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Iron Metabolism and Iron Supplementation in Anemia of Cancer

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Iron is an essential trace element important for hematopoiesis, oxygen transport and delivery, and other biologic functions. Iron uptake and utilization are strictly regulated but severely altered in anemia of chronic disease. In this condition, availability of iron for erythropoiesis is insufficient and a limiting factor for red blood cell production, in spite of normal or increased storage iron. Although concomitant oral iron supplementation is recommended in guidelines for treatment of cancer-associated anemia with erythropoietic agents, its efficacy is not documented. Recent studies evaluated the impact of parenteral iron supplementation in comparison with oral iron therapy and with control in anemic cancer patients treated with epoetin alfa or beta, or with darbepoetin. Concomitant treatment with parenteral iron proved superior to oral iron or no treatment. Hematologic response rates were higher, time to increase of hemoglobin was shorter, the need for red blood cell transfusions lower, and the quality of life better than in patients treated with oral or no iron at all. Severe side effects were rare and tolerance was remarkably good in most patients. However, information on long-term safety is not available as yet. Taken together, parenteral iron administration seems likely to evolve as an important adjunct to treatment with erythropoietic agents in patients with treatment-induced or chronic anemia of cancer. *Semin Hematol* 43(suppl 6):S13-S17 © 2006 Elsevier Inc. All rights reserved.

The human body contains 30 to 40 mg/kg iron, adding up to approximately 3 to 4 g iron per individual. Body iron is mostly contained in hemoglobin (~2.5 g), ferritin (1 g), myoglobin, and other heme proteins (~0.5 g). Only 3 mg is transported in plasma. Intestinal iron absorption is tightly regulated by four important proteins. The divalent iron transporter binds intestinal iron and incorporates it into the enterocytes. Ferroportin binds to and exports divalent iron into the circulation where it is taken up by the main iron transporter, transferrin. Finally, hepcidin, a recently described acute-phase protein, is the major regulator of iron absorption. Hepcidin is mainly synthesized in the liver and its production increases significantly during inflammation. Hepcidin interacts with membrane-bound ferroportin and leads to its internalization and degradation, thereby limiting the transport of iron into the circulation. Increased hepcidin levels result in significant reduction of iron absorption, decreased iron release from cells of the reticuloendothelial system, and an increase in storage iron. The normal daily dietary iron supply amounts to 10 to 15 mg, but only 1 to 2 mg are

actually absorbed and the same amount is lost by cells sequestered from the gastrointestinal tract and skin.

Formation of red blood cells depends on adequate formation of hemoglobin, which consists of two alpha and two beta globin subunits and four heme groups, each of which contains one atom of iron bound to protoporphyrin. Adequate iron supply, hence, is an important rate-limiting factor of erythropoiesis. Iron is mainly supplied via transferrin, which normally contains two atoms of trivalent iron. Transferrin saturation is significantly decreased (<20%) in iron deficiency and in functional iron deficiency, defined as a state with suboptimal iron supply to the erythron in spite of adequate body iron stores. Functional iron deficiency ensues in inflammatory diseases, infections, and chronic anemia of cancer when a cascade of inflammatory cytokines, as well as hepcidin, induces a major shift of circulating iron into the reticuloendothelial system and almost abolishes intestinal iron absorption, resulting in an inadequate iron supply to the proliferating erythroid compartment that finally results in anemia.

Iron Status in Patients With Anemia of Cancer

Patients with anemia of cancer usually present with normocytic, normochromic red blood cells with reduced serum iron (<60 µg/mL) and normal or increased serum ferritin

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Table 1 Main Features of Functional Iron Deficiency

Serum ferritin	>20 $\mu\text{g/L}$
Serum iron	<60 $\mu\text{g/dL}$
Transferrin saturation	<20%
Percentage of hypochromic red blood cells	>5%
Reticulocyte hemoglobin content	<26 pg
Soluble transferrin receptor	Normal
Erythrocyte protoporphyrin	>70 $\mu\text{g/dL}$

NOTE. Cutoff values may vary slightly depending on the test system used.

levels, reduced transferrin saturation (<20%), but normal or increased iron stores, and normal levels of circulating transferrin receptors. Other, usually not generally available, parameters include increased percentage of hypochromic red blood cells (>5%), increased erythrocyte protoporphyrin levels (>70 $\mu\text{g/dL}$), and decreased reticulocyte hemoglobin content (<26 pg) (Table 1). In these patients, inflammatory cytokines usually inhibit iron release from storage pools, leading to rapid depletion of the labile serum iron pool and hence to insufficient iron supply to proliferating red blood cell precursors. However, some cancer patients, particularly those with gastrointestinal blood loss, may present with true iron deficiency (serum iron <20 $\mu\text{g/dL}$, serum ferritin <15 $\mu\text{g/L}$, transferrin saturation <20%, empty iron stores, and increased circulating transferrin receptors >7 mg/L).¹ In patients with chronic inflammation, absolute iron deficiency may be associated with impaired iron utilization. Information on iron stores and parameters of iron metabolism in different types of anemia is given in Figure 1.

Iron Supplementation in Non-cancer Anemia

Iron supplementation is standard treatment in patients with absolute iron deficiency, and parenteral application results in faster replenishment of iron stores and increased erythropoiesis in patients with absolute or functional iron deficiency. The efficacy of this approach has been documented in patients with increased iron needs due to increased erythropoiesis^{2,3} and in patients with functional iron deficiency due to chronic inflammatory diseases such as rheumatoid arthritis⁴ and chronic inflammatory bowel disease.^{3,5} Besides the increase in circulating iron, inhibition of tumor necrosis factor (TNF) production by intravenous iron has been postulated as an important contributory factor.⁶

In renal anemia, parenteral iron therapy resulted in a rapid increase in hemoglobin levels, whereas oral iron supplementation remained without significant effect.⁷ These observations led to the incorporation of intravenous iron supplementation into the guidelines for treating anemia in renal diseases.⁸ Additional studies revealed a 40% reduction in erythropoietin doses in iron-supplemented patients compared to patients without iron therapy during maintenance therapy.⁷

Oral Iron Supplementation

Although supplementation with oral iron is recommended for patients with anemia of cancer and concomitant erythropoietin treatment in the guidelines issued by the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH),⁹ the National Comprehensive Cancer Network (NCCN),¹⁰ and the European Organisation for Research and Treatment of Cancer (EORTC),¹¹ evidence supporting the efficacy of such supplementation is scarce. The only published prospective randomized trial was a study that also evaluated the efficacy of parenteral iron substitution. The four-arm study showed no significant improvement with twice-daily 325 mg oral iron (ferrous sulfate) over no iron administration in erythropoietin-treated patients with chemotherapy-induced anemia.¹² However, the treatment duration was rather short for a meaningful comparison. Interestingly, the deterioration in certain parameters of quality of life and general activity observed in patients receiving no iron was not seen in patients receiving oral iron supplementation.

Parenteral Iron Supplementation

The hypothesis that unresponsiveness to initial erythropoietin treatment can be overcome by concomitant treatment with intravenous iron was recently tested by Katodritou et al¹³ in a small phase II study. The investigators treated 27 anemic patients with myeloma or lymphoma with erythropoietin (30,000 IU once weekly) and observed a hematologic response in 19 patients (70%). Subsequently, intravenous iron (iron sucrose 200 mg once weekly over 6 weeks) was given to the eight patients who did not respond to erythropoietin treatment alone. Six of the eight patients finally responded to combined therapy with erythropoietin and intravenous iron.

Henry et al¹⁴ conducted a larger prospective randomized trial in 187 patients with chemotherapy-induced anemia

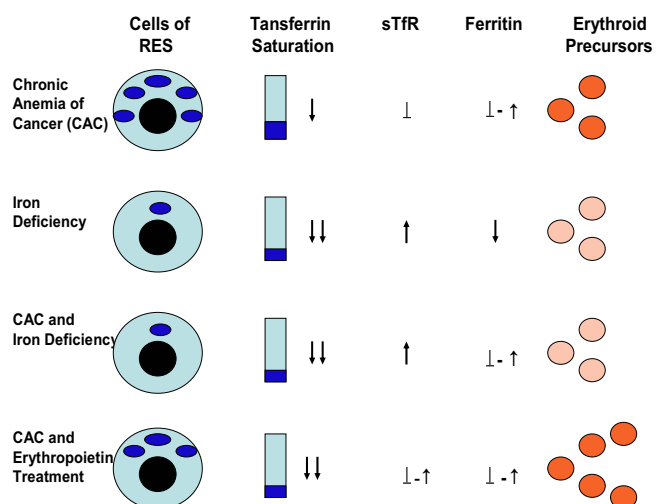


Figure 1 Parameters of iron metabolism and erythropoiesis in different types of anemia. Blue granula in RES cells denote iron deposits. RES, reticuloendothelial system; sTfR, soluble transferrin receptor.

treated with erythropoietin. Patients were randomized to either oral iron supplementation (ferrous sulfate 325 mg, twice daily), parenteral iron therapy (ferric gluconate, 125 mg/wk), or to an untreated control group. Intravenous iron in addition to erythropoietin led to a significantly higher response rate (73%) compared to oral iron (45%) or no iron at all (41%). Median increases in hemoglobin were 2.4 g/dL, 1.6 g/dL, and 1.5 g/dL in patients receiving intravenous, oral, or no iron supplementation, respectively. Furthermore, transferrin saturation fell by 13.7% in patients without iron supplementation but only by 2.7% and 1.8%, respectively, in those with oral or intravenous iron therapy.

The only hitherto fully published prospective randomized trial comparing intravenous iron with oral iron or no iron at all has been published by Auerbach et al.¹² The authors treated 157 anemic patients (hemoglobin <10.5 g/dL, serum ferritin \leq 450 nmol/mL, or \leq 675 nmol/mL and transferrin saturation \leq 19%) with solid tumors receiving erythropoietin therapy (40,000 IU/wk) concomitantly to standard chemotherapy. Patients were randomized to no additional iron, oral iron (iron sulfate 325 mg, twice daily), weekly parenteral iron (iron dextran 100 mg weekly), or single iron-dextran infusion with the calculated total iron demand according to the formula: $0.0442 \times (\text{target hemoglobin [14 g/dL]} - \text{observed hemoglobin}) \times \text{body weight} + (0.26 \times \text{body weight})$.¹⁵ After 6 weeks of treatment, hematologic responses were observed in 25%, 36%, 68%, and 68% of patients, respectively (Table 2). Mean increases in hemoglobin levels from baseline were 0.9 g/dL, 1.5 g/dL, 2.5 g/dL, and 2.4 g/dL for the non-iron, oral, intravenous bolus, and total-dose iron groups, respectively. Importantly, the hemoglobin response was found to be independent of the baseline transferrin saturation: no difference was seen between patients who had very low or only low (<15% or >15%) transferrin saturation, which indicates a benefit of iron supplementation even in patients with less

pronounced functional iron deficiency. In addition, a significant improvement in several parameters of quality of life (especially energy, activity and general quality of life) was observed in the latter two groups. Quality of life deteriorated in patients without any iron therapy and remained unchanged—with the exception of a minor increase in energy—in patients on oral iron.

Two other randomized studies comparing parenteral iron substitution with standard treatment in anemic patients treated with erythropoietic agents have only been presented at meetings as yet.^{16,17} Vandebroek et al.¹⁶ randomized 198 patients with non-myeloid cancers and treated with darbepoetin alfa every 3 weeks into a group treated with intravenous iron sucrose and a control group treated according to standard practice including oral iron substitution. The full analysis data set was available for 196 patients. Seventy-nine percent of the patients receiving intravenous iron achieved a hemoglobin level of \geq 11 g/dL, compared to 70.8% in the standard practice group. The median time to target hemoglobin (\geq 11 g/dL) was 34 days in the former and 43 days in the latter group. The higher response rate in the intravenous iron group was also reflected by the percentage of patients achieving a hemoglobin level of \geq 11g/dL between week 5 and the end of treatment: 79.8% of patients treated with intravenous iron achieved the target level compared to 65.3% on standard therapy. The requirement for transfusion until week 5 was almost halved in patients on intravenous iron (10.6% v 22.8%). Quality of life measured by a FACT-F (Functional Assessment of Cancer Therapy: Fatigue) score and by a FACT-G (Functional Assessment of Cancer Therapy: General) score was significantly better in the first 5 treatment weeks in the group receiving parenteral iron. The increases in the mean FACT-F and FACT-G scores were 3.1 versus 1.6 and 2.4 versus 0.94, respectively. Side effects were similar in

Table 2 Hematologic Response (increase of Hb \geq 2 g/dL, or achievement of Hb \geq 12 g/dL) in Erythropoietin-Treated Anemic Cancer Patients Randomized to Either Oral or Intravenous Iron Supplementation or to an Untreated Group

Authors	Erythropoietic Agent Dose	Untreated Control	Oral Iron Sulfate	Intravenous Iron, Once Weekly	Intravenous Iron, Total Dose Infusion
Henry et al (2004) ¹	Epoetin alfa 40,000 IU once weekly	41%	45%	73%*	
Auerbach et al (2004) ¹²	Epoetin alfa 40,000 IU once weekly	25%	36%	68%†	68%‡
Vandebroek et al (2006) ¹⁶	Darbepoetin alpha 500 μ g, every 3 weeks	70.8%§		79%	
Hedenus et al (2006) ¹⁷	Epoetin beta 30,000 IU once weekly	50%¶		79%¶	

Abbreviation: Hb, hemoglobin.

*Ferric gluconate 125 mg weekly over 8 weeks.

†Iron dextran 100 mg weekly over 6 weeks.

‡Calculated total dose of iron needed given as iron dextran in one infusion.

§Control group included patients with oral iron substitution.

||Hematologic response defined as achievement of Hb \geq 11 g/dL, 200 mg iron sucrose every 3 weeks or two doses (2 \times 100 mg) over a 3-week period.

¶Hematologic response defined as increase in Hb \geq 2 g/dL, iron sucrose 100 mg once weekly over 6 weeks.

the two groups and no specific adverse events related to parenteral iron substitution were noted.

Hedenus et al¹⁷ randomized 67 patients with indolent lymphoproliferative disease (non-Hodgkin's lymphoma: 19, chronic lymphocytic leukemia: 23, and multiple myeloma: 25) treated with epoetin beta 30,000 IU once weekly to a group receiving 100 mg iron sucrose once weekly (for 6 weeks) or to a control arm. Sixty patients remained on erythropoietin treatment for 16 weeks and, hence, completed the study. Three of them needed red blood cell transfusion during the study and were considered as failures but had been included in the intention-to-treat analysis. The patient group treated with epoetin plus intravenous iron achieved a significantly higher mean change in hemoglobin levels from baseline to the end of the study (2.76 v 1.56 g/dL, $P < .0002$). Significantly more patients achieved a hemoglobin response (increase in hemoglobin >2 g/dL) in a shorter time (79% v 50%, $P < .02$). Furthermore, a lower dose of erythropoietin was required in the group receiving intravenous iron ($P = .051$).

The side effects of parenteral iron therapy depend largely on the iron preparation used as well as on the dose and velocity of the injection or infusion but are usually less frequently observed with iron sucrose and ferric gluconate than with iron dextran. In the Auerbach study, side effects were noted in 7% of the 41 patients with single infusion of the total iron dose, and in 8% of the 37 patients with weekly infusions of iron dextran.¹² A significant side effect in terms of an anaphylactic reaction with flush, hypotension, emesis, and vomiting was noted in one patient after a test dose of iron dextran. Common side effects of intravenous iron reported in other studies included arthralgias, exanthemas, and increased body temperature. Oral iron supplementation is usually well tolerated but gastrointestinal side effects such as nausea, abdominal discomfort, and constipation are not uncommon and may necessitate discontinuation of treatment in some patients.

Treatment Considerations

Patients with anemia of cancer and absolute iron deficiency are candidates for intravenous iron therapy, particularly if severe symptoms of anemia demand for fast improvement. In anemic cancer patients with functional iron deficiency, there is increasing evidence for the benefits of intravenous iron substitution. In all studies in anemic cancer patients conducted so far, iron was given concomitantly to erythropoietin therapy, indicating the need for data on the efficacy of iron as sole therapy in this situation. Importantly, in the presently available studies, iron was given for very short periods only and information on long-term use is lacking. It is, however, questionable whether iron should be given over prolonged periods to patients with cancer. Iron has been identified as an important growth factor for microorganisms and tumor cells, and some authors consider the shift of circulating iron into iron stores as an important defense mechanism of the body against the aforementioned threats.¹⁸ In addition, free circulating iron results in the formation of hydroxyl radicals that are toxic to various tissues. An increase in cancer incidence

has been noted in patients with elevated serum or body iron,¹⁹ while no increase in cancer incidence has been reported in patients with continuous parenteral iron supplementation due to renal anemia.²⁰ In contrast, in patients on hemodialysis, treatment with iron sucrose resulted in reduced hospitalization and mortality.²⁰ Treating anemic patients with red blood cell transfusions is always associated with substantial iron supply, and perioperative use of allogeneic blood transfusions has been associated with increased risk of infections.²¹ One unit of red blood cells usually confers 200 mg of iron to the recipient. Nevertheless, the unresolved questions regarding the safety of long-term parenteral iron supplementation in patients with anemia of cancer illustrate the need for further studies evaluating the true benefit of long-term iron supplementation. However, short-term use of intravenous iron seems to be relatively safe, efficient, and cost-effective, and represents the only option in patients who do not tolerate oral iron therapy and in those with gastrointestinal deficiency in iron absorption. Intravenous iron in conjunction with erythropoietin should shorten the time to hematologic response, enhance response rate, spare doses of erythropoietin, and help to distinguish responders to erythropoietin from nonresponders.

Practical Considerations

Although formulas to calculate total body iron needs are available,¹⁵ it is still unclear whether the administration of the calculated total body iron need (2 to 3 g) in one infusion is really safe and represents the optimal approach for iron administration, particularly for the treatment of functional iron deficiency. For the time being, there are more arguments in favor of administering parenteral iron in weekly or at least adequately timed treatment intervals.

The major goal of treatment is of course to rapidly increase the hemoglobin concentration to the recommended target level of 12 to 13 g/dL,¹¹ and thereby to improve quality of life and reduce transfusion needs. In renal anemia the target levels of important parameters of iron metabolism have been defined as 25% to 40% for transferrin saturation, 200 to 500 $\mu\text{g/L}$ for serum ferritin and $<2.5\%$ for hypochromic red cells. High levels of circulating iron expressed by high transferrin saturation ($>50\%$) and high serum ferritin levels ($>1,000$ $\mu\text{g/L}$) are considered toxic and should therefore be avoided.²²

In anemia of cancer, adaptation of these practices seems plausible with the exception of the recommended target level of serum ferritin, which is often increased in patients with cancer without any correlation with body iron store because of its nature as an acute phase protein and nonspecific tumor marker as well.

The selection of the appropriate drug depends on local conditions. Presently, three major iron formulations, namely, iron sucrose, iron gluconate, and iron dextran, are available, both in the United States and in Europe, for intravenous supplementation therapy. The maximal dose for one infusion is ≤ 500 mg for iron sucrose, ≤ 125 mg for ferric gluconate, and less than 3,000 mg for iron dextran. The former two

formulations may even be administered by slow injection, but intravenous infusion may be preferable. Before administration of the planned dose of iron sucrose or iron dextran, a test dose should be given in order to assure adequate tolerance.

Conclusion

Evidence for the advantages of intravenous iron therapy concomitantly with erythropoietin treatment in patients with anemia of cancer is increasing. Although still not accepted as standard therapy, parenteral iron supplementation seems to shorten the time to hematologic response (hemoglobin ~12 g/dL), increase response rate, convert erythropoietin nonresponder to erythropoietin responder, and to reduce costs by limiting expensive erythropoietin therapy only to those patients who respond within few weeks to combined intravenous iron–erythropoietin therapy. It benefits not only patients with true iron deficiency but, importantly, also those with functional iron impairment induced either by chronic inflammation or by a highly increased demand for iron supply in patients with erythropoietin-stimulated erythropoiesis. However, the optimal use of intravenous iron preparations, the best treatment regimen, and treatment duration remain to be defined. Moreover, additional data on the safety of intravenous iron administration, particularly in patients with cancer, is needed.

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