Total Dose Iron Dextran Infusion in Cancer Patients: Is it Safe?*

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Abstract
The feasibility of the large, single-dose intravenous iron repletion method, which is known today as total dose infusion (TDI), has been demonstrated over decades. However, this method of iron repletion was chiefly developed for patients with large iron deficits, such as those with pregnancy-induced anemia, chronic bleeding disorders, and absolute iron-deficiency anemia (serum ferritin < 30 ng/mL, transferrin saturation < 15%) who were unable to receive frequent small doses of intravenous iron. Today, 50 years after the advent of TDI, more is known about iron metabolism and storage, but the optimal dosing strategy for intravenous iron in patients with cancer is still not well defined. The proinflammatory state of cancer, or its treatment, may influence the response to intravenous iron therapy. Additionally, the long-term adverse effects of large single doses or smaller more frequent doses have yet to be studied in the oncology population. Historically, safety concerns surrounding the administration of intravenous iron have centered on anaphylaxis. Newer concerns are being raised, such as oxidative stress, iron overload, venous thromboembolism, infection risk, and tumor growth. Therefore, with the original premise of TDI assuming low levels of inflammation, coupled with the recent data surrounding the adverse effects of blood transfusions and erythropoietic-stimulating agents, this article reviews the risks and benefits of TDI administration specifically for patients with cancer. (JNCCN 2012;10:669–676)

History of Total Dose Infusion
Parenteral iron administration was introduced approximately 60 years ago. In 1954, high-molecular-weight (HMW) iron dextran (Imferon) became available as an intramuscular injection in which a “total dose” could be given in 1 to 4 injections for children with iron-deficiency anemia. Soon thereafter, clinicians began experimenting with large, single-dose intravenous repletion methods, which are known today as total dose infusion (TDI). The efficacy of this method has been demonstrated over decades. However, TDI was chiefly developed for patients with large iron deficits, such as those with pregnancy-induced anemia, chronic bleeding disorders, and absolute iron deficiency anemia (AIDA) who were unable to receive frequent small intravenous iron doses.

Historically, safety concerns surrounding the administration of intravenous iron have centered on anaphylaxis and associated symptoms, such as dyspnea, wheezing, respiratory arrest, hypotension, syncope, cyanosis, and hives. Less recognized but more common adverse events include arthralgia and myalgia, which usually occur within the first 48 to 72 hours after intravenous iron infusion. Most of the serious, anaphylaxis-type symptoms were attributable to the HMW formulation of iron dextran, and therefore clinicians have recommended that it be removed from the market in the United States. Now, approximately 50 years later, much more is known about iron metabolism and storage...
in the body. Newer concerns are being raised, such as oxidative stress, infection risk, iron overload, venous thromboembolism (VTE), and tumor growth.\textsuperscript{7,9,10} Patients with cancer may be at a higher risk for some of these long-term adverse effects because of more frequent blood transfusions, high degrees of inflammation from the cancer itself or its treatment, and risk of infection resulting from myelosuppressive chemotherapies.\textsuperscript{9} Because of the original premise behind TDI, which assumed low levels of inflammation, and the recent data surrounding adverse effects in patients with cancer when receiving other treatments for anemia, such as blood transfusions\textsuperscript{11} and erythropoietic-stimulating agents (ESAs),\textsuperscript{9} this article explores the risks and benefits of iron dextran TDI in patients with cancer.

Methods
PubMed was searched using the terms cancer, total dose infusion, and iron. Although the search returned 3 articles, only 1\textsuperscript{12} was pertinent to treating anemia in patients with cancer. Therefore, a general search was conducted for benefits, risks, and safety of total dose iron dextran infusion in other populations. We also used references contained within the articles found from our initial searches.

Treatment Options for Anemia in Patients With Cancer
As summarized in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer- and Chemotherapy-Induced Anemia (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org), anemia is very common in patients with cancer, especially in those receiving chemotherapy.\textsuperscript{9} Iron deficiency may be the most common cause and the most easily correctable factor contributing to anemia.

Treatment options for cancer- and chemotherapy-induced anemia (CIA) include red blood cell transfusion, ESAs, and iron therapy.\textsuperscript{13} Risk assessment of the patient with cancer-related anemia should first identify those who need urgent correction of anemia with red cell transfusion.\textsuperscript{9} Otherwise, patients should be informed about the risks and benefits of long-term treatment choices: red blood cell transfusion versus ESA with or without intravenous iron therapy.\textsuperscript{9} Patients who select an ESA should receive intravenous iron treatment, not oral iron therapy.\textsuperscript{9} Data from several randomized trials comparing oral and intravenous iron indicate the superiority of intravenous iron therapy.\textsuperscript{12,14,15}

In 2007, the Centers for Medicare and Medicaid Services imposed restrictions on ESA reimbursement in response to concerns over ESA safety in patients with CIA. With these restrictions, ESA use among older patients has declined approximately 30\%.\textsuperscript{16} Although the ESA restrictions only apply to Medicare and Medicaid patients, generalization of these restrictions to all patients with CIA could potentially increase blood resource use to a greater extent. One report described a modeling simulation to show that limiting ESA use in patients with CIA would impose significant pressure on the available blood supply margin in the United States.\textsuperscript{17} Current restrictions on ESA use and a limited blood supply raise the question as to whether using intravenous iron in a more optimal fashion might be one solution to treating CIA.\textsuperscript{18}

AIDA Versus Functional Iron Deficiency Anemia
The distinction between AIDA (transferrin saturation [TSAT] < 15\%, ferritin < 30 ng/mL) and functional iron deficiency anemia (FIDA; TSAT < 20\%, ferritin < 800 ng/mL) is an important one, because patients with AIDA may be able to avoid unnecessary exposure to an ESA. Patients with AIDA may have lower levels of inflammation, as evidenced by low serum ferritin, which is an acute-phase reactant. As a result, these patients should respond to oral or small doses of intravenous iron, because the iron will not be sequestered within the reticuloendothelial system (RES). The prevalence of AIDA, however, is currently unknown for specific cancers. Presumably, patients with gastrointestinal malignancies would be at greatest risk for AIDA, because iron losses are easily realized when these tumors bleed.

In patients with FIDA, the goal is to increase the availability of iron in the marrow to restore or increase erythropoiesis. This is possible, even during times of systemic inflammation, because the human body is physiologically ill-prepared to handle and sequester large doses of iron. This concept is supported by a study performed roughly 40 years ago, in which Henderson and Hillman\textsuperscript{19} showed the existence of an acute and chronic phase of increased erythropoiesis after doses of 1700 to 2100 mg of intravenous iron were administered to 25 patients with iron-deficiency anemia. To further illustrate their point,
in a single patient who received one dose of 1700 mg of intravenous iron dextran, reticulocyte production increased to levels greater than 4 times normal by the eighth day postinfusion (Figure 1). Interestingly, by the end of the second week, reticulocytosis dropped to roughly 2.5 times that of baseline, and marrow production of red cells fell steadily to as low as 1.5 times normal by the end of the sixth week. The authors concluded that a defect in iron release and subsequent delivery to the marrow occurs with such large doses of iron. They tested this hypothesis by infusing an additional 300 mg to the same patient during the seventh week. Red cell production again rapidly increased to 2.5 times baseline, thereby ruling out a defect in marrow production.

Although the demographics of this single patient are unknown, this study shows that reticulocytosis can be greatly increased by using either TDI or small frequent doses of intravenous iron. This single-patient experience is included to show a potential analogous situation that may be seen in patients with cancer. Additionally, lessons learned from aggressively dosing ESAs raise concerns as to whether stimulating reticulocytosis to greater than 4 times baseline with intravenous iron is safe. A study by Auerbach et al. was performed to determine if patients with cancer have the same response to TDI compared with smaller intermittent doses, and is discussed later.

Definition of TDI

The use of iron dextran TDI was first reported in 1963. However, this method of administration of low-molecular-weight (LMW) iron dextran is currently approved for use only in Europe (CosmoFer), whereas the United States formulation (INFeD) does not carry the same indication. The current maximum FDA-approved single dose of any iron product is 510 mg of ferumoxytol (Feraheme); however, ferumoxytol has yet to be studied in patients with cancer. The maximum FDA-approved single daily dose of iron dextran (INFeD) is 100 mg. Despite this labeling restriction, numerous trials have shown the efficacy of TDI for various indications, including CIA.

The subsequent rise in hemoglobin after iron dextran TDI is not proportional to the dose administered. However, the premise of TDI is to replace a patient’s total iron deficit in a single administration. The total iron deficit is based on body weight, the amount of iron needed to restore erythropoiesis to a near-normal level, and replenishment of iron stores. Several formulas to calculate the total iron deficit are available, including the Ganzoni formula used in the labeling for CosmoFer, the formula provided in the labeling for INFeD, and the Hanson formula (see Table 1). The total iron deficit and, subsequently, the quantity of iron per kilogram can vary between the equations, as shown in Table 1. The total calculated iron deficit is then given as a single infusion up to a total dose of 20 mg of iron per kilogram of body weight per administration, although some clinicians may choose not to cap the dose. Alternatively, the deficit can be corrected through intermittent infusions of various dose thresholds over days to months. This TDI “divided dose” (TDI-DD) methodology, as listed in the INFeD package insert, is used for various iron salt formulations, including iron dextran.

Figure 1  Erythropoietic response to total dose iron dextran versus smaller intermittent doses in an individual patient. On infusion of a single 1700-mg dose of intravenous (IV) iron dextran, the rate of reticulocytosis increased to more than 4 times baseline. Approximately 6 weeks later, a second infusion of iron dextran, 300 mg, was administered to the same patient, resulting in an increase in reticulocytosis of roughly 2.5 times baseline. According to the authors, the increased rate of erythropoiesis began to decline within 2 weeks of administration and was sustained for a short time (≤6 weeks) despite adequate iron stores in the reticuloendothelial system. These data suggest that small intermittent doses of intravenous iron may be as effective as total dose infusion. Adapted from Henderson PA, Hillman RS. Characteristics of iron dextran utilization in man. Blood 1969;34:369; with permission.
other iron salts, TDI-DD is recommended only at the manufacturer’s recommended dose because of the high incidence of adverse effects.9

**Benefits of TDI in Patients With Cancer**

Treating CIA with intravenous iron is well supported in the oncology literature. LMW iron dextran (TDI and intermittent bolus), ferric gluconate, and iron sucrose all improve erythropoiesis in combination with ESAs in iron-deficient and iron-replete patients with cancer, reducing transfusion requirements and improving quality of life.12,15,31–33

Additionally, intravenous iron may prevent thrombosis as thrombocytosis is commonly seen in iron deficiency anemia.10,34–38 Iron repletion may provide a theoretical protective benefit against thrombosis in iron-deficient patients with anemia, because a subsequent normalization of the platelet count may reduce the risk of VTE.37–40 Iron-deficient patients with cancer, especially those with advanced stage disease, may receive more red blood cell transfusions, which may also increase the risk of VTE and death.41

Because the benefits of intravenous iron appear exclusive of the salt formulation or method of delivery12,15,31,32 (TDI vs. intermittent bolus), TDI of iron dextran offers a convenient, patient-friendly method of complete iron repletion. Besides reducing the number of iron infusions and clinic visits required, TDI may also reduce cost and improve compliance.41

**Short-Term Risks of TDI**

Several short-term risks exist when giving iron parenterally, including infusion-related adverse effects, extravasation, and infection. Iron dextran products carry an FDA black box warning advising of the potential risks of anaphylaxis with iron dextran. However, most of the serious adverse events, including anaphylaxis associated with iron dextran, occur with high-molecular-weight (HMW) iron dextran (Dexferrum).52,43 A 2006 survey of FDA MedWatch reports indicated that the absolute rates of life-threatening adverse events were 3.3 per million doses administered for LMW iron dextran and 11.3 per million for HMW iron dextran.44 These serious adverse events can be minimized by avoiding HMW iron dextran,

### Table 1  Total Dose Intravenous Iron Equations, Example Calculations, and Administration

<table>
<thead>
<tr>
<th>Example Patient: 70 kg; 69 in; actual Hb 8 g/dL; target Hb 12 g/dL; depot iron 500 mg</th>
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<tbody>
<tr>
<td>**CosmoFer®/Ganzoni®**9: Total iron deficit [mg] = body weight [kg] × (target Hb – actual Hb) [g/dL] × 2.4 + depot iron [mg], add 500 if weight &gt; 35 kg</td>
</tr>
<tr>
<td>Total iron deficit for example patient: 1172 mg</td>
</tr>
<tr>
<td>Milligram of iron per kilogram of body weight: 16.7 mg/kg</td>
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<tr>
<td><strong>INFed</strong>31: Total iron deficit [mg] = (0.0442 [target Hb – observed Hb] × LBW + [0.26 x LBW]) × 50 mg/mL [concentration of INFed]</td>
</tr>
<tr>
<td>Total iron deficit for example patient: 1530 mg</td>
</tr>
<tr>
<td>Milligram of iron per kilogram of body weight: 21.9 mg/kg</td>
</tr>
<tr>
<td><strong>Hanson</strong>36: Total iron deficit [mg] = 0.3 × weight [lb] × (100 – [observed Hb × 100]/14.8 [or target Hb])</td>
</tr>
<tr>
<td>Total iron deficit for example patient: 1540 mg</td>
</tr>
<tr>
<td>Mg of iron per kilogram of body weight: 22 mg/kg</td>
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**Example of Premedications and Template for Preparation and Administration of LMW Iron Dextran**

**Premarkedications:**
1. Acetaminophen, 650 mg by mouth before iron dextran infusion
2. Methylprednisolone, 125 mg intravenously over 30 min before iron dextran infusion

**Preparation and administration:**
3. Test dose: Iron dextran (INFed), 25 mg slow intravenous push over 5 min starting 30 min after premedications; if no reaction after 30 min, give remaining iron infusion
4. Test dose: Iron dextran, ______mg in 500 mL 0.9% sodium chloride intravenously over 4 h x 1 dose total, at a rate not to exceed 50 mg/min

**Abbreviations:** Hb, hemoglobin; LBW, lean body weight; LMW, low-molecular-weight.
using test doses, and using appropriate premedication, such as corticosteroids and acetaminophen, for patients with multiple drug allergies. Premedication with diphenhydramine is not recommended because this practice has not been shown to decrease the incidence of adverse effects and may increase the incidence of hypotension and somnolence after the infusion.\textsuperscript{5,7,45}

Minor adverse events may occur with any iron product, including skin rash, arthralgias, nausea, vomiting, fever, and backache. These adverse events may be more common in patients receiving TDI, and events may not occur until 1 to 2 days postinfusion. When premedications are used, the adverse event rate (non life-threatening) of LMW iron dextran therapy is approximately 4%.\textsuperscript{6,46}

The extravasation risk of intravenous iron appears to be low. No published data indicate that either iron dextran product (Dexferrum or InFed), ferric gluconate, iron sucrose, or ferumoxytol are irritants or vesicants. One published report described an extravasation event with iron sucrose\textsuperscript{37}; the only notable finding was skin discoloration, which lasted several months.

Iron sequestration in the RES is the hallmark of functional iron deficiency seen in chronic diseases, such as cancer and infection. A theoretical risk of intravenous iron therapy would be promotion of bacterial growth, because parenteral iron therapy would rapidly provide usable iron, not only for host red cell production but also for infectious organisms. However, no firm evidence shows that intravenous iron actually increases the risk of infection.\textsuperscript{15} Nevertheless, postponing parenteral iron administration for patients with an active infection may be prudent until resolution of infection occurs, and for patients receiving chemotherapy with a high rate of febrile neutropenia.\textsuperscript{9} Table 2 displays the benefits and potential risks of parenteral iron administration reported in a variety of patient populations or studied in animal models. Because these risks have not specifically been studied in patients with cancer, the actual incidence of these adverse effects in this population is not known. Studies specifically assessing these adverse effects in patients with cancer receiving total dose intravenous iron dextran are warranted.

Additionally, as seen in the hemodialysis population, a significantly increased risk of mortality was seen with iron given over 6 months or less at cumulative doses exceeding 1000 mg (adjusted hazard ratio [HR], 1.09; 95% CI, 1.01–1.17) and greater than 1800 mg (adjusted HR, 1.18; 95% CI, 1.09–1.27).\textsuperscript{48} Interestingly, the authors found no association between iron level and mortality. Furthermore, the study was not powered to detect a difference, but a statistically nonsignificant elevated HR for mortality (HR, 1.16; 95% CI, 0.94–1.44 vs. no iron) was found for cumulative iron doses greater than 1800 mg given over 12 to 18 months before death.\textsuperscript{48} As a result, the authors recommend the cautious use of aggressive dosing of intravenous iron in patients with cancer until confirmatory data are published.\textsuperscript{48}

**Long-Term Risks of TDI**

High-dose iron repletion has potential long-term risks, including carcinogenesis, organ damage, and thrombosis. These long-term risks are often overshadowed in clinical trials by the acute reactions described earlier. Therefore, data from long-term, prospective studies do not exist addressing these concerns of high-dose iron repletion.

A growing concern is the possible role of iron in the initiation and progression of cancer.\textsuperscript{49} Iron overload may play a role in carcinogenesis or progres-

<table>
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<tr>
<th>Table 2</th>
<th>Benefits and Risks of Total Dose Iron Dextran Therapy in Patients With Cancer</th>
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<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td><strong>Short-Term Risks</strong></td>
</tr>
<tr>
<td>• Increased hemoglobin level (2.4 g/dL from baseline)\textsuperscript{12}</td>
<td>• Arthralgia/myalgia (1%–5%)\textsuperscript{12,64}</td>
</tr>
<tr>
<td>• Improved quality of life\textsuperscript{12,64}</td>
<td>• Nausea, vomiting, abdominal pain (≤ 2%)\textsuperscript{64}</td>
</tr>
<tr>
<td>• Reduced cost\textsuperscript{41}</td>
<td>• Anaphylaxis (≤ 1%)\textsuperscript{52,71,44,64}</td>
</tr>
<tr>
<td>• Improved compliance\textsuperscript{65}</td>
<td>• Urticaria or pruritus (≤ 1%)\textsuperscript{64}</td>
</tr>
<tr>
<td></td>
<td>• Fever (≤ 1%)\textsuperscript{20}</td>
</tr>
<tr>
<td></td>
<td>• Headache (≤ 1%)\textsuperscript{52,64}</td>
</tr>
<tr>
<td></td>
<td>• Folate deficiency\textsuperscript{25}</td>
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sion of many cancer types, including hepatocellular carcinoma, ovarian cancer, mesothelioma, and colorectal cancer. Importantly, increased serum iron levels and increased transferrin saturation could increase the risk of cancer death. Interestingly, iron reduction through phlebotomy decreases the risk of lung, colorectal, prostate, and other cancers in patients with peripheral arterial disease, and long-term phlebotomy combined with a low-iron diet reduces the progression to hepatocellular carcinoma in patients with hepatitis C. The mechanism of iron-induced carcinogenesis is thought to lie in the ability of free iron to produce hydroxyl radicals (•OH) via the Fenton reaction:

\[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^- \]

These free radicals may then induce oxidative damage to DNA or proteins, thereby inactivating tumor suppressor genes, activating oncogenes, or producing epigenetic alterations.

Because patients with cancer often have many comorbidities, iron-related oxidative stress may be detrimental in those with atherosclerosis and cardiovascular disease. Additionally, because high levels of ESA-induced erythropoiesis (“over-erythropoiesis”) increases the risk of cardiovascular disease, thrombosis, and mortality, one must also question the role of iron, especially TDI, in this process.

Controversy: How Do We Know That TDI Iron With or Without an ESA is Safe for Patients With Cancer?

Only 2 published trials currently exist that implemented total iron repletion as a single dose in patients with cancer. The first study by Auerbach et al. was a prospective, multicenter, open-label trial that randomized 157 patients with nonmyeloid malignancies to either no iron (n = 36); oral ferrous sulfate, 325 mg by mouth twice daily (n = 43); repeated iron dextran boluses of 100 mg (n = 37); or iron dextran TDI (n = 41). The study followed patients receiving the intravenous bolus for up to 24 weeks. For the other arms, the end point was defined as the point at which the maximum hemoglobin (Hb) was achieved, but not to exceed 6 weeks. For patients receiving intravenous iron, the total dose of iron dextran was calculated using the InFed formula to reach a desired Hb concentration of 14 g/dL. Patients assigned to the intravenous iron groups received between 1100 and 2400 mg (bolus group) and 1000 to 3000 mg in the TDI group. The authors did not report the percent of patients with absolute or functional iron deficiency in any group; however, they did note that Hb response did not differ for patients with a baseline TSAT percentage less than or greater than 15%. The results showed that not only was the Hb response slightly better in the bolus group compared with the TDI group (increase of 2.5 g/dL vs. 2.4 g/dL, respectively), but also no statistically significant difference was seen in mean Hb increase between the intravenous iron groups (P = .53). This is the first study to prospectively compare TDI with oral iron and placebo in patients with cancer. This study was limited by the short follow-up period of less than 6 months to assess the long-term safety of TDI.

The second study examining TDI was designed to show the safety of giving 1000 mg of LMW iron dextran over 1 hour. However, because only 4.2% of the patients included in this study had cancer, it is unclear whether the short- or long-term safety of TDI in patients with cancer cannot be made.

Currently, no long-term safety data exist for the use of TDI in patients with cancer. After lessons learned from aggressively dosing ESAs in these patients, practitioners must ask themselves whether they are also pushing the safety limits with total dose iron infusion. The optimal dosing of intravenous iron in any population remains controversial. Six studies exist using intravenous iron in patients with cancer, and these studies have used 3 different agents (iron dextran, iron sucrose, sodium ferric gluconate) at variable dosing and frequency. However, none of the studies have reported long-term safety data.

Discussion

Optimal dose and frequency for iron dextran in patients with cancer is unknown and may differ based on cancer type, stage, or treatment. Certain cancers may progress in the face of supraphysiologic doses of iron. Additionally, as seen with ESAs, patients with cancer may be at a higher risk for VTE if Hb levels rise too quickly. Until studies are performed proving iron to be nonthrombogenic, like its ESA counterpart, clinicians should be wary about aggressively dosing iron. Future studies are needed to determine which patients are at higher risk for AIDA versus FIDA; whether large single doses or smaller more
frequent doses are safer in patients with cancer; if certain types of cancer preclude the use of intravenous iron; and whether TDI increases or decreases the risk of VTE and mortality. A readily available assay that will distinguish between inflammation and true iron deficiency is currently being tested; however, more study is needed before this assay can be implemented clinically.66

Conclusions
The total dose equation that appears in the package insert for iron dextran is designed to elucidate the dose that is to be administered in multiple, intermittent infusions. Currently, iron dextran is not FDA-approved as a single-dose repletion method. As a result, the authors suggest using smaller, intermittent dosing in patients with cancer, which has been shown to be equally efficacious as TDI. In addition, because TDI has been shown to initially increase the rate of reticulocytosis by 4 to 5 times normal, the authors raise the question of whether this erythropoietic rate mimics that of aggressively dosing ESAs. Although no clinical data support an increased risk of iron overload, free-radical generation, thrombus formation, or mortality with large single doses of iron, neither are data available showing that these phenomena do not occur in patients with cancer. Therefore, the authors recommend TDI divided-dose administration until long-term safety data refute these concerns. Ultimately, clinicians must balance the convenience benefits of single-dose TDI with its possible short-term, long-term, and unknown risks.

References

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70. Ramakrishna G, Rooke TW, Cooper LT. Iron and peripheral arterial disease: revisiting the iron hypothesis in a different light. Vasc Med 2003;8:203–210.