The Role of Intravenous Iron in Cancer-Related Anemia

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Patients with cancer may have an absolute or functional iron deficiency as a result of their disease or its treatment. These conditions can lead to an insufficient supply of iron for incorporation into erythrocytes during supportive care with erythropoiesis-stimulating proteins for chemotherapy. The use of supplemental iron therapy is well established in patients with chronic kidney disease and anemia, but less well studied in the oncology/hematology setting. Furthermore, the use of oral iron formulations in patients with cancer and anemia is limited by poor absorption in the duodenum, arduous dosing requirements (three times a day), and a high likelihood of gastrointestinal side effects. Two recent studies have shown that intravenous (IV) iron (iron dextran or ferric gluconate) increases the hematopoietic response rates in cancer patients who were receiving chemotherapy and treated with epoetin alfa (Procrit) for anemia. The effects on hemoglobin levels and measures of iron metabolism were notably greater with IV iron formulations than with oral iron formulations. The results from several ongoing trials of IV iron in patients treated with epoetin alfa or darbepoetin alfa (Aranesp) for chemotherapy-induced anemia should lead to a greater understanding of the role of IV iron supplementation in improving the hematopoietic responses in these patients.

Anemia is a common complication of cancer and its treatment, and can be attributed to several factors, the most evident being the myelosuppressive effects of chemotherapy[1] and the immunosuppressive effects of chronic disease.[2] The anemia of chronic disease in cancer is mediated by the emergence of malignant cells that induce the expression of a variety of proinflammatory cytokines from immune cells. The consequences of this inflammatory state include insufficient production of erythropoietin by the kidneys, a blunted response to erythropoietin that leads to inhibition of erythropoiesis, impaired proliferation of erythroid progenitor cells, and dysregulation of iron homeostasis (reviewed by Weiss and Goodnough).[2] In addition, direct effects of chemotherapeutics, particularly platinum compounds, on the kidneys can also lead to a decrease in the production of erythropoietin. These factors all contribute to lower hemoglobin (Hgb) levels and, consequently, impair quality of life in patients with cancer receiving chemotherapy.

Current management of chemotherapy-induced anemia centers on therapeutic erythropoiesis-stimulating proteins (ESPs) such as recombinant human erythropoietin (epoetin alfa [Procrit]) and the novel long-acting ESP darbepoetin alfa (Aranesp). Epoetin alfa has been shown to increase Hgb levels in patients with cancer treated with chemotherapy, with associated reductions in the need for red blood cell transfusions and improvements in quality of life.[3-9] Likewise, darbepoetin alfa alleviates chemotherapy-induced anemia and improves quality of life in patients with cancer, with the additional benefit of making a reduced dosing schedule possible.[10-15] The responses to therapy with ESPs are inadequate, however, in approximately one-third of patients with cancer and anemia who undergo chemotherapy,[3-7,10-12] possibly owing to an insufficiency of iron for erythrocyte incorporation during the rapid induction of erythropoiesis stimulated by ESPs. Analysis of pretreatment laboratory values in patients who were being considered for treatment with epoetin alfa found that iron deficiency was a significant cause of their anemia, with 17% of patients having ferritin levels less than 100 ng/mL, 59% having transferrin saturation (TSAT) less than 20%, and 27% having content of reticulocyte Hgb less than 32 g/dL.[16] The use of supplemental iron is well established in patients with chronic kidney disease and anemia,[17] but its effectiveness in patients with cancer is less clear.

Dysregulation of Iron Metabolism in Anemia
Labile iron and iron stores are generally kept in dynamic equilibrium in the reticuloendothelial system. Developing erythrocytes in the bone marrow obtain iron from the pool of labile iron.[18] Anemia related to iron deficiency may result from a patient not having sufficient labile iron available for incorporation into erythrocytes despite having adequate iron stores (as in patients with anemia of chronic disease) or from a state of iron depletion within the iron stores (as in patients with an
TABLE 1

Serum Markers of Iron Homeostasis in Anemia of Chronic Disease and Absolute Iron Deficiency

A number of markers of iron homeostasis can be used to differentiate between anemia of chronic disease and absolute iron deficiency (Table 1).[2,19-21] In a population of patients with anemia of any cause, a serum ferritin level of 100 ng/mL or less was the most sensitive and specific marker of iron deficiency. Total iron-binding capacity and TSAT were less able to differentiate between iron deficiency and iron sufficiency.[19] Furthermore, because serum ferritin levels reflect the stored iron component and soluble transferrin receptor (sTfR) levels reflect the available iron component, the sTfR/log ferritin index makes it possible to differentiate iron deficiency into iron-depleted and iron-sufficient functional iron deficiency states. The correlation between this index and the hemoglobinization of red blood cells makes it possible to map the progression of iron deficiency.[20]

Iron Supplementation

The clinical practice guidelines of the National Comprehensive Cancer Network recommend iron supplementation in patients with cancer when the ferritin levels are less than 100 ng/mL and TSAT is less than 20%.[22] The guidelines of the American Society of Clinical Oncology and the American Society of Hematology are less specific, noting the paucity of evidence for using iron supplementation in cancer-related anemia.[23] Oral iron supplementation is often used in patients with iron deficiency, but its effectiveness in patients receiving ESPs for chemotherapy-induced anemia is limited in that it does not provide iron rapidly enough for ESP-induced erythropoiesis. Elevated levels of interleukin-6 and lipopolysaccharides as a consequence of inflammation lead to greater expression of the acute-phase protein hepcidin in the liver, which in turn decreases the intestinal absorption of iron.[24,25] To attempt to overcome this limited absorption, it may be necessary to give oral iron three times a day to produce sufficiently high serum levels, but this can be associated with adherence problems and gastrointestinal adverse effects and may still be ineffective because of inflammatory cytokines and hepcidin.

Parenteral iron may be an alternative to oral iron supplementation. Several intravenous (IV) formulations of iron have been developed: iron dextran, iron sucrose, and ferric gluconate (reviewed in Silverstein and Rogers).[26] Iron dextran has been available for use in the United States for several decades, and iron sucrose and ferric gluconate have been approved only in the past few years. Iron dextran has a half-life of 5 to 20 hours, and the patient's total dose can be given in one infusion (total dose infusion [TDI]).[27] However, delayed reactions of arthralgia, backache, chills, dizziness, fever, headache, myalgia, malaise, and nausea and vomiting have been associated with TDI; therefore, it is recommended that patients be given a test dose before the total dose is administered.[27]

Iron sucrose and ferric gluconate are more readily available for erythropoiesis than iron dextran.[26] Iron sucrose has a half-life of 5 to 6 hours and is transferred directly to both the reticuloendothelial system and transferrin,[28,29] while ferric gluconate has a half-life of approximately 1 hour and is transferred directly to the reticuloendothelial system, after which a bioactive form is released for binding to transferrin.[30] The rates of serious anaphylaxis hypersensitivity, hypersensitivity reactions, and adverse drug reactions are lower with iron sucrose and ferric gluconate than with iron dextran, and test doses are not required with these agents.[26]

Use of IV Iron in Patients Treated With Chemotherapy

Two recent open-label randomized controlled studies evaluated the effects of iron therapy and its optimal administration route in the oncology/hematology setting.[31,32] In the first study, 157 patients with a histologic diagnosis of cancer, Hgb levels of 10.5 g/dL or less, and serum ferritin levels of 200 ng/mL or less (or ≤ 300 ng/mL with a TSAT ≤ 19%) were randomized to no iron, oral iron (ferrous sulfate) 325 mg twice a day, iron dextran 100 mg IV bolus at each visit to the calculated dose for iron replacement (based on a desired Hgb level of 14 g/dL), or a TDI of iron dextran.[31] All patients were being treated with chemotherapy and with epoetin alfa 40,000 U once a week for their
anemia, with no dose adjustments permitted.

FIGURE 1

Hemoglobin Levels

After 6 weeks of therapy, there were significant increases in Hgb levels in all treatment groups in the intent-to-treat analysis ($P < .001$), with a clear greater benefit in the IV bolus and TDI groups (both $P < .05$ vs no iron and oral iron). Treatment group differences in Hgb response appeared to be independent of the pretreatment TSAT ($< 15\%$ vs $\geq 15\%$). Furthermore, there was a hematopoietic response (defined as an increase of $\geq 2\text{g/dL}$ in the Hgb level or an Hgb level $\geq 12\text{ g/dL}$ in the absence of red blood cell transfusions during the study) in significantly more patients treated with IV bolus or TDI iron than in those treated with no iron or oral iron ($P < .01$; Figure 1). There was also a trend toward a greater response in patients with a pretreatment ferritin level of less than 100 ng/mL than in those with a level of 100 ng/mL or higher.

Assessment of quality of life with the Linear Analog Scale Assessment showed improvements in energy, ability to perform daily activities, and overall quality of life in those treated with IV and TDI iron, no changes in those treated with oral iron, and decreases in those not treated with iron. Analysis of pooled data from all groups showed significant correlations between increases in Hgb levels and increases in energy ($r = .32; P < .001$), ability to perform daily activities ($r = .30; P < .001$), and overall quality of life ($r = .31; P < .001$). Seven possibly drug-related adverse events were reported (three each in the IV and TDI iron groups and one in the oral iron group), none of which necessitated discontinuation of treatment.

In the second study, 187 patients who were being treated with chemotherapy for nonmyeloid malignancies and who had Hgb levels less than 11 g/dL and serum ferritin levels greater than 100 ng/mL or TSAT greater than 15% were randomized to no iron, oral iron (ferrous sulfate) 325 mg three times a day, or IV ferric gluconate 125 mg once a week for 8 weeks.[32] All patients were treated with epoetin alfa 40,000 U once a week, with dose adjustments permitted after 4 weeks. In the assessable population ($n = 129$; intent-to-treat population with no protocol deviations who completed $\geq 7$ weeks of the study and were given $\geq 4$ doses of epoetin alfa and $\geq 7$ doses of ferric gluconate or $\geq 67\%$ oral iron), there was an increase in Hgb levels of 2 g/dL or more in significantly more patients treated with IV ferric gluconate (73%) than in those treated with oral iron (46%; $P < .01$) and those not treated with iron (41%; $P = .003$). This benefit was greatest in patients with a pretreatment TSAT less than 20%.

Furthermore, the improvements in Hgb and ferritin levels and reticulocyte Hgb content were greater in the patients treated with IV ferric gluconate than in those treated with oral iron or no iron (Table 2). The TSAT values decreased in all treatment groups, suggesting that the dose of iron may have been insufficient even in the IV group. Drug-related adverse events were reported in 19 (31%) of 61 patients in the oral iron group, 4 of whom discontinued treatment, and in 8 (13%) of 63 patients in the IV ferric gluconate group, 2 of whom withdrew from treatment.

The findings in these two studies clearly suggest that using IV iron therapy increases the hematopoietic responses to epoetin alfa in cancer patients with anemia who are receiving chemotherapy, possibly by increasing the iron supply available for epoetin alfa-stimulated erythropoiesis.

**Summary**

Functional iron deficiency as a consequence of the underlying inflammatory component of cancer may translate clinically into a diminished response to erythropoietic therapy in patients receiving chemotherapy. Data suggest that IV iron improves measures of hematopoiesis and iron metabolism in patients with cancer and anemia who are treated with chemotherapy and epoetin alfa. Several other studies of IV iron in cancer patients treated with epoetin alfa or darbepoetin alfa for chemotherapy-induced anemia are underway, and as both drugs act on the same receptor with the same mechanism of action, it is expected that the iron response will be similar for both drugs in...
these studies. The study results should aid in understanding the role of IV iron supplementation in improving hematopoietic responses and quality of life in patients with cancer. Questions remain to be answered about the monitoring, timing, and cost-effectiveness of iron supplementation, as well as the potential for the use of iron in lowering ESP dosing requirements.

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References:


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