Iron Deficiency Anemia in Cancer Patients

Mark Janis, MD

Attending Hematologist/Oncologist, Los Alamitos Hematology Oncology Medical Group, Los Alamitos, California, US

Abstract

Anemia is highly prevalent, affecting approximately 40 % of cancer patients, and results in a significant decrease in health-related quality of life while also being associated with shorter cancer survival times. A recent survey of 15,000 cancer patients in Europe found that 39 % were anemic at the time of enrolment. In addition, anemia is a recognized complication of myelosuppressive chemotherapy, and it has been estimated that, in the US, around 1.3 million cancer patients who are not anemic at the time of diagnosis will develop anemia during the course of their disease. The etiology of anemia in cancer patients is variable and often multifactorial, and may be the result of an absolute or a functional iron deficiency. Cancer produces an enhanced inflammatory state within the body—causing hepcidin levels to increase and erythropoietin production to decrease—and results in a reduction in erythropoiesis due to impaired iron transport. This type of anemia is known as functional iron deficiency, where the body has adequate iron stores but there are problems with mobilization and transport of the iron. Absolute iron deficiency is when both iron stores and iron transport are low. The National Comprehensive Cancer Network (NCCN) treatment guidelines for cancer-related anemia recommend intravenous (IV) iron products alone for iron repletion in cancer patients with absolute iron deficiency, and erythropoiesis-stimulating agents (ESAs) in combination with IV iron in cancer patients (currently undergoing palliative chemotherapy) with functional iron deficiency. Although IV iron has been demonstrated to enhance the hematopoietic response to ESA therapy, the use of supplemental iron has not yet been optimized in oncology. Here we discuss the significance of iron deficiency anemia in cancer patients and the need to implement tools to properly diagnose this condition, and we provide an overview of the management strategies and recommendations for patients with iron deficiency anemia as outlined in the NCCN guidelines.

Keywords

Anemia, functional iron deficiency, absolute iron deficiency, iron deficiency anemia, hepcidin, erythropoiesis, erythropoiesis-stimulating agents (ESAs), cancer-related anemia, National Comprehensive Cancer Network (NCCN) guidelines

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Correspondence: Mark Janis, MD, Suite 207, 3801 Katella Avenue, Los Alamitos, CA 90720, US. E: dinkylee@aol.com

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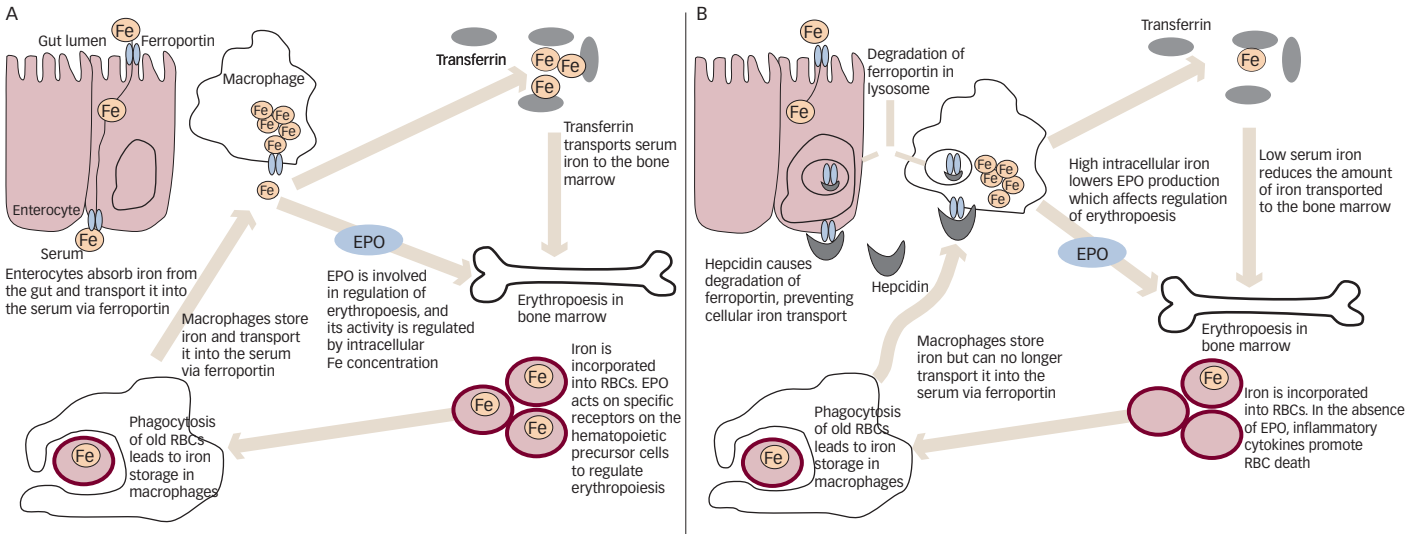
Anemia is defined by the World Health Organization as a hemoglobin (Hb) level <13 g/dl for men and <12 g/dl for women,[1] and can be further subcategorized into mild (>10 g/dl), moderate (8–10 g/dl), severe (6.5–8 g/dl), and life-threatening (<6.5 g/dl) ranges. Anemia is a common comorbidity in cancer patients. It is multifactorial, with causes including nutritional deficiencies of iron, folate, or vitamin B12; renal disease; bone marrow involvement; blood loss; effects of cancer therapies; inflammation or activation of the immune system; and autoimmune hemolysis. Signs and symptoms of anemia include weakness, fatigue, pallor, tachycardia, dizziness, shortness of breath, and cognitive impairment. Anemia is highly prevalent in cancer patients; in fact, the analysis of data from over 15,000 patients enrolled in the European cancer anemia survey (ECAS) showed that 39 % were anemic at the time of enrolment in the survey[2,3] and, in patients undergoing certain anticancer therapies or with particular types of cancer, this number can be as high as 90 %.[4] Other factors that affect the frequency of anemia in cancer include advanced age and comorbidities such as renal dysfunction.[5] It has been estimated that, of the approximately 10 million individuals in the US who have cancer, about 1.3 million who are not anemic at the time of diagnosis will develop anemia at some point during the course of their disease.[6]

In the previously mentioned ECAS study, cancer-related anemia was most frequently reported in patients with gynecological cancer (81.4 %), lung cancer (77 %), and lymphoma/myeloma (72.9 %).[2] In addition, this study indicated that the longer patients received chemotherapy, the higher their risk of becoming anemic. Anemia is also a recognized complication of myelosuppressive chemotherapy in cancer patients.

Figure 1: Iron Transport and Erythropoiesis in a Healthy Patient (A) and in a Patient with Functional Iron Deficiency (B)



EPO = erythropoietin; RBC = red blood cell.

Platinum-based chemotherapy regimens—such as those commonly used in lung, ovarian, and head and neck cancers—have combined kidney and bone marrow toxicity, and are well known as inducers of anemia.[7] The myelosuppressive effects of chemotherapeutic regimens accumulate during therapy, meaning that the rate of anemia in cancer patients increases with additional treatment cycles.[8] This cumulative effect has been documented in the ECAS survey, where the prevalence of anemia was shown to increase from 19.5 % in the first cycle of chemotherapy to 46.7 % after the fifth cycle.[2] Significant predictive factors for the risk of developing anemia following chemotherapy include having a lower initial Hb level prior to treatment; having lung or gynecologic cancer versus gastrointestinal (GI)/colorectal cancer; having cancer at any other site versus GI/colorectal cancer; and treatment with platinum-based chemotherapies.[9]

Pathophysiology of Cancer-related Anemia

Although causes of cancer-related anemia can include bone-marrow infiltration, hemolysis, nutritional deficiencies, blood loss, and renal, hepatic, or endocrine disorders, there are times when the cause of the anemia cannot be explained. Patients with cancer can develop anemia as a result of having a functional or an absolute iron deficiency.

Functional Iron Deficiency

Cancer promotes the production of inflammatory cytokines, such as interleukin-6, that subsequently suppress erythropoiesis and erythropoietin (EPO) production.[10] In response to these inflammatory cytokines, the hormone hepcidin induces degradation of the iron transport protein ferroportin.[5] This results in impaired iron transport, both from the GI tract and from reticuloendothelial cells (which acquire iron stores during the phagocytosis and breakdown of red blood cells [RBCs]), and leads to diminished access to iron for the circulating RBCs and their precursors, suppressing RBC proliferation. The bone marrow has a daily requirement of ~20–25 mg of iron for the synthesis of Hb for new RBCs, which is usually balanced by the removal of old RBCs by phagocytosis, resulting in a return to the macrophage iron stores of ~20–25 mg daily.[11] Ferroportin is a key player in iron recycling and is responsible for exporting intracellular iron stores from macrophages and enterocytes (see *Figure 1A)*. In the absence of ferroportin, iron recycling is severely affected. This leads to functional iron deficiency, where the body has adequate iron stores but they cannot be delivered to the bone marrow where they are needed, resulting in decreased erythropoiesis and in anemia (see *Figure 1B*).

A second mechanism in the development of anemia in cancer is a diminished response by endogenous EPO (eEPO) to specific levels of Hb, which is mediated by inflammatory cytokines. EPO is a hormone that acts on specific receptors on hematopoietic precursor cells to regulate erythropoiesis. The presence of inflammatory cytokines can impair the response of erythroid cells to EPO, as well as inhibiting proliferation and differentiation.[12] Hypoxia-inducible factor-1 alpha (HIF-1α) is the transcription factor responsible for EPO gene transcription, and its activity is regulated by intracellular iron concentrations.[10] In the absence of ferroportin, intracellular iron concentrations are increased, leading to reduced activity of HIF-1α and lowered transcription of EPO. *Figure 1B* summarizes the pathophysiology of anemia in cancer patients.

These factors, involved in the pathogenesis of anemia in cancer patients, are also seen frequently in the anemia of chronic conditions such as kidney disease.[13] As in cancer, the presence of chronic inflammation induces a state of functional iron deficiency.

Absolute Iron Deficiency Versus Functional Iron Deficiency

Absolute iron deficiency is defined by the National Comprehensive Cancer Network (NCCN) as a transferrin saturation (TSAT) value of <15 % and serum ferritin (which reflects iron stores) <30 ng/ml,[14] meaning that iron transfer and iron stores are low. TSAT is calculated by dividing serum iron by the total iron-binding capacity (TIBC). There are a number of reasons why cancer patients may develop absolute iron deficiency; poor bioavailability can result from dietary elements, and over the

counter medications or prescription drugs may chelate iron or interfere with iron absorption. Additionally, cancer patients may have increased iron loss due to bleeding from the GI tract or urogenital system. Although no universal definition exists, functional iron deficiency (also known as iron-restricted erythropoiesis) can be classified as a TSAT value of <20 %, but with normal or elevated serum ferritin (≥100 ng/ml); further, as discussed below, ferritin levels can be falsely elevated in cancer patients.[15] In functional iron deficiency, there are adequate iron stores in the body but there are problems with mobilization and transport of the iron and this in turn affects erythropoiesis.

Detrimental Effect of Cancer-related Anemia

Anemia is associated with shorter survival time in cancer patients.[16] In the ECAS survey, the level of anemia had a significant impact on performance status and, using the physician-reported WHO performance score, there was a significant correlation between decreasing Hb and worsening performance status.[2] A comprehensive literature review of the effects of anemia as an independent prognostic factor for survival determined that approximately 33 % of patients were diagnosed as anemic and in this patient population the median survival time was reduced by 20–43 %.[16] A 19 % greater risk of death was noted if a patient with lung carcinoma was also anemic. The relative risk of death was much higher in other cancer types: 75 % in head and neck carcinoma; 47 % in prostate carcinoma; and 67 % in lymphoma.

The reason for reduced survival time of cancer patients with anemia may be linked to the fact that anemia results in impaired tissue oxygenation, which in turn may promote tumor invasiveness and metastasis.[17,18] Hypoxia both induces changes in the transcription of genes involved in angiogenesis and selects for p53 mutations.[19] Mutations in p53 have been shown to increase genetic instability in tumor cells and allow them to escape cell cycle arrest. In addition, hypoxia is known to confer resistance to some radiation and chemotherapy regimens,[20,21] in turn leading to treatment failures.

Anemia has a significant adverse impact on the health-related quality of life (HRQoL) of cancer patients[22] and is associated with increased fatigue and the reduced ability to work productively.[23] In one patient survey, 12 % of cancer patients suffering from fatigue considered it so debilitating that they reported an urge to die.[24]

Testing for Anemia in Cancer Patients

The NCCN guidelines for the treatment of cancer-related anemia indicate that initial characterization should involve a complete blood count and peripheral blood smear in combination with a detailed history and physical exam. Morphologic examination of the average RBC size in conjunction with measuring the reticulocyte count is recommended. In addition, further testing should be completed to rule out common ailments such as vitamin B12 or folate deficiency, hemorrhage, hemolysis, renal causes, or inherited anemia. The mean corpuscular volume (MCV) and red blood cell distribution width (RDW) values may also be clues regarding the cause of anemia and the status of the iron stores.

Testing of serum ferritin, TIBC, and TSAT are all suggested to determine whether anemia is due to absolute or functional iron deficiency. Unfortunately, ferritin is an acute-phase reactant, meaning that concentrations increase during inflammation and malignancy, and therefore ferritin levels no longer reflect the body's iron stores. This makes interpreting ferritin levels during widespread infection, malignancy, or inflammation very difficult; however, concurrent measurement of C-reactive protein—another acute phase protein—can aid in interpreting the results. Normal ferritin concentrations can vary by age and gender, and elevated ferritin can occur during periods of acute malnutrition, such as in anorexia nervosa.[25] Several studies have evaluated the accuracy of serum ferritin and TSAT.[26–28] Serum ferritin was found to have a 35–41 % probability of accurately identifying iron deficiency compared with TSAT (59–88 %). These results suggest that, if serum ferritin is the sole diagnostic criterion employed, there could potentially be an underdiagnosis of iron deficiency.

Two further tests can be useful in determining iron availability. The reticulocyte Hb content (CHr) is a measure of the amount of Hb in the reticulocytes (i.e., RBCs that are just one or two days old) and is indicative of how much iron was available in bone marrow at the time of erythropoiesis.[15] Several studies have evaluated the use of CHr levels along with serum ferritin content and TSAT values in predicting the response to intravenous iron.[29–31] It was found that CHr was less variable and more accurate than serum ferritin or TSAT.[31] Measuring the percentage of hypochromic red blood cells (PHRC) is another test for the diagnosis of iron deficiency based on the Hb concentration in RBCs, which is derived by measuring the total Hb concentration while taking into account the size of the cell. Unfortunately, RBCs tend to expand during storage; so, while this method is comparable to CHr in terms of its utility,[28] if there is a significant time lag between sample collection and testing, this can affect the results of the test. Although both CHr and PHRC have good sensitivity and specificity, not all clinical laboratories have automated blood counters that can perform the measurements. In diagnostically challenging patients, a bone marrow biopsy may be helpful in determining iron stores.

Treatment Guidelines for Anemia in Cancer Patients

The NCCN guidelines for the treatment of cancer-related anemia indicate that clinicians should first define the etiology of anemia in the patient prior to treatment choice.[14] Decisions on treatment must be based on the individual patient, the severity of anemia, the presence of comorbidities, and the results of iron studies (as treatment recommendations differ depending on whether anemia is due to absolute or functional iron deficiency). The NCCN treatment guidelines recommend intravenous (IV) iron products alone for iron repletion in cancer patients with absolute iron deficiency. Synthetic recombinant human erythropoietin (commonly known as erythropoiesis-stimulating agent [ESA]) in addition to IV iron is recommended for cancer patients (currently undergoing palliative chemotherapy) with functional iron deficiency. Because ESAs have been associated with promoting tumor growth, they should not be used in patients where the anticipated treatment outcome is cure—e.g., in the chemotherapy of early-stage cancers. In addition, iron studies should also be regularly undertaken during ESA therapy to monitor the development of both functional and absolute iron deficiency.

RBC transfusions are recommended for patients with severe or high-risk anemia, or with certain comorbidities such as congestive heart failure or

chronic pulmonary disease, as they rapidly increase Hb levels. RBC transfusions are the fastest way to alleviate symptoms caused by anemia, but have associated risks, including transmission of infectious disease agents; transfusion reactions; iron overload due to repeat transfusions; possible fluid overload; and lastly the occurrence of alloimmunity.

Erythropoiesis-stimulating Agents

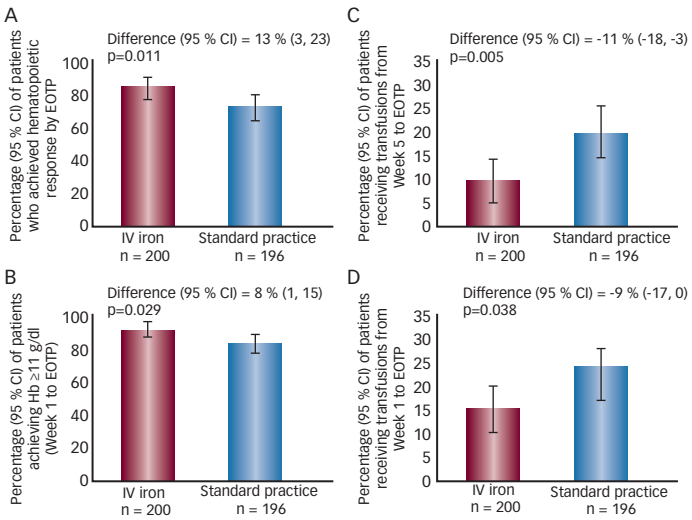
At present, three ESAs are available in the US: epoetin alfa, darbepoetin alfa, and peginesatide. Historically, ESAs were used more frequently in anemic cancer patients and were often administered at very high doses. However, several studies have reported a possibly decreased survival in cancer patients receiving ESAs,[32–36] and therefore physicians are advised to only administer ESAs to patients with cancer-related anemia during chemotherapy. There is conflicting evidence from five meta-analyses examining the mortality risk with the use of ESAs, with three studies indicating an increased risk[37–39] and two studies indicating no effect on mortality or disease progression.[40,41] In addition to possible decreased survival, thrombosis is also a potential adverse side effect of ESAs. The US Food and Drug Administration requires ESAs to be prescribed and used under a risk evaluation and mitigation strategy (REMS), and patients must be aware that ESAs may induce tumors to grow faster, may cause some patients to die sooner, and may promote the development of blood clots. The avoidance of transfusion is the main benefit of ESAs, and decreases in transfusion rates have been noted in randomized trials of patients with anemia receiving chemotherapy, in those treated with ESAs versus those receiving placebo.[42, 43] Unfortunately, it has been noted that 30–50 % of cancer patients with cancer-related anemia do not respond to ESAs.[42,44–47] Several trials have demonstrated that IV iron supplementation increases the patient response rate, suggesting that the lack of response to ESAs in these patients may be due to functional iron deficiency.[44,48–51]

Supplemental Iron

Oral iron is a simple way to supplement iron intake, however, it requires prolonged administration and is associated with poor and variable absorption, adverse effects such as GI disturbances, and poor patient adherence.[52] Currently available oral iron formulations include ferrous sulfate, ferrous fumarate, and ferrous gluconate. Newer preparations, such as carbonyl iron powder and polysaccharide–iron complex, are now available, but have not been tested in patients with cancer-related anemia. Oral iron is not recommended for functional iron deficiency, and evidence from several randomized studies utilizing supplemental iron in conjunction with an ESA suggests that oral iron is inferior to IV iron at improving hematopoiesis in patients with chemotherapy-induced anemia.[44,50,53] This observation is not surprising given what is known about hepcidin and the effect it has on absorption of iron from the gut.

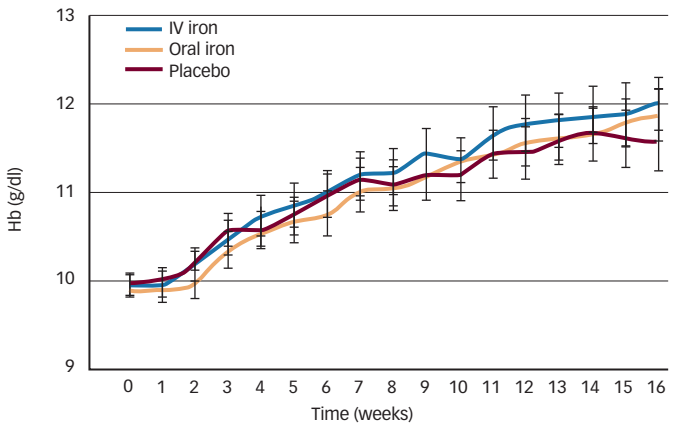
Five IV iron preparations are currently available in the US. They are high-molecular weight (HMW) iron dextran, low-molecular weight (LMW) iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol. All of these products consist of iron oxyhydroxide with a protective carbohydrate shell, which contains sugar polymers. Following injection, iron is slowly released from the complex into the circulation and becomes attached to plasma transferrin; this rate of dissolution varies between products.[54] All products are administered in low doses by a short IV infusion or injection. Ferumoxytol is unique because 510 mg can be administered in under a minute compared to the lower doses and multiple administrations required with the other agents. Currently, only the iron dextrans, which carry a boxed safety warning, are approved for the treatment iron deficiency in patients without chronic kidney disease.

Figure 2: Effect of Intravenous Iron on Hematopoietic Response



CI = confidence interval; EOTP = end-of-treatment phase; Hb = hemoglobin; IV = intravenous; RBC = red blood cell. A total of 396 patients with non-myeloid malignancies and Hb less than 11 g/dl were randomized to receive darbepoetin alfa 500 µg with IV iron ('IV iron' group, n=200) or without IV iron ('standard practice' group, n=196) once every three weeks for a total of 16 weeks. Kaplan–Meier methods, adjusting for randomization strata and treatment group, were used to calculate the proportion of patients achieving an endpoint. A: Kaplan–Meier proportion of patients achieving hematopoietic response (Hb ≥12 g/dl or an Hb increase from baseline of ≥2 g/dl). B: Kaplan–Meier proportion of patients achieving Hb ≥11 g/dl. C: Kaplan–Meier proportion of patients receiving an RBC transfusion between Week 5 and the EOTP. D: Kaplan–Meier proportion of patients receiving an RBC transfusion between Week 1 and the EOTP. Source: data from Bastit et al., 2008.[48]

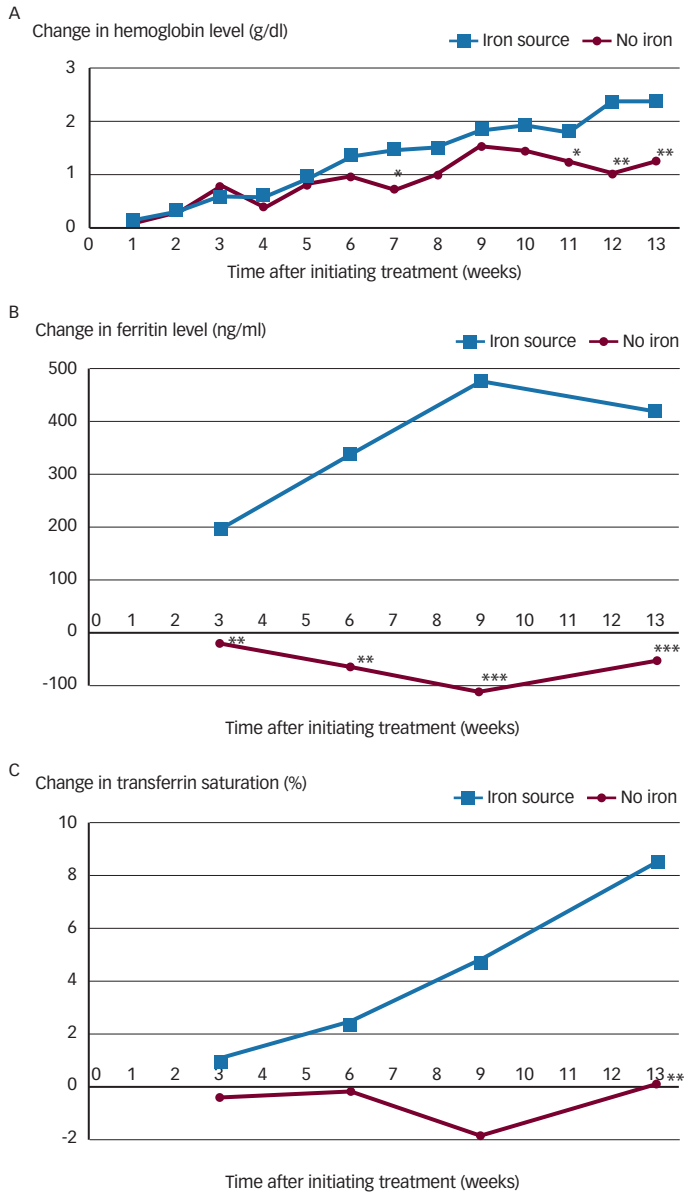
Figure 3: Mean Hemoglobin Week by Week for Intravenous Iron, Oral Iron, and Oral Placebo Cohorts of Patients Receiving Darbepoetin Alfa Treatment



No. at risk																	
IV iron	164	163	153	152	146	140	135	140	132	124	117	116	111	108	101	102	101
Oral iron	163	162	155	148	148	147	139	141	134	124	125	125	121	118	110	109	114
Placebo	163	162	156	157	151	144	143	142	131	128	115	115	113	112	105	102	98

Hb = hemoglobin; IV = intravenous. Source: data from Steensma et al., 2011.[57]

Figure 4: Hematopoietic Response Following Intravenous Iron Supplementation After Erythropoiesis-stimulating Agent Therapy—Change in Hemoglobin Level (A), Change in Ferritin Level (B), and Change in Transferrin Saturation (C)



** p<0.05; **p <0.01; *** p<0.001. Source: Lowell et al., 2011.[59] This figure was published in* Community Oncology *8: 270–8., Lowell B, Anthony MD, Nashat Y, et al., IV iron sucrose for cancer and/or chemotherapy-induced anemia in patients treated with erythropoiesis stimulating agents, Copyright Elsevier (2011).*

Clinical Studies Evaluating the Efficacy of Intravenous Iron in Cancer-related Anemia

Several studies have investigated whether the addition of supplemental iron to ESAs improves hematopoietic response in anemic cancer patients.[44,48–51,53,55–57] Bastit et al. investigated the response of patients with cancer-related anemia to darbepoetin alfa and whether anemia is improved with concomitant IV iron.[48] In this trial, a total of 396 patients were randomized to receive darbepoetin alfa 500 µg with (n=200) or without (n=196) IV iron once every three weeks for a total of 16 weeks. A significantly higher hematopoietic response (defined as patients achieving Hb ≥12 g/dl or an Hb increase of ≥2 g/dl) was noted in patients in the IV iron group (86 %) versus the group receiving darbepoetin alfa alone (73 %), and fewer RBC transfusions occurred in the IV iron group—9 % compared with 20 % in the darbepoetin alfa alone group (see *Figure 2*).

A similar Phase III trial enrolled 502 patients with Hb <11 g/dl undergoing chemotherapy for non-myeloid malignancies.[57] Patients received darbepoetin alfa once every three weeks and were randomly assigned to receive ferric gluconate (187.5 mg IV) every three weeks (n=167), oral daily ferrous sulfate (n=168), or oral placebo (n=167). No significant differences in erythropoietic response between patients receiving IV iron, oral iron, or no iron supplementation with darbepoetin alfa treatment were seen (see *Figure 3*), thereby calling into question the benefits of IV iron supplementation. The hematopoietic response rate was 69.5 % in the IV iron group, compared to 66.9 % in the oral iron group and 65.0 % in the placebo group; adverse events were more common in the IV iron arm (54 % of patients), compared with 44 % who received oral iron and 46 % who received placebo. It is unclear why the results of this trial conflict with those of several other trials that have demonstrated an increased patient response rate with the use of IV iron; however, there are differences in the dosing schedule that are worth noting. Although the cumulative IV iron dose was similar to other trials,[48–50] a total of 187.5 mg of IV iron was administered every three weeks. In comparison, in the study by Pedrazzoli et al., although the total cumulative IV iron dose administered was only 725 mg, the dose delivered weekly was 125 mg.[51] It has been suggested that the doses of IV iron may have been insufficient to show a positive result.[58] In addition, in the study by Steensma et al., the average TSAT of patients receiving IV iron was 22.5 %.[57] This is higher than the traditional definition for functional iron deficiency in the NCCN guidelines and may perhaps explain the lack of significant response to the IV iron.

Results of a Phase III randomized controlled study comparing IV iron sucrose to no IV iron treatment in patients who had previously been treated with ESAs demonstrated that IV iron alone may significantly impact hematopoietic response.[59,60] A total of 375 patients received fixed ESA doses for 12 weeks. The patients were then classified as responders or non-responders based on whether or not Hb levels had improved by 1 g/dl. For 12 weeks, responders and non-responders either received no IV iron, or were treated with 1,500 mg of IV iron sucrose (three doses of 500 mg). Interestingly, both responders and non-responders in the IV iron sucrose group had significantly greater Hb responses than patients who did not receive IV iron (see *Figure 4*).

A recent meta-analysis of eight trials[44,48–51,55–57] comparing IV iron, oral iron, or no iron when added to ESAs in anemic cancer patients found that IV iron reduces the rate of transfusions by 23 % and increases the chance of hematopoietic response by 29 % compared with ESAs alone.[53] In addition, the median time for obtaining a hematopoietic response was shortened by a month, which has both clinical and economic benefits.

Future Directions

Although new strategies and therapies for treating cancer-related anemia are being developed, it is also necessary to make better use of the products that are currently available. In a recent review by Glaspy, it

was suggested that oncologists employ three times the amount of ESAs to gain 50–60 % of the benefit in transfusion reduction achieved by nephrologists treating dialysis-associated anemia.[61] This difference may be due to the almost universal use of iron supplementation for nephrology patients taking ESAs.

A study by Kim et al. examined the effect of IV iron on the prevention of anemia in cervical cancer patients undergoing chemotherapy.[62] Although hematopoietic response was not measured, 64 % of patients in the control group required blood transfusions, while only 40 % of those treated with IV iron needed transfusions. Dangsuwan and Manchana saw a similar effect when evaluating the incidence of blood transfusions in anemic gynecologic patients taking either oral iron or receiving IV iron.[63] In their study, 22.7 % of patients receiving IV iron needed RBC transfusions, while 63.6 % of those taking oral iron required transfusions. Although additional data are needed to determine whether IV iron supplementation as a monotherapy can improve anemia, this therapeutic approach could potentially save on the costs, inconvenience and toxicities of ESA therapy, leading to better and more-cost-effective care. Future studies are needed to determine the optimal iron dosing requirements for achieving increased Hb (especially when IV iron is used in combination with ESAs). In addition, further questions must be answered. First, is IV iron alone capable of eliciting a hematopoietic response in cancer-related anemia patients? Second, more importantly, are there long-term toxicity effects associated with the use of IV iron? A Phase III randomized study of IV iron isomaltoside as monotherapy (without ESAs) compared with oral iron sulfate in subjects with non-myeloid malignancies associated with cancer-related anemia is currently ongoing and may begin to address these questions.[64]

Concluding Remarks

Anemia is a common comorbidity in cancer patients and has a significant adverse impact on HRQoL. Cancer-related anemia is associated with shorter survival times and may be due to impaired tissue oxygenation, which in turn promotes tumor invasiveness and metastasis. Both absolute and functional iron deficiency anemia occur in patients with cancer. Functional iron deficiency is common in cancer patients due to the fact that cancer produces an enhanced inflammatory state, leading to an increase in hepcidin levels and a decrease in EPO production. In this scenario, the body has adequate iron stores but they are unable to be delivered to the bone marrow where they are needed, resulting in decreased erythropoiesis and anemia. The NCCN treatment guidelines recommend IV iron products alone for iron repletion in cancer patients with absolute iron deficiency, and ESAs in combination with IV iron in patients (currently undergoing palliative chemotherapy) with functional iron deficiency. IV iron has an important role to play in the management of anemia and has been demonstrated to enhance the hematopoietic response to ESA therapy. However, the use of supplemental iron, although a comparatively inexpensive intervention, is not optimized in oncology; this may be due to a disinclination among physicians to use iron, or to a limited understanding of how IV iron can help in the management of cancer-related anemia. ■

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