

Intravenous iron in chemotherapy and cancer-related anemia

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Recent guidance from the Centers for Medicare and Medicaid Services restricting erythropoiesis-stimulating agents (ESAs) in chemotherapy and cancer-related anemias has resulted in an increase in transfusions. Nine studies, without published contradictory evidence, have shown optimization of the response to ESAs by intravenous (IV) iron when the iron was added to the treatment of chemotherapy-induced anemia. The synergy observed, although greater in iron deficiency, was independent of pretreatment iron parameters. Three studies demonstrated decreased transfusions when IV iron is administered without ESAs. Discordant recommendations regarding IV iron currently exist among the American Society of Hematology/American Society of Clinical Oncology guidelines, the National Comprehensive Cancer Network, and the European Society of Medical Oncology. This discordance is at least partly the result of misconceptions about the clinical nature and incidence of adverse effects with IV iron. Other reasons for this discordance are presented in this review. Based on thousands of studied patients, we conclude that IV iron is safe and probably safer than most physicians realize. Education is needed relating to the interpretation of minor, subclinical infusion reactions that resolve without therapy. IV iron without ESAs may be an effective treatment for chemotherapy-induced anemia and warrants further study. We present evidence supporting the conclusion that baseline serum hepcidin levels may predict responses to IV iron, and we examine the published evidence supporting the conclusion that IV iron should be a standard addition to the management of chemotherapy and cancer-related anemia.

In February 2008, the Centers for Medicare and Medicaid Services issued new guidance for erythropoiesis-stimulating agents (ESAs) in cancer and chemotherapy-induced anemia (CIA) based on 8 of 60 studies, all of which targeted hemoglobin levels above existing recommendations¹ and demonstrated negative outcomes with ESA use compared with controls. The new recommendations suggested initiation of treatment with ESAs in patients with hemoglobin levels of less than 10g/dL and the cessation of ESAs in those with levels greater than 10 g/dL, the proscription of ESAs when cure is a goal or in patients with cancer-associated anemia who are not receiving cytotoxic chemotherapy, and reductions in dosages and frequency of treatment. There was no guidance for ESA treatment to relieve fatigue or other anemia-related symptoms, and there was no reference made to the concomitant use of intravenous (IV) iron. Subsequent to the memo, there has been a significant increase in transfusions in patients with CIA, which has im-

posed considerable pressure on the stressed blood supply and has increased the negative effects of blood transfusion in this population.²

The current National Comprehensive Cancer Network guidelines recommend the addition of IV iron to ESA for chemotherapy-induced anemia whenever absolute iron deficiency or iron restricted erythropoiesis (also known as functional iron deficiency) is present.³ The European Society of Medical Oncology considers the concomitant use of IV iron to be standard when there is level A evidence to support the recommendation.⁴ However, the 2010 guidelines⁵ from the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) state that there is insufficient evidence to support recommending IV iron as a standard concomitant of ESAs in any CIA subset. In this article, we will review the published evidence on the use of IV iron in CIA and cancer-associated anemia. We will address the reasons for the disparate recommendations from the NCCN, ESMO, and ASH/ASCO and will present evidence-based recommendations for the routine use of IV iron as part of the anemia treatment paradigm in cancer patients.

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TABLE Studies of Intravenous Transfusion in Oncology

	Auerbach⁶	Henry⁷	Hedenus⁸	Bastit¹⁰	Pedrazzoli⁹
No. patients randomized	157	187	67	396	149
Patient population	Nonmyeloid malignancy; receiving CTX	Nonmyeloid malignancy; starting cycle of CTX	Lympho-proliferative malignancy; no CTX	Nonmyeloid malignancy; planned CTX	Breast, lung, colorectal, or gynecologic cancer; planned CTX
Treatment arms	IV iron vs oral iron vs no iron	IV iron vs oral iron vs no iron	IV iron vs no iron	IV iron vs no iron or oral iron	IV iron vs no iron
Study period, wks	6, or until end of treatment	9	16	16	16
Inclusion criteria Hb, g/dL	≤ 10.5	< 11	9-11	< 11	≤ 11
SF and TSAT, ng/mL and %	SF ≤ 200 or SF ≤ 300, TSAT ≤ 19	SF ≥ 100 or TSAT ≥ 15 or SF ≤ 900 and TSAT ≤ 35	SF ≤ 800 and stainable iron in bone marrow	SF ≥ 10 and TSAT ≥ 15; or SF ≤ 800	SF ≥ 100 and TSAT ≥ 20%, or SF ≤ 800 and TSAT ≤ 40%
Dosing					
IV iron	Iron dextran, TDI or 100 mg to calculated dose	Ferric gluconate, 125 mg QW for 8 wks	Iron sucrose, 100 mg QW (wks 1-6) then 100 mg Q2W	Ferric gluconate or iron sucrose, 200 mg Q3W	Ferric gluconate, 125 mg QW for 6 wks
ESA	Epoetin alpha, 40,000 U/wk	Epoetin alpha, 40,000 U/wk	Epoetin alpha, 30,000 U/wk At Wk 15, epoetin dose was ~10,000U lower with IV iron	Darbepoetin, 500 mcg Q3W	Darbepoetin, 150 mcg QW for 12 wks
Hb response, %	IV iron, 68 Oral iron, 36 No iron, 25	IV iron, 73 Oral iron, 45 No iron, 41	IV iron, 93 No iron, 53	IV iron, 86 No/oral iron, 73	IV iron, 77 No iron, 62
Patients transfused, %	IV iron, 12 Oral iron, 7 No iron, 19	Wk 5 to EOTP: IV iron, 3 Oral iron, 8 No iron, 11	IV iron, 7 No iron, 3	Wk 5 to EOTP: IV iron, 9 No/oral iron, 20	IV iron, 3 No iron, 7

Abbreviations: CTX, chemotherapy; EOTP, end of treatment period; ESA, erythropoiesis-stimulating agents; FCM, ferric carboxymaltose; Hb, hemoglobin; HCT, hematopoietic cell transplantation; IV, intravenous; LMW, low-molecular weight; NA, not applicable; QOW, one every other week; QW, once weekly; Q2W, once every 2 weeks; Q3W, once every 3 weeks; SF, serum ferritin; TDI, total dose infusion; TSAT, transferrin saturation; wk, weeks.

IV iron in cancer and CIA

The addition of IV iron to ESA therapy in dialysis-associated anemia has been standard since the early 1990s and has been associated with improvements in hemoglobin levels; time to treatment targets; ESA requirements; transfusion needs; patient energy and activity levels, sexual function, and cognitive ability; and even survival.

However, the use of parenteral iron as an adjunct to ESAs for cancer patients has been slow to evolve. Although there was little reason to believe that the addition of IV iron to ESAs for cancer patients would be less beneficial than it was in dialysis-associated anemia, it was not used until the first prospective, randomized study with IV iron added to ESA for CIA was published in 2004⁶ (see Table). In that trial, patients who received the added IV iron—low-molecular-weight (LMW) iron dextran administered as either a total dose infusion or bolus injections until the

calculated deficit was replaced—showed significant improvements in hemoglobin responses, time to maximal response, and quality of life outcomes, compared with those who received either no iron or oral iron. The responses were independent of method of IV iron administration, type of cancer, intensity of chemotherapy, and baseline iron parameters (ie, percent of transferrin saturation and serum ferritin). It should be noted that in this study, the entrance criteria required a serum ferritin of < 200 ng/mL or < 300 ng/mL with a percent transferrin saturation of ≤ 19. Although the mean serum ferritin level across the treatment groups was > 200 ng/mL, the perception that many of the patients were truly iron deficient led to a criticism of the conclusions that baseline iron status did not predict for a response to IV iron, and left open questions regarding the subset with CIA who would benefit from the addition of parenteral iron to ESA therapy.

TABLE Continued

Auerbach ¹⁴	Beguin ¹³	Steinmetz ¹⁹	Kim ¹¹	Dangsuwan ¹²	Anthony ¹⁵	Steensma ¹⁷
238	127	135	75	44	375	502
Nonmyeloid malignancy; receiving CTX	Lymphoid malignancy; autologous HCT	CTX-induced anemia	Cervical cancer; concurrent chemoradiotherapy	Gynecologic cancer; receiving CTX	Nonmyeloid, nonleukemia malignancy; planned/receiving CTX; ESA responsive and non-responsive	Nonmyeloid malignancy; receiving CTX
IV iron vs no iron at 2 ESA doses	No therapy vs ESA vs ESA+IV iron	Individual doses < 500 mg vs \geq 500 mg FCM	IV iron vs no iron	IV iron vs oral iron	ESA vs ESA+IV iron	ESA+IV iron vs ESA+oral iron vs ESA
15	18 post HCT	12	6, or until end of treatment	2 weeks/2 consecutive cycles	20: stage 1, 8; stage 2, 12	16
< 10	Unspecified	Unspecified	< 12	< 10	< 10	< 11
SF \geq 10 and TSAT \geq 15	SF 100-2500 and TSAT < 60	N/A	N/A	N/A	N/A	SF > 20 and TSAT < 60
Dosing						
LMW iron dextran, 400 mg Q3W	Iron sucrose, 200 mg on days 28, 42, 56 after HCT	FCM, < 500 mg or \geq 500 mg	Iron sucrose, 200 mg QW	Iron sucrose, 200 mg one time only	Iron sucrose, 7 mg/kg to max 500 mg; 1-3 infusions Q1-3W for 9 wks	Ferric gluconate, 187.5 mg Q3W
Darbepoetin, 300 or 500 mcg Q3W	Darbepoetin, 300 mcg QOW starting on day 28 (7 doses)	N/A	N/A	N/A	Epoetin alpha or darbepoetin, dose not available	Darbepoetin, 500 mcg Q3W until Hb > 11 g/dL then 300 mcg Q3W
IV iron, 82 No iron, 63	No treatment, 24 ESA, 81 ESA+IV iron, 92	Unspecified	Not mentioned in study	Not mentioned in study	ESA+IV iron, 58 ESA, 29	ESA+IV iron, 80 ESA+oral iron, 67 ESA, 65
IV iron, 36 No iron, 40	No treatment, 8 ESA, 8 ESA+IV iron, 4	Unspecified	IV iron, 40% No iron, 64%	IV iron, 22.7 Oral iron, 63.6	ESA+IV iron, 5.1 ESA, 10.4	ESA+IV iron, 9 ESA+oral iron, 13 ESA, 13

The second study with IV iron in CIA was published in 2007.⁷ The design and population were similar to those in the first trial, although the inclusion criteria were structured to address the previous criticism that overt iron deficiency was the sole indication for parenteral iron. For this study, the inclusion criteria were serum ferritin levels of > 100 ng/mL or percent transferrin saturation of > 15. In all, 187 patients were randomized to receive ESA alone (no iron), or ESA plus oral iron, or ESA plus IV ferric gluconate administered weekly as 125-mg boluses. An increase of more than 2 g/dL in hemoglobin concentration was seen in 73% of the IV iron-treated group, compared with 46% of patients in the oral iron group and 41% in the ESA-alone group. That finding supported the conclusion that patients with CIA but without absolute iron deficiency benefited from the addition of parenteral iron to ESA therapy.

The results of two subsequent publications that excluded iron-deficient patients strongly supported the con-

clusion that the benefit of IV iron added to ESA therapy is independent of baseline iron parameters. In a trial by Hedenus and colleagues,⁸ patients with lymphoproliferative malignancies who were not on chemotherapy and who all had marrow hemosiderin present were randomized to receive either ESA alone or ESA plus IV iron sucrose. There was a statistically significant improvement in hemoglobin response with IV iron, compared with ESA alone, as well as a reduction in the weekly dose of 10,000 IU. Based on the value of the Swedish krona at the time of the publication, the authors demonstrated a savings of \$100 per patient per week after allowing for the cost of the IV iron and its administration. Pedrazzoli and colleagues⁹ stipulated that participants in their trial had to have a serum ferritin of > 100 ng/mL and percent transferrin saturation > 20 to exclude those with absolute or iron-restricted erythropoiesis. The investigators randomized 149 anemic patients with solid tumors who were

receiving cytotoxic chemotherapy to either ESA alone or 125 mg weekly of IV ferric gluconate plus ESA for 6 weeks. The hematopoietic response in the intent-to-treat analysis was 76.7% in the ESA-plus-IV iron group, compared with 61.8% in the ESA-alone group ($P = .0495$).

Three studies on the effects of IV iron in CIA were powered to detect a reduction in the number of transfusions, the only current indication for ESAs in the United States. Bastit and colleagues¹⁰ randomized 396 patients with anemia and nonmyeloid malignancies to receive either ESA alone or ESA plus IV iron, which was administered either as iron sucrose or ferric gluconate given on the day the ESA was administered. The hematopoietic response was significantly higher in the IV iron group than in the ESA-alone group (86% vs 73%, respectively), and transfusions were required by a smaller proportion of patients who received IV iron than those who received ESA-alone (9% vs 20%). Kim and colleagues¹¹ randomized 75 patients with cervical cancer who were receiving radiation and cisplatin chemotherapy to receive either 200 mg of IV iron sucrose administered weekly without ESAs, or no therapy. No baseline or in-study iron parameters were provided. However, there was a significant difference in the number of blood transfusions that were needed for the IV iron and control groups (40% vs 64%). Dangsuan and colleagues¹² randomized 44 patients with gynecologic malignancies who were receiving chemotherapy and had previously been transfused to either IV iron sucrose or oral iron, again without ESAs. The authors reported that 22.7% of those receiving IV iron needed a transfusion, compared with 63.6% of those who received oral iron.

The only study in which long-term oncologic outcomes were evaluated was presented at the annual meeting of the American Society of Hematology in 2008.¹³ In that trial, 127 patients with lymphoproliferative malignancies who underwent autologous bone marrow transplants and were still anemic 30 days after the transplant were randomized to no treatment, to ESA alone, or to ESA plus IV iron. A hemoglobin response was seen in 24%, 81%, and 82%, respectively, and the number of transfusions was reduced to 4% in the IV iron group, compared with 8% in the other groups. Unlike previously published studies, the investigators followed patients for 5 additional years and found no differences in survival or increases in the relapse rates in the IV iron-treated group.

In a study of 238 patients with CIA, participants were randomized to receive 300- μg or 500- μg darbepoetin alfa every 3 weeks with or without IV iron, which was administered as short 400-mg infusions of LMW iron dextran.¹⁴ There was no evidence of a significant interaction

between darbepoetin alfa dose and IV iron use, so the authors pooled the efficacy results and summarized for IV iron usage regardless of darbepoetin alfa dose. Of the patients who received 300 μg of darbepoetin alfa, 75% achieved target hemoglobin, compared with 78% of those who received the 500- μg dose. An analysis by IV iron usage showed that 82% of those receiving IV iron achieved target hemoglobin, compared with 72% of patients who did not receive IV iron. In addition, those receiving IV iron (irrespective of the darbepoetin alfa dosage) achieved target hemoglobin 4 weeks earlier than those who did not receive the IV iron.

Anthony and colleagues examined whether IV iron added to an ESA could restore ESA responsiveness in established ESA nonresponders.¹⁵ They treated 375 CIA patients with an ESA alone for the first 8 weeks; then for the subsequent 12 weeks, both responders and nonresponders were randomized either to 1,500 mg of iron sucrose, administered in 3 divided doses plus ESA, or to an ESA alone. Both IV iron groups had significantly greater hemoglobin responses. However, it should be noted that doses of iron sucrose greater than 300 mg are not recommended.¹⁶

The only trial that failed to demonstrate a benefit with IV iron in CIA was published by Steensma and colleagues in early 2011.¹⁷ In that study, 502 patients with CIA were randomized to darbepoetin with or without the addition of IV ferric gluconate, oral ferrous sulfate, or oral placebo. There were no baseline differences in hemoglobin levels or iron parameters. The investigators measured pre- and posttreatment hepcidin levels. There was no observed difference in hemoglobin or hematopoietic response, darbepoetin dose, or quality of life parameters among those treated with IV iron and the controls. Shortly after this study was published, the ASH/ASCO guidelines recommended that IV iron not be a routine part of the treatment paradigm for CIA.⁵

At ASCO's 2011 annual meeting, Steensma and colleagues presented an update stratifying results in the IV iron arm to those who received at least 4 of 5 planned doses and those who did not.¹⁸ A further stratification had been performed based on pretreatment hepcidin levels. Consistent with the results of the other studies, the investigators showed that in patients who received at least 80% of the planned IV iron dose, a hematopoietic response of 80% was achieved, compared with 56% for those who did not. There was no statistical difference between darbepoetin alone or with oral iron. Those with low pretreatment hepcidin levels who received IV iron had an erythropoietic response of 92%-95%, compared with 69% with high pretreatment levels. Dr. Patricia Ganz, the discussant for this abstract, noted that those

who received at least 4 of 5 planned doses and had low hepcidin levels also had no blood transfusions and an exceptionally high erythropoietic response rate. She further concluded that patients with lower pretreatment serum hepcidin levels seemed to have a better clinical response to the combination of darbepoetin and IV iron, and that serum hepcidin levels may help predict response to ESAs and supplemental iron. Dr. Ganz noted that if those assertions could be confirmed in other data sets, then the current policy to not reimburse for IV iron and ESAs when both were given at the same visit—as well as the current ASH/ASCO guidelines—may need to be reconsidered.

The obvious question is whether or not ESAs are required for the benefits of IV iron to be observed. In a prospective trial of ferric carboxymaltose or no treatment in 135 patients with CIA, investigators observed significant hemoglobin and hematopoietic responses without concomitant ESA use,¹⁹ which suggested that IV iron alone merits further study as a strategy to reduce the increase in transfusions since the 2008 CMS decision memo that restricted ESA usage.

Is IV iron underused in oncology patients?

Findings in prospective studies have demonstrated a clear benefit for the addition of IV iron to ESAs in CIA. Nonetheless, the perception remains that IV iron is dangerous. In the 12 trials reviewed here,^{6–15,17,19} there was 1 serious adverse event (SAE) among the more than 2,000 participants across the 12 studies. That SAE occurred in 1 of 2 patients who received high-molecular-weight (HMW) iron dextran, during a short period when LMW iron dextran was not available.⁶ None of the remaining 79 patients who received LMW iron dextran in the trial experienced an SAE. Five IV iron preparations are available in the United States. Only iron dextran is approved for CIA, but the literature supports the efficacy and safety of ferric gluconate and iron sucrose in this population. Ferumoxytol, the newest IV iron formulation to be approved in the United States, is currently undergoing clinical investigation in patients with CIA.

The most reliable method for comparing safety among formulations is a head-to-head prospective trial. Two small prospective studies that compared LMW iron dextran and iron sucrose showed no difference in safety or efficacy.^{20,21} A recent retrospective analysis of all IV iron products administered at a single institution from April 1, 2008, to March 31, 2010, showed that among 510 patients, IV iron was safe and that LMW iron dextran was as safe as ferric gluconate and iron sucrose.²² Although there are no head-to-head data that compare HMW iron dextran with the other products, the preponderance of

published literature—all retrospective—suggests that it should be used only with caution.²³ HMW iron dextran is proscribed by the NCCN, which recommends LMW iron dextran when IV iron is indicated for CIA.

In a recent prospective, multicenter, open-label study, investigators randomized 162 patients with chronic kidney disease to receive either iron sucrose or ferumoxytol, and concluded that rates of adverse events (AEs) were equivalent or possibly lower with ferumoxytol.²⁴ These data support the conclusion that when HMW iron dextran is avoided, as recommended by guidelines, the remaining IV iron formulations are safe and SAEs are rare.

Another issue that may lead to misinterpretation of the safety of IV iron is the nature and frequency of minor infusion reactions that occur with all of the formulations. Physicians frequently premedicate with diphenhydramine without any evidence to support its use. Diphenhydramine can cause hypotension, flushing, somnolence, and both sinus and supraventricular tachycardia, all of which prompt physicians to intervene therapeutically and turn a minor infusion reaction into an SAE that is subsequently attributed to the IV iron, though there is some evidence that most AEs that are attributed to IV iron are actually the result of the premedication.²⁵ It is extremely important to note that the administration of any of the available IV iron preparations can be associated with acute chest and back tightness, without accompanying hypotension, tachypnea, tachycardia, wheezing, stridor, and periorbital edema.²⁶ These infrequent reactions abate without therapy and rarely recur with rechallenge. The reactions are more frequent in patients with an allergic diathesis.²⁷ It is important not to overreact to these minor AEs: tryptase levels (a marker for mast cell degranulation in anaphylaxis) are normal after these reactions.⁷ A few patients will experience self-limited arthralgias and myalgias the day after iron infusions. These reactions abate without therapy, and never leave residual; nonsteroidal anti-inflammatory drugs may shorten their duration.

Administrating IV iron

The setting in which IV iron is administered will have a bearing on how IV iron should be administered. For dialysis-associated anemia, the decision about which IV iron should be used is based on economics and makes little clinical difference with thrice weekly visits. A similar statement can be made for CIA patients with weekly visits. However, for all other clinical settings in which IV iron is preferred, an infusion of the total dose (TDI; 1 g or more) in a single setting is as effective and safe as are bolus injections, but less expensive and more convenient, according to findings from several prospective clinical

trials.^{20,21,28} Only LMW iron dextran and ferumoxytol (both available only in the United States) and isomaltoside and carboxymaltose (both available only in Europe) can be given as a TDI in 1 hour or less. The two salts should not be administered in doses of more than 250 mg for gluconate and 300 mg for sucrose because of the possibility of significant infusion reactions owing to free iron with the less tightly bound smaller carbohydrate carriers. Of the 2 iron dextrans that are available in the United States, the HMW formulation should be used with caution based on published evidence.^{23,29} We recently completed a 60-patient pilot with ferumoxytol administered as a 1,020-mg infusion in 15 minutes. Consistent with published evidence, no SAEs were observed with the other products, which could also be administered as TDIs.^{28–34}

Conclusion

In thousands of patients studied across a broad spectrum of disorders associated with iron deficiency, IV iron has been safe, and certainly safer than most physicians realize. This is particularly true when parenteral agents other than HMW iron dextran are used. In the 12 reported prospective studies in CIA and cancer-associated anemia, comprising a total of more than 2,000 patients, no clinically significant toxicity was observed.^{6–15,17,19} It has become clear that parenteral iron can be administered with reasonable safety to patients with cancer. The data support a conclusion that ESA therapy is more efficacious when supplemented by intravenous iron in the setting of CIA, and that IV iron is probably ESA dose sparing. There are provocative data that suggest that parenteral iron alone may be effective in the treatment of CIA, and they merit further study.

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