Improving Hemoglobin Response in Patients With Chemotherapy-Induced Anemia

Michael Auerbach, MD, FACP
Clinical Professor of Medicine
Georgetown University School of Medicine
Washington, DC

Anemia is not an unavoidable side effect of chemotherapy

Anemia is a common complication in patients receiving chemotherapy, and its treatment challenges clinicians daily. The etiology...
of anemia related to cancer treatment is multifactorial and is precipitated by the myelosuppressive effects of repeated cycles of chemotherapy or radiation therapy due to the release of cytokines (e.g., tumor necrosis factor and interleukin-1) resulting from an inflammatory or neoplastic process. Moreover, the myelosuppressive effects of chemotherapy decrease the production of endogenous erythropoietin by inducing nephrotoxic effects on the renal tubules and destroying mature hematopoietic cells. Radiation therapy that damages stem cells in the bone marrow also exacerbates anemia.

The risk for developing anemia from chemotherapy is a critical issue for patients. There are currently 1.24 million individuals in the United States who are receiving chemotherapy, and approximately 800,000 (64.5%) of these patients are anemic. A patient’s quality of life (QoL) is often profoundly affected by anemia, with extreme fatigue cited as a major consequence. However, anemia frequently remains undiagnosed and undertreated—partly due to the misconception that it is an unavoidable side effect of cancer treatment. In order to effectively address this problem, it is necessary for the oncology community to change its fundamental attitude regarding anemia treatment.

Rethinking the Current Anemia Treatment Philosophy

 Observation of inadequate erythropoietin production in patients with CIA has prompted investigators to use ESA therapy in hopes of achieving benefits of ESA similar to those seen in patients undergoing dialysis. Clinical oncology trials with recombinant human erythropoietin (epoetin alfa) and the novel, longer-acting darbepoetin alfa consistently demonstrated increased hemoglobin (Hb) levels, decreased transfusions, and measurable improvements in QoL. Unfortunately, 30% to 50% of patients treated with an ESA who have CIA do not achieve meaningful hematologic responses.

According to the clinical practice guidelines developed by the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), there is no benefit to continuing ESA therapy if the Hb concentration has not increased at least 1 g within the first 6 to 8 weeks of treatment after appropriate dose increments. The guidelines recommend that ESA nonresponders should be investigated for other causes of anemia, such as blood loss, hemolysis, and iron deficiency.

Recent ESA Studies Impact Approach to Anemia Management

New evidence has fueled concern about the safety of ESA therapy and appropriate target Hb levels. The DAHANCA 10 (Danish Head and Neck Cancer Study Group) trial, which was designed to assess outcomes when treating anemia with an ESA to an Hb of 14.0 to 15.5 g/dL, was terminated prematurely in late 2006 by the data-monitoring committee because interim results showed that the 3-year locoregional disease control in patients receiving radiation therapy plus an ESA was significantly worse than in patients not treated with an ESA (P=0.01). Overall survival also favored patients not receiving an ESA, although this outcome was not statistically significant (P=0.08). In an earlier published study, patients were randomized to receive either placebo or ESA therapy, with treatment discontinued when target Hb concentrations were achieved (≥14.0 g/dL in women and ≥15.0 g/dL in men). The study suggested that ESA therapy might increase the rate of tumor progression and mortality in patients with head and neck cancer undergoing radiation therapy. Likewise, a retrospective case-control study of patients with cervical cancer undergoing chemoradiotherapy found an association between ESA treatment and thrombotic events. In February 2007, recruitment was suspended for a midstage trial of an experimental ESA product because of safety concerns in anemic patients with lung cancer who were receiving chemotherapy. The suspension was credited to a disparity of deaths across the study’s 4 treatment arms, further casting a cloud of uncertainty over the whole class of erythropoietic drugs. A recently completed randomized trial involving 989 anemic patients who had active malignant disease but were not receiving chemotherapy or radiation therapy failed to meet its primary end point of reducing red blood cell (RBC) transfusions in the ESA treatment group. The absolute number of deaths at the end of the study was also higher in patients receiving ESA therapy compared with patients receiving placebo.

These data are consistent with the risks found in studies in patients with chronic kidney disease. The investigations of the CHOIR (Correction of Hemoglobin in Renal Insufficiency) trial enrolled more than 1,400 patients randomized to receive an ESA dosed to a higher-target Hb of 13.5 g/dL or lower Hb of 11.3 g/dL. The results of CHOIR demonstrated an increased risk of death and cardiovascular-related hospitalizations when ESA was administered to reach the higher Hb level versus the lower Hb level. These findings were further strengthened by the 600-patient CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta) trial, which showed a trend toward more cardiovascular events with ESA dosing to a higher Hb target and no cardiovascular benefit.

Although these findings may not be generalized to all ESA-treated cancer patients receiving chemotherapy, clinicians need to recognize that ESAs may stimulate tumor growth. Accordingly, the FDA has recommended that clinicians use the lowest possible ESA dose to slowly increase the Hb concentration to avoid blood transfusions. Interventions that are ESA response-enhancing and/or dose-sparing are needed, and research suggests that intravenous iron therapy is a viable option for patients with CIA. The ASCO/ASH guidelines emphasize that initiating iron repletion when indicated is valuable in reducing the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for poor responses to ESA therapy.

Treating Iron Deficiency to Improve Hb Response

Although ESA therapy is a recognized treatment option for CIA, clinicians need to recognize that healthy erythropoiesis involves the close interaction of both erythropoietin and iron. RBC development initiates in the bone marrow with the proliferation and differentiation of hematopoietic stem cells into erythroid precursor cells (Figure 1). These maturing precursor cells express erythropoietin receptors; thus, erythropoietin needs to be readily available during this stage. Erythropoietin facilitates the maturation of burst-forming units into erythroid colony-forming units, and eventually into mature erythroblasts. Although erythropoietin is a primary regulator of RBC production, iron is required in the later stage of the process for the production of new Hb. At this point, transferrin receptors are at a maximum on the cell surface and iron is taken up by the cells and incorporated into Hb. If iron is inaccessible, anemia will develop.

An imbalance between iron requirements in the erythropoietic marrow and iron supply can be a response-limiting factor.
for ESA therapy. Many patients with CIA have persistent anemia despite ESA administration, possibly as a result of iron deficiency or inaccessibility of available iron. Increased iron use stimulated by ESAs can rapidly transform iron repletion with a satisfactory hematopoietic response to iron deficiency with unresponsiveness. In-depth ferrokinetic studies conducted during ESA treatment revealed that an erythrocyte mass increase of about 8 mL/kg, which corresponds to a hematocrit (Hct) increase of 10%, can deplete iron stores in patients if concomitant intravenous iron is not administered.

There are 2 forms of iron deficiency that can have a negative impact on a patient’s response to an ESA. Absolute iron deficiency limits the body’s ability to produce Hb and can occur as a result of occult blood loss, impaired iron absorption, blood loss due to surgery, and malignancy or its treatment. Conversely, iron-restricted erythropoiesis occurs when ESA therapy stimulates erythropoiesis, thereby increasing the demand for iron above the body’s ability to mobilize iron from the storage pool to the erythron. In such cases, ESA administration results in reduced erythroid responses, iron-restricted erythropoiesis, and inefficient use of costly drugs. Therefore, despite sufficient iron stores, patients may require substantial amounts of intravenous iron to enhance their response to ESAs. Interestingly, patients with hereditary hemochromatosis, who are otherwise healthy, do not develop iron-restricted erythropoiesis and have better responses to ESAs.

At the same time that ESA therapy increases the demand for iron transport in CIA, iron availability is further restricted by inflammatory cytokines associated with anemia of chronic disease, which upregulate the iron-regulatory protein hepcidin. Hepcidin, produced in the liver, decreases iron absorption in the small intestinal epithelium by binding to the iron transport protein, ferritin, the exporter of iron from cells, thus limiting the movement of iron into the circulation. Ultimately, this process leads to reduced intestinal absorption of dietary iron. HePCID1 further decreases iron availability by inhibiting the release of recycled iron by macrophages and the transfer of stored iron from hepatocytes. These factors lead to a depletion of the usable iron pool, delaying the response to ESAs in patients with CIA. Therefore, the aim of anemia management should be to avoid the “iron trap” and administer intravenous iron to provide an accessible iron supply to overcome iron-restricted erythropoiesis and ESA hyporesponsiveness in chemotherapy-treated cancer patients. Currently there are 4 parenteral iron products available: iron sucrose (Venofer, Luitpold), sodium ferric gluconate (Ferrlecit, Watson), high-molecular-weight (HMW) iron dextran (Dexferum, Luitpold), and low-molecular-weight (LMW) iron dextran (INFeD, Watson).

Can Intravenous Iron Dextran Fill the Void Unaddressed by ESA Therapy?

The first trial evaluating different methods of iron administration in ESA-treated patients with CIA was published in 2004. This 6-week, randomized, controlled, open-label, multicenter study included anemic patients with a histologic diagnosis of cancer who were scheduled to undergo chemotherapy and had laboratory parameters of Hb less than 10.5 g/dL and...
serum ferritin 200 ng/mL or less or serum ferritin 300 ng/mL or less concurrently with a transferrin saturation (TSAT) of 19% or less. Patients were randomized to 1 of 4 groups: no iron (n=36), oral iron (n=43), iron dextran repeated 100-mg dose until calculated dose was achieved (n=37), or iron dextran total calculated dose as 1 dose (n=41). All patients received LMW iron dextran, except for 2 patients who received HMW iron dextran when LMW iron dextran was unavailable. All patients were administered ESA therapy at 40,000 U subcutaneously weekly. Outcome variables were measured at baseline and weekly, and included Hb (primary variable) as well as energy, activity, and QoL (secondary variables using a linear analog scale analysis).

Efficacy evaluations demonstrated that the mean Hb increase was significantly higher in ESA-treated patients receiving intravenous iron dextran compared with those receiving no iron or oral iron (P<0.02). There was no significant difference in mean Hb increase between those receiving oral iron and those receiving no iron (P=0.21). Figure 2 shows Hb changes from baseline to end point. Additionally, 68% of ESA-treated patients receiving intravenous iron dextran achieved a hematopoietic response, compared with only 25% in the ESA-treated no-iron group and 36% in the ESA-treated oral iron group (P<0.01) (Figure 3). Patients were considered to have a hematopoietic response to ESA therapy if they had an increase in Hb of 2 g/dL or more or achieved an Hb of 12 g/dL or more during the study. Noteworthy, responders achieved a mean Hb increase of 2 g/dL or more after only 6 weeks of ESA and intravenous iron dextran therapy, whereas it has been reported that this degree of Hb increase is usually achieved after 8 or more weeks with ESA therapy alone.72

Analysis of the QoL data showed that ESA-treated patients receiving intravenous iron dextran had substantial increases in energy, activity, and QoL compared with those receiving no iron or oral iron (Figure 4). Conversely, ESA-treated patients in the no-iron group had small decreases in energy, activity, and overall QoL, and those in the oral iron group had small increases in these 3 parameters. Pooled data for the 4 treatment groups demonstrated a significant correlation between an increase in Hb and improvements in energy (P<0.0001), activity (P=0.0002), and overall QoL (P=0.0001).

Safety data in the intravenous iron dextran group demonstrated that only 3 of 37 patients experienced the following adverse reactions: delayed arthralgia/myalgia syndrome (n=1), fatigue (n=1), and shortness of breath (n=1). These were all short, self-limited, and clinically insignificant, except for 1 of the 2 patients treated with HMW iron dextran who experienced anaphylaxis. This patient was intubated, recovered, and received LMW iron dextran uneventfully months later. These data are consistent with numerous published papers supporting the significantly increased toxicity with the HMW iron dextran preparation.34-41

This study validates that LMW iron dextran is a practical option for optimizing the efficacy of ESA therapy in patients with CIA. Additionally, the findings support the consideration of a more comprehensive approach to anemia treatment that includes administering iron dextran in patients receiving ESAs. Interestingly, the benefits seen with iron dextran in CIA are similar to the benefits seen in anemia related to renal disease.
FIGURE 3. PERCENTAGE OF RESPONDERS IN EACH GROUP FOR THE INTENT-TO-TREAT POPULATION

Responders had achieved a maximal Hb level ≥12 g/dL or an increase in Hb of ≥2 g/dL during the study.

*P<0.01 versus no-iron and oral iron group.

ESA, erythropoiesis-stimulating agent


FIGURE 4. CHANGE IN ENERGY, ACTIVITY, AND QUALITY OF LIFE FROM BASELINE TO END-POINT EVALUATION FOR THE INTENT-TO-TREAT POPULATION

ESA, erythropoiesis-stimulating agent; LASA, linear analog scale assessment

Investigations in the Nephrology Population

The supplementation of ESA therapy with intravenous iron has been standard in nephrology for more than a decade. A clear benefit in Hb and hematopoietic responses, independent of baseline iron stores, has been published in numerous papers.44-46 Three published studies in oncology provide nearly identical results in the CIA patient population.21-23 Nonetheless, there exists a clear resistance to intravenous iron use in oncology.

One prospective analysis set out to study the effects of multiple, slow injections of 100 mg of LMW iron dextran in repleting iron stores in a small sample of patients undergoing hemodialysis.43 This was followed by maintenance doses of either a 25- or 50-mg dose per week. Findings showed that LMW iron dextran rapidly repleted and maintained iron stores, thereby supplying accessible iron for improved erythropoiesis. After 6 months on protocol, ESA doses decreased an average of 3,100 U per patient, with an estimated cost savings of $5,070 per patient annually. No adverse effects, including anaphylaxis or hypersensitivity reactions, were observed in any of the patients. This report suggests the importance of sufficient iron stores and the possibility that repletion using iron dextran could delay the reinitiation of ESA therapy significantly.

Another study compared the efficacy of oral iron with that of LMW iron dextran in 52 ESA-treated patients undergoing hemodialysis who had initial serum ferritin of more than 100 ng/mL and TSAT of more than 15%.42 At study completion (4 months), patients randomized to receive LMW iron dextran (100 mg weekly) had significantly higher mean Hct levels compared with the oral iron group. This enhanced erythropoietic response, ostensibly a result of enhanced iron availability provided by intravenous iron, was accompanied by a 46% reduction in mean ESA dose in patients receiving LMW iron dextran, with resultant enormous cost savings. These findings suggest that similar benefits may be extended to patients with CIA. In these patients, the cost of ESA therapy in 2007 is estimated to be between $3,700 and $6,600 per patient per chemotherapy cycle, validating efforts to enhance the efficiency of ESA therapy.43

Despite having a well-established efficacy profile in patients with anemia of renal disease, iron dextran is not universally accepted in the oncology community because of concern for the development of life-threatening reactions. This apprehension can significantly contribute to the nationwide problem of patients with cancer who are treated with ESA being unable to achieve an adequate erythropoietic response. A review of the nephrology literature has demonstrated that serious adverse reactions associated with LMW iron dextran administration were not typical. One analysis of iron dextran administration in 573 patients on hemodialysis across 4 centers between July 1993 and July 1995 found that 0.7% of patients had a serious adverse reaction.44 In the largest retrospective review of patients on hemodialysis conducted to date, serious adverse reactions associated with LMW iron dextran were classified as low (3.3 per 1 million doses of 100 mg), whereas 11.3 per 1 million were associated with HMW iron dextran.37 Although serious adverse reactions have been associated with iron dextran, their occurrence is infrequent; nevertheless, clinicians are advised to have treatment of anaphylactic shock available during administration. A test dose is still recommended for both iron dextrans.

In a single clinical practice experience with more than 20,000 doses of LMW iron dextran, there were no observed serious adverse reactions, and the recommendation of a test dose did not alter the therapeutic plan.40 Furthermore, apprehension associated with iron dextran may be attributed to inappropriate treatment of reactions. Acute myalgias (chest and back tightness) without tachycardia, hypotension, wheezing, stridor, or periorbital edema subsequent to a test dose have occurred infrequently.46 This event subsided in minutes without treatment and does not return upon rechallenge.46 These reactions should not be treated with diphenhydramine or epinephrine, which have vasoactive reactions of their own that can be misconstrued as a serious acute event.40 Misinformation and misconceptions about the rate and clinical nature of serious adverse reactions can lead to the underuse of iron dextran or to a misguided use of oral iron preparations, which are relatively ineffective in enhancing the erythropoietic response.

Intravenous Iron vs Oral Iron

The route of iron administration can influence a patient’s response to ESA therapy. Clinical trials conducted in patients with anemia of renal disease have documented the ineffectiveness of oral iron supplementation in meeting the demands of accelerated erythropoiesis driven by ESA therapy.45,47 Additionally, oral iron requires a frequent dosing schedule and has been associated with a poor gastrointestinal side-effect profile—factors that lead to poor compliance.42,48 Furthermore, oral iron administration is limited by reduced absorption in the duodenum.31 In patients who are unable to efficiently absorb oral iron to compensate for daily iron losses, parenteral iron is an effective treatment option.40

The insufficient response to oral iron therapy demonstrated in the nephrology setting corresponds with findings in oncology and suggests that the use of oral iron be abandoned.21 According to the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN), the efficacy profile of intravenous iron is superior to that of oral iron. These guidelines fall short of recommending intravenous as the preferred route of iron administration in all patients with CIA and receiving ESAs.50

Intravenous iron dextran has many possible advantages compared with oral iron, and the decision to use iron dextran can involve the weighing of its potential advantages and disadvantages (Table). Comparative studies of oral versus intravenous administration of iron have established the superiority of intravenous iron therapy in improving response to ESA therapy in patients on hemodialysis.43 As a result, intravenous iron therapy, in combination with ESA treatment, is the standard of care in treating anemia in patients with renal failure.51

Call to Action: Using Iron Dextran to Enhance the Erythropoietic Response in Chemotherapy-Induced Anemia

The goal of managing anemia related to cancer chemotherapy is to slowly increase the Hb level to the recommended target of 12 g/dL, thereby improving QoL and reducing the need for blood transfusions.33 In order to facilitate this treatment process, clinicians should consider the following recommendations of the NCCN clinical practice guidelines: perform iron status testing (eg, measuring serum iron, total iron-binding capacity, and serum ferritin) before initiating ESA therapy to identify patients with absolute iron deficiency.50

Henry et al uncovered a surprising prevalence of iron deficiency while screening participants for enrollment in a study conducted in patients with CIA and anticipating ESA therapy.52
Of 261 patients screened for study participation, many were found to be iron-deficient, with 59% having a TSAT less than 20%, 17% having a serum ferritin less than 100 ng/mL, and 27% having a reticulocyte Hb content less than 32 pg. Interestingly, 56% of patients who had a TSAT less than 20% also had a serum ferritin of more than 100 ng/mL, indicating that clinicians should not rely solely on serum ferritin to assess iron status.

The use of serum ferritin is straightforward in the diagnosis of absolute iron deficiency, but this marker has limited value in detecting iron-restricted erythropoiesis in patients with chronic disease. Therefore, there are no available tests that reliably predict synergy with intravenous iron. Because the responses to intravenous iron in the 3 published studies were independent of serum ferritin and TSAT, a more comprehensive paradigm for intravenous iron use in oncology appears indicated. In conclusion, studies conducted to date have demonstrated that intravenous iron is relatively safe and effective in optimizing the erythropoietic response in ESA-treated patients with CIA. In clinical practice, however, intravenous iron treatment, in conjunction with ESA, for CIA has received inadequate attention. There is a need for additional research that will place intravenous iron in its proper perspective, as the preferred route of administration of iron in treatment of CIA and an important area of research in oncology.

### References


---

### TABLE. POTENTIAL ADVANTAGES AND DISADVANTAGES OF INTRAVENOUS IRON DEXTRAN VS ORAL IRON

<table>
<thead>
<tr>
<th></th>
<th>Intravenous Iron Dextran</th>
<th>Oral Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Provide more rapid Hb production in patients with severe anemia (Hb &lt;9 g/dL) and in patients with continuous bleeding</td>
<td>• Easy to administer</td>
</tr>
<tr>
<td></td>
<td>• Saturate tissue stores</td>
<td>• Relatively inexpensive</td>
</tr>
<tr>
<td></td>
<td>• Avoid GI intolerance</td>
<td>• Convenient</td>
</tr>
<tr>
<td></td>
<td>• Circumvent malabsorption</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Potential anaphylactoid reactions</td>
<td>• GI side effects</td>
</tr>
<tr>
<td></td>
<td>• Potential allergic reactions</td>
<td>• Low patient adherence</td>
</tr>
<tr>
<td></td>
<td>• Less convenient</td>
<td>• Poor enteral absorption</td>
</tr>
<tr>
<td></td>
<td>• Cannot provide iron rapidly enough to support erythropoiesis in ESA-treated patients</td>
<td></td>
</tr>
</tbody>
</table>

ESA, erythropoiesis-stimulating agent; GI, gastrointestinal; Hb, hemoglobin

Based on references 27, 38, and 49.


