iron. Thus, more cancer patients with anemia would be eligible for treatment with IV iron monotherapy versus IV iron with ESAs or an ESA alone.

What Do Cancer Society Guidelines Recommend?

Several cancer society and consensus guideline panels have promulgated recommendations on the use of IV iron in CIA patients. The National Comprehensive Cancer Network (NCCN) guidelines in 2009 recommended IV iron over oral iron therapy in CIA, and subsequent annual updates continue to recommend IV iron [4, 5]. The European Society for Medical Oncology (ESMO) originally recommended IV iron in their 2010 guideline and confirmed the utility of IV iron in their 2018 update [6]. Another European society (European Organization for the Research and Treatment of Cancer, EORTC) agreed with these recommendations in their 2008 publication [7].

The outlier guideline on this subject has been the American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO), whose last anemia guideline was in 2010 and did not recommend the use of IV iron in CIA [8]. Unfortunately, the ASH/ASCO guideline has not been updated in many years. The consensus of guidelines that have considered the most recent clinical trial results is that IV iron therapy is recommended to treat CIA.

Which Patients Should Receive IV Iron and/or ESAs?

Iron deficiency can be considered as a spectrum of iron panel laboratory results (Fig. 2). As shown, at the extreme of absolute iron deficiency (ferritin <30 ng/mL or a transferrin saturation (TSAT) <20%, patients would be expected to respond to iron monotherapy. At the opposite extreme of iron repletion (ferritin ≥800 ng/mL and TSAT ≥50%), anemic patients could be optimally treated with ESA monotherapy should they qualify using the aforementioned criteria. In the intermediate state of FID (ferritin 30–800 ng/mL or TSAT 20–50%), clinicians have 2 options that are supported by clinical trial data in Tables 2 and 3 – IV iron monotherapy or IV iron with ESA. Some physicians and patients may prefer to avoid using ESAs due to the limitations discussed above, as well as the potential risks of ESA therapy. Based upon goals and preferences, IV iron monotherapy may be an appropriate option for these patients. A third option, RBC transfusion, is available and recommended as an appropriate choice by the NCCN guidelines. Physicians should make patients aware of these options and their benefit-risk profiles. Although the risks of ESA therapy are well known, the long-term risks of IV iron therapy in cancer patients are unknown [25].

The Future of IV Iron Is Uncertain

To date, no IV iron formulation has gained FDA approval specifically for the treatment of patients with cancer. Despite this fact, a common approach to treating FIDA in patients with cancer is to administer parenteral iron with the goal of bypassing the macrophage “iron

Fig. 2. The relationship between transferrin saturation (TSAT), ferritin, and iron stores, and likelihood of hemoglobin response to iron therapy. **a** Absolute iron deficiency anemia (AIDA); very responsive to oral or intravenous (IV) iron therapy. These patients should not receive ESAs until iron replete. **b** Functional iron deficiency anemia (FIDA); although these patients have normal iron stores, TSAT values are low, indicating iron-restricted erythropoiesis. These patients will likely not respond to oral iron but should respond to IV iron. ESAs should not be used in this group until normal TSAT values are achieved. **c** Two groups of patients who may have FID: those with increased ferritin levels but low TSAT

values (**c₁**) and those with normal TSAT values but lower ferritin levels (**c₂**). Each group per clinical trial data in cancer patients suggests possible responsiveness to IV iron. **d** This group of patients has normal TSAT values and elevated ferritin levels and will likely be nonresponsive to IV iron. ESA monotherapy is an option for these patients. **e** Iron overload state. These patients have elevated serum ferritin levels over 800 ng/mL and TSAT values over 50%. ESA monotherapy is an option for these patients. Cutoff values for this figure were obtained from the NCCN guideline (version 3.2018) [4, 5].

block” for a short period of time. As previously mentioned, the long-term consequences of this strategy are largely unknown as most studies assessing the safety of IV iron in cancer patients cease monitoring after 16 weeks, with the exception of one study [23] which followed patients for 6 months. Moreover, the impact of IV iron on tumor growth has been entirely ignored. As ESAs were initially thought to be safe, and doses in clinical trials were escalated, long-term safety concerns surrounding thrombosis, and to a lesser degree poorer survival, in certain populations proved through meta-analyses that “more is not always better.” Lessons learned from the ESA era should not be forgotten and must be applied to IV iron as well. Although grossly lacking, prospective studies looking at overall survival in patients with cancer who receive IV iron are sorely needed. Until these data are available, a false sense of security should not obscure or supplant good clinical judgment.

IV vs. Oral Iron

The study by Birgegård et al. [23], which studied the effect of iron isomaltoside, calls the superiority of the parenteral route into question. Although the Hb response

was similar between the oral and IV iron groups, IV iron was associated with a more rapid Hb response and more rapid iron repletion. This is in contrast to the findings by Auerbach et al. [9], who found IV iron to be superior to oral iron in terms of magnitude of Hb increase. More studies are needed in patients with varying degrees of FIDA to determine who will or will not respond to oral iron.

Novel Approaches

If more iron is not the answer or perhaps not an option, new approaches designed to make endogenous sequestered iron more bioavailable may provide a valuable alternative solution. Targeting the hepcidin pathway is most logical as iron is primarily sequestered in the spleen within the reticuloendothelial system. Macrophages within the reticuloendothelial system lack ferroportin as a result of an overabundance of hepcidin. Through either inhibiting the production of hepcidin or limiting its biological activity through neutralization, ferroportin receptors could flourish allowing macrophages to regain their ability to export iron. It has long been known that coadministration of oral iron with ascorbic acid (vitamin C)

enhances iron absorption [26]; however, few publications have investigated the mechanism by which this occurs. Dietary iron is absorbed by the divalent metal transporter DMT [27]. The most widely accepted hypothesis is that ascorbic acid reduces ferric iron (Fe^{3+}) to the bioavailable form ferrous iron (Fe^{2+}), but data to support this as the sole mechanism for increased iron absorption are lacking. Other possibilities include a role for ascorbic acid in hepcidin synthesis. Interestingly, Chiu et al. [28] showed in an in vitro model that ascorbic acid has the ability to modify hepcidin mRNA gene transcription. Whether vitamin C has the ability to fully downregulate hepcidin production in vivo remains to be determined. Clinical studies assessing the impact of IV ascorbic acid in patients with chronic kidney diseases and FIDA have been conducted. Increases in Hb, with or without ESA use, have been noted [29]. Presumably, the mechanism by which ascorbic acid allowed for iron mobilization lies in its ability to decrease hepcidin production. Other possible targets aim to modify components of the hepcidin synthesis pathway through augmentation of SMAD signaling,

which is regulated by many components, including transferrin receptor 1 and 2, hemojuvelin, BMP-2, BMP-6, matriptase, human hemochromatosis protein (HFE), and others [2, 30]. Modification of these targets remains to be tested clinically in patients with cancer.

Ultimately, a more complete understanding of iron metabolism will hopefully lead to the development of novel erythropoietic adjuncts to help ameliorate FIDA and improve quality of life without compromising outcome.

Statement of Ethics

Not applicable.

Disclosure Statement

The authors do not have financial affiliation or involvement with any organization relating to the subject matter discussed in this paper.

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