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## S U P P L E M E N T

Iron replacement therapy in cancer-related  
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## Iron replacement therapy in cancer-related anemia

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Articles based on the proceedings of a symposium held March 24, 2010, during the Hematology/Oncology Pharmacy Association 6th Annual Conference in New Orleans, Louisiana, and supported by an educational grant from Watson Pharmaceuticals.

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# Iron replacement therapy in cancer-related anemia

## Introduction

DAVID BARIBEAULT AND MICHAEL AUERBACH

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Most patients with cancer will develop anemia during the course of their illness. Anemia, which is defined by the World Health Organization as a hemoglobin (Hb) concentration of <13 g/dL in men and <12 g/dL in women,<sup>1</sup> has been reported to occur in up to 90% of patients with cancer.<sup>2</sup> Although its incidence and severity in patients with cancer is dependent on the stage of cancer, the treatment regimen, and other factors,<sup>3</sup> the symptoms of anemia have been shown to affect overall function, quality of life, tolerance to treatment, and even survival.

The use of erythropoiesis-stimulating agents (ESAs) can increase hemoglobin levels, decrease the need for transfusions, and improve the quality of life of patients with chemotherapy-induced anemia. However, up to half of all patients who receive these drugs do not respond to treatment, typically due

to absolute or functional iron deficiency.<sup>4-8</sup> Functional iron deficiency occurs when iron is not released from iron stores or absorbed from nutritional sources quickly enough to meet the demands of erythropoiesis.

Numerous studies have shown that i.v. iron supplementation can improve outcomes in ESA-treated patients with cancer-related anemia.<sup>9-13</sup> Accumulating evidence prompted the National Comprehensive Cancer Network (NCCN) to recommend the use of i.v. iron supplementation in patients with functional iron deficiency due to its superior efficacy compared with that of oral iron.<sup>14</sup> Despite these recommendations and the evidence supporting its use, i.v. iron therapy remains underutilized in patients with cancer-related anemia,<sup>15</sup> partly due to misinformation and misinterpretation of the clinical nature of adverse events. Based on available published evidence, more

frequent use of i.v. iron in patients with absolute or functional iron deficiency is warranted.

This supplement will review the incidence and etiology of cancer-related anemia, as well as the most recent NCCN guidelines for its management. The current roles of i.v. and oral iron therapy in the treatment of cancer-related anemia will also be described.

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# Iron replacement therapy in cancer-related anemia

DAVID BARIBEAULT AND MICHAEL AUERBACH

In patients with cancer, the prevalence of anemia is between 30% and 90%, depending on the tumor type, stage of the disease, and definition of anemia.<sup>1</sup> In patients with lymphoma, lung cancer, and gynecologic or genitourinary tumors, the prevalence can be as high as 60%, and as high as 70% to 90% in patients receiving myelosuppressive chemotherapy or radiation therapy.<sup>2,3</sup>

Anemia is defined by the World Health Organization as a hemoglobin concentration of <13 g/dL in men and <12 g/dL in women.<sup>4</sup> A vast body of evidence has demonstrated that anemia is associated with symptoms that affect overall function, quality of life, tolerance to treatment, and survival in patients with cancer. Increasing age and the presence of comorbid conditions may also increase a patient's susceptibility to anemia and its complications.<sup>2,3,5</sup>

One of the most common and debilitating symptoms caused by cancer-related anemia is fatigue, which has a significant impact on the capacity for physical activity.<sup>6,7</sup> Fatigue is frequently associated with depression and possible reductions in cognitive function.<sup>6,7</sup> Evidence

**Purpose.** The incidence, etiology, and management of cancer-related anemia is reviewed and the role of i.v. iron therapy in its treatment is described.

**Summary.** Between 30% and 90% of patients with cancer develop anemia due to direct effects of the disease, its treatment, underlying nutritional deficiencies, and the inflammation that characterizes chronic disease. Although the use of erythropoiesis-stimulating agents (ESAs) increases hemoglobin levels and decreases the need for transfusions, up to 50% of patients do not respond to these drugs, usually due to the presence of absolute or functional iron deficiency. Multiple clinical trials have demonstrated that i.v. iron supplementation in patients with cancer-related anemia improves the response rate to ESAs, reduces the time to target hemoglobin levels, decreases ESA requirements, reduces costs, and is

more efficacious than oral iron. These benefits are seen without increased toxicity. Nonetheless, i.v. iron remains underused in patients with cancer, partly due to misinformation and misinterpretation of the clinical nature of adverse events.

**Conclusion.** Intravenous iron is underutilized in patients with cancer-related anemia. Based on published evidence, i.v. iron supplementation in patients with absolute or functional iron deficiency can improve patient responses to ESAs and reduce ESA requirements and may also reduce the need for transfusions and improve quality of life.

**Index terms:** Anemia; Blood; Drug administration; Hematopoietic agents; Injections; Iron preparations; National Comprehensive Cancer Network; Neoplasms; Protocols; Toxicity

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suggests that fatigue is the symptom that has the greatest effect on patients' everyday life.<sup>8</sup>

## Pathophysiology of anemia in cancer

Cancer-related anemia can be caused by blood loss, hemolysis, impaired production of red blood cells,

or a combination of these mechanisms (Table 1).<sup>1,2,6,9</sup> Blood loss can result from hemorrhage from the tumor itself (e.g., gastrointestinal, bladder, gynecologic), surgery, or even frequent venipunctures.<sup>2,6</sup> Perhaps most important, cancer and its treatments impair erythropoiesis. Erythropoiesis is controlled by

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interactions between the kidneys, which synthesize erythropoietin, and the bone marrow. Erythropoietin stimulates the proliferation and maturation of erythroid precursors in the bone marrow. Cancer can disturb erythrocyte production by directly affecting the bone marrow (e.g., infiltration of the tumor into the marrow), blunting the erythropoietin response, and reducing the synthesis and release of endogenous erythropoietin.<sup>2</sup> Chemotherapy and radiation cause myelosuppression.<sup>6</sup> Cancer and its treatment may also result in the development of nutritional deficiencies that can lead to the development of anemia.

Cancer-related anemia most closely resembles the anemia of chronic disease. In anemia of chronic disease, cytokines alter iron homeostasis, erythroid progenitor cell proliferation, and erythropoietin production, all of which contribute to its pathogenesis.<sup>10</sup> Proinflammatory states can affect erythropoiesis by stimulating the production of cytokines that can cause erythroid progenitor cell damage,<sup>10</sup> reduce erythropoietin production, inhibit the release of iron from iron stores, and decrease duodenal iron absorption.<sup>2</sup> The discovery of hepcidin, an iron regulatory peptide produced by the liver, has improved our understanding of anemia associated with cancer and other chronic inflammatory states.<sup>11,12</sup> Hepcidin inhibits iron transport across cell membranes, decreases available iron from iron stores, and reduces gastrointestinal absorption of dietary iron by inactivating the only known exporter of iron, ferroportin.<sup>13</sup> Hepcidin is upregulated in most chronic inflammatory conditions and cancer. Upregulation of hepcidin results in the sequestration of iron in macrophages, reduction of iron levels in plasma due to decreased absorption from the intestinal epithelium, and a restricted delivery of iron to erythroid marrow. The result is the development of iron-restricted

Table 1.  
Causes of Cancer-related Anemia<sup>1,2,6,9</sup>

Direct effects of disease
Bone marrow infiltration by malignant cells or fibrosis
Blunted erythropoietin response
Blood loss
Hemorrhage
Surgery
Phlebotomy
Effects of treatment
Myelosuppression by chemotherapy or radiotherapy
Hemolytic anemia
Nephrotoxicity
Thrombocytopenia or bleeding
Neutropenia or infection
Iron, folate, or vitamin B <sub>12</sub> deficiency
Inflammation or activation of the immune system, anemia of chronic disease
Autoimmune hemolysis

erythropoiesis, or functional iron deficiency.<sup>12,13</sup> Functional iron deficiency, a state in which iron is not released from iron stores or absorbed from nutritional sources quickly enough to meet the demands of erythropoiesis, is often observed in patients with cancer.<sup>12</sup>

#### Assessment of anemia and iron deficiency

Symptoms of anemia in patients with cancer include pallor, weakness, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness. These symptoms are not pathognomonic for anemia because they may also be seen with malignancy, its treatment, or both.<sup>13,14</sup>

According to the most recent update of the guidelines for managing cancer-induced and chemotherapy-induced anemia published by the National Comprehensive Cancer Network (NCCN),<sup>5</sup> patients with hemoglobin concentrations of  $\leq 11$  g/dL or concentrations that are  $\geq 2$  g/dL below their baseline level should undergo a complete blood count with iron indices and an evaluation of blood smear morphology.<sup>5</sup> The NCCN also recommends checking

the reticulocyte count and mean corpuscular volume. Stool guaiac tests and assessments of vitamin B<sub>12</sub> and folate levels are also recommended.<sup>2,5</sup> Causes of anemia that should be considered include hemorrhage, hemolysis, nutritional deficiency, renal causes, and radiation-induced myelosuppression, as well as anemia due to an inherited illness (Table 1).

#### Iron assessments in cancer

Functional iron deficiency in patients with cancer is characterized by hypoferrremia, normal or decreased transferrin concentrations, and a low transferrin saturation (TSAT) value in the presence of normal ferritin concentrations ( $\geq 100$  ng/mL).<sup>15</sup> Absolute iron deficiency, defined by the NCCN as a ferritin concentration of  $< 30$  ng/mL and TSAT value of  $< 15\%$ ,<sup>5</sup> limits the body's ability to produce hemoglobin because the iron values are inadequate for basal erythropoiesis. The most commonly ordered laboratory tests to determine the presence of absolute or functional iron deficiency include assessments of serum ferritin levels, a measure of iron stores; total iron-binding capacity (TIBC), an indirect measure of the amount of iron on

circulating transferrin, which is the plasma protein responsible for iron delivery; and TSAT, the ratio of serum iron and TIBC, which is the most reliable indicator of iron availability.<sup>2</sup> Unfortunately, ferritin acts as an acute-phase reactant and levels may be increased due to the physiologic changes associated with the growth of malignancies.<sup>12,16</sup> Therefore, in the absence of levels below the lower limit of normal, ferritin assessments are not reliable markers of iron stores in patients with cancer or other chronic diseases, and are of limited clinical utility.

### Treatment of chemotherapy-related anemia

Erythropoiesis-stimulating agents (ESAs), epoetin alfa and darbepoetin alfa, are recommended for the treatment of chemotherapy-induced anemia when chemotherapy is given for a noncurative intent.<sup>5</sup> This stipulation of ESA use is related to revisions in the Food and Drug Administration (FDA)-approved labeling of these drugs, based on the possible increased risk of tumor progression and shortened survival in patients with advanced breast, cervical, head and neck, lymphoid, and non-small-cell lung cancers. ESAs should continue to be considered in patients with cancer and moderate or severe chronic kidney disease, those undergoing palliative treatment, and those with anemia caused by myelosuppressive chemotherapy.

Approximately 30–50% of cancer patients with chemotherapy-related anemia do not achieve a meaningful response to ESAs (defined as a 2 g/dL increase in hemoglobin concentration or achieving a hemoglobin concentration of 12 g/dL without transfusion use), regardless of their baseline iron status.<sup>17–21</sup> Several trials have recently demonstrated that i.v. iron supplementation in patients receiving ESAs improves hemoglobin response rates in patients without absolute iron deficiency, confirming

that functional iron deficiency may be responsible for the suboptimal response to ESAs often seen in this population.<sup>22–24</sup>

### Management of iron deficiency in cancer

According to NCCN guidelines, iron supplementation is recommended in patients with ferritin concentrations of <30 ng/mL and TSAT values of <15% (absolute iron deficiency).<sup>5</sup> Intravenous iron supplementation should be considered in combination with ESAs in those patients with ferritin concentrations of ≤800 ng/mL and TSAT values of <20% (functional iron deficiency).<sup>5</sup> The guidelines state that neither i.v. nor oral iron supplementation is needed in patients with serum ferritin concentrations of >800 ng/mL or TSAT values of ≥20%.

Oral iron is poorly absorbed and is commonly associated with gastrointestinal adverse effects and poor rates of patient adherence.<sup>2,25</sup> Intravenous administration of iron reduces gastrointestinal adverse effects associated with oral iron supplementation and avoids problems with nonadherence to therapy.<sup>2</sup> More important, i.v. iron effectively replenishes iron stores and reduces ESA use.

The NCCN recommends the use of i.v. iron supplementation in patients with functional iron deficiency due to its superior efficacy compared to oral iron.<sup>5</sup> For patients without functional or absolute iron deficiency before the initiation of ESAs, the possibility that functional iron deficiency occurred during ESA therapy should be considered if hemoglobin levels do not increase after four weeks of therapy, and appropriate treatment administered.<sup>5</sup> For patients treated with ESAs who have functional iron deficiency, i.v. iron is recommended as first-line treatment.<sup>5</sup>

**Oral iron preparations.** Oral iron is a simple and convenient method of iron supplementation. Currently available oral iron formulations in-

clude ferrous sulfate, ferrous fumarate, and ferrous gluconate. Despite their simplicity, these products are associated with poor absorption, significant adverse effects, and suboptimal patient adherence.<sup>2,25,26</sup> For example, immediate-release oral iron products are taken three to four times daily and are often associated with gastrointestinal adverse effects, including abdominal pain, nausea, vomiting, and constipation, which can lead to nonadherence.<sup>2</sup> While reductions in gastrointestinal adverse effects have been observed with extended-release products, their use may result in decreased iron absorption.<sup>2</sup> Newer oral preparations, such as carbonyl iron powder and polysaccharide-iron complex, may overcome some of these obstacles but remain untested in patients with chemotherapy-induced anemia.

Oral iron products are not recommended in patients with functional iron deficiencies due to their lack of efficacy in this population,<sup>5</sup> and the discovery of hepcidin has shed light on the reason for this.<sup>11</sup> In a significant fraction of patients with cancer-related and chemotherapy-related anemia, increased levels of inflammatory cytokines cause an upregulation of hepcidin.<sup>15</sup> In such patients, orally administered iron is not sufficiently absorbed and therefore i.v. iron is recommended.

**Intravenous iron preparations.** Parenteral iron products currently available in the United States include high-molecular weight (HMW) iron dextran, low-molecular weight (LMW) iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol (Table 2).<sup>2,11,27</sup> The FDA-approved labeling for both iron dextran formulations includes indications for use in patients with chronic kidney disease and cancer, whereas the labeling for sodium ferric gluconate, ferumoxytol, and iron sucrose only include indications for use when chronic kidney disease is present.<sup>22</sup> Adverse reactions from i.v.

Table 2.  
Intravenous Iron Preparations<sup>2,11,27,a</sup>

Characteristic	LMW Iron Dextran	Iron Sucrose	Sodium Ferric Gluconate	Ferumoxytol	HMW Iron Dextran
Test dose required	Yes	No	No	No	Yes
Vial volume (mL)	2	5	5	17	1 to 2
Elemental iron conc. (mg/mL)	50	20	12.5	30	50
Boxed warning	Yes	No	No	No	Yes
TDI	Yes	No	No	No	Yes
Premedication	TDI only	No	No	No	TDI only
Preservative	None	None	Benzyl alcohol	None	None
Molecular weight measured by manufacturer (Da)	165,000	34,000–60,000	289,000–440,000	750,000	265,000

<sup>a</sup>LMW = low-molecular weight; HMW = high-molecular weight; TDI = total-dose infusion.

iron replacement therapy include hypotension, nausea, vomiting, diarrhea, pain, hypertension, dyspnea, pruritus, headache, and dizziness. These reactions have been reported with all the i.v. iron formulations.

### Comparative efficacy of oral and i.v. iron in patients receiving ESAs

The introduction of recombinant human erythropoietin (epoetin alfa) in 1989 revolutionized anemia management.<sup>28</sup> Because the efficacy of ESAs is blunted by both absolute and functional iron deficiency, the role of iron therapy in patients receiving ESAs has been carefully evaluated. As early as 1987, Eschbach et al.<sup>29</sup> demonstrated the clinical efficacy of i.v. iron dextran in patients with serum ferritin concentrations greater than 500 ng/mL undergoing hemodialysis who did not respond to standard dosages of epoetin alfa.

In 1995, Fishbane et al.<sup>30</sup> randomized patients undergoing dialysis and receiving epoetin alfa to receive iron dextran (100 mg administered as a two-minute i.v. bolus injection twice weekly during hemodialysis) or a continuous oral iron regimen (either ferrous sulfate 325 mg three times daily or polysaccharide-iron complex 150 mg twice daily) for the four-month study duration. At one month and at all subsequent time periods, patients receiving i.v. iron had

higher mean  $\pm$  S.D. hematocrit values ( $34.4\% \pm 0.7\%$ ) than patients receiving oral iron therapy ( $31.8\% \pm 0.4\%$ ) ( $p < 0.05$  at four months). Both serum ferritin levels and TSAT values were significantly higher in patients receiving i.v. iron than in those receiving oral iron at completion of the study. Additionally, the total dosage of epoetin alfa used was decreased by 46% in the i.v. iron group compared with those receiving oral iron. Subsequently, the National Kidney Foundation recommended the use of iron supplementation in patients with chronic kidney disease, with i.v. iron as the preferred intervention in hemodialysis patients.<sup>31</sup> Nearly all patients undergoing dialysis who receive an ESA also receive i.v. iron,<sup>28</sup> eliminating the need for transfusions in this population.

In patients with chemotherapy-induced anemia, i.v. iron has demonstrated superiority compared to oral iron in improving responses to ESAs.<sup>17,32</sup> In a randomized, open-label study comparing epoetin alfa with no iron, oral iron twice daily, or i.v. iron dextran, patients receiving i.v. iron had improved hemoglobin response and improved quality of life (based on scores using a visual linear analog self-assessment scale) compared to those in patients receiving oral iron or no iron.<sup>17</sup> Study participants ( $n = 157$ ) were randomized

into four treatment groups: no iron, ferrous sulfate 325 mg orally twice daily, iron dextran 100 mg i.v. by bolus injection at each visit until the calculated dosage for iron replacement was reached, or a total-dose infusion of iron dextran. After six weeks of therapy or completion of the treatment regimen by patients receiving iron dextran by i.v. bolus injection, hemoglobin levels increased in all groups ( $p < 0.001$ ), but greater increases were observed in those patients receiving i.v. iron dextran than in those receiving oral iron or no iron ( $p < 0.02$ ). Mean increases in hemoglobin concentrations were 0.9 g/dL, 1.5 g/dL, 2.5 g/dL, and 2.4 g/dL for the no iron, oral iron, i.v. bolus iron, and total-dose infusion iron groups, respectively. No significant difference in mean increase of hemoglobin levels was observed between the no iron group and oral iron group ( $p < 0.21$ ). Additionally, the proportion of patients who had a hematopoietic response was higher in the i.v. iron groups (68%) than in the no iron group (25%) and oral iron group (36%) ( $p < 0.01$ ).

Another open-label study compared the use of ESA therapy with no iron, sodium ferric gluconate (125 mg i.v. once weekly), or ferrous sulfate (325 mg orally three times daily) for 8 weeks in 187 patients with cancer-related anemia receiv-

ing ESA therapy.<sup>32</sup> Mean increases in hemoglobin concentrations were greater with i.v. sodium ferric gluconate (2.4 g/dL) than with oral iron (1.6 g/dL,  $p = 0.009$ ) or no iron (1.5 g/dL,  $p = 0.004$ ). Response rates were higher with i.v. iron (73%) than with oral iron (45%) ( $p = 0.01$ ) or no iron (41%) ( $p = 0.003$ ). In a subgroup of 50 patients with a baseline TSAT value of <20%, the response rate was 81% for the sodium ferric gluconate group, while the response rates for the oral iron group and no iron group were 37% ( $p = 0.0091$ ) and 27% ( $p = 0.0027$ ), respectively. In a subgroup of patients ( $n = 79$ ) with a baseline TSAT value of  $\geq 20\%$ , the response rate in patients receiving sodium ferric gluconate was 68%, while the response rates in patients receiving oral iron or no iron were 52% and 48%, respectively, but these differences were not significant. These data suggest that iron supplementation may be indicated in patients with absolute or functional iron deficiency undergoing stimulated erythropoiesis with ESAs.

### Intravenous iron in iron-replete patients

Hedenus and colleagues<sup>33</sup> enrolled 67 patients with lymphoproliferative malignancies and hemoglobin concentrations of 9–11 g/dL who were not receiving chemotherapy or blood transfusions and had positive hemosiderin stains on a bone marrow aspirate. Patients were randomized to subcutaneous epoetin beta (30,000 international units once weekly for 16 weeks) with or without i.v. iron sucrose supplementation. There was a significant difference in the mean change in hemoglobin concentration from baseline in patients receiving iron (2.76 g/dL) compared with those who did not receive iron (1.56 g/dL) ( $p = 0.0002$ ). Rates of treatment response, defined as an increase in hemoglobin concentration of  $\geq 2.0$  g/dL compared with baseline without transfusion, were

93% in the i.v. iron group and 53% in the group that did not receive iron ( $p = 0.0012$ ). In addition, in the per-protocol population, the median time to achieve a hemoglobin response was 6 weeks in the iron group compared with 12 weeks in the no iron group. After 15 weeks of therapy, the mean weekly epoetin beta dose was more than 10,000 international units lower ( $>25\%$ ) in patients receiving iron supplementation, which translated to a saving of \$100 per patient weekly, based on the value of the Swedish krona at the time of the publication.

Corroborating these findings, Pedrazzoli and colleagues<sup>23</sup> evaluated the use of darbepoetin alfa (150  $\mu\text{g}$  weekly) with or without i.v. sodium ferric gluconate in 149 patients without absolute or functional iron deficiency who were receiving chemotherapy for the treatment of solid tumors. To exclude patients with absolute or functional iron deficiency, patients with serum ferritin concentrations of <100 ng/mL and TSAT values of <20% were excluded from the trial. Darbepoetin alfa dosages were doubled at four weeks if the increase in hemoglobin concentration was  $\leq 1$  g/dL. Patients receiving i.v. iron had higher hematopoietic response rates (93%) compared to the control group (70%) ( $p = 0.0033$ ).

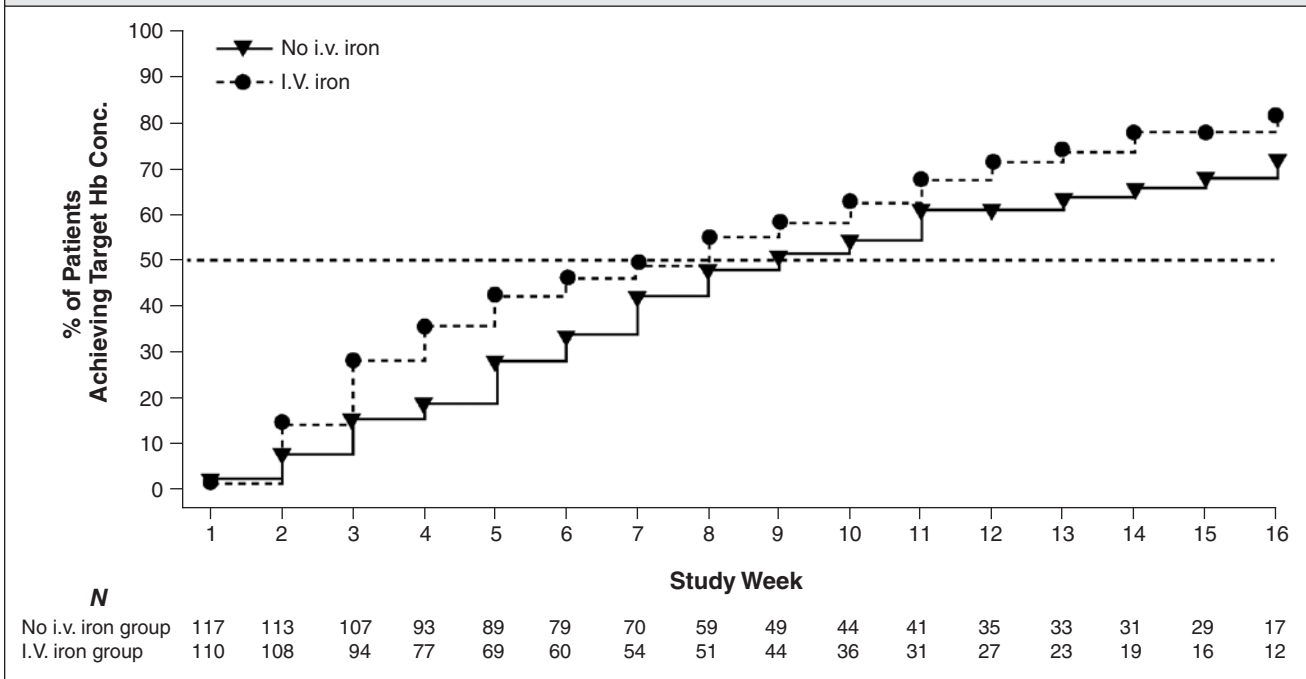
A Phase II, double-blind,  $2 \times 2$  factorial study evaluating the efficacy and safety of fixed-dose darbepoetin alfa (300  $\mu\text{g}$  or 500  $\mu\text{g}$  every three weeks) with or without open-label LMW iron dextran (administered as five 400-mg infusions over 30 minutes), reported similar findings.<sup>34</sup> Patients ( $n = 242$ ) included in the trial had nonmyeloid malignancies, hemoglobin concentrations of  $\leq 10$  g/dL, and no absolute iron deficiency. Because no evidence of a statistically significant interaction between ESA dosage and i.v. iron usage was observed, results were provided separately comparing ESA dosages and i.v. iron status. Although

target hemoglobin concentrations ( $\geq 11$  g/dL) were achieved by similar percentages of patients using either darbepoetin alfa dose (75% in the 300- $\mu\text{g}$  group and 78% in the 500- $\mu\text{g}$  group), more patients who received i.v. iron achieved target hemoglobin levels (82%; 95% confidence interval [CI], 73–90%) compared with those who did not receive i.v. iron (72%; 95% CI, 62–82%) (Figure 1). In an exploratory analysis, a slightly higher percentage of patients receiving 300  $\mu\text{g}$  darbepoetin alfa plus i.v. iron achieved target hemoglobin levels compared to those receiving 500  $\mu\text{g}$  of darbepoetin alfa alone. None of the studies were powered to detect a difference in transfusion rates.

However, another study was powered to detect differences in transfusion requirements. Bastit et al.<sup>24</sup> studied 396 patients with anemia (hemoglobin concentration of <11 g/dL) who were receiving chemotherapy for nonmyeloid malignancies. In this open-label study, patients were randomized to receive darbepoetin alfa (500  $\mu\text{g}$  once every 3 weeks) with i.v. iron (either as sodium ferric gluconate complex or iron sucrose) or standard care (no iron or oral iron) for 16 weeks. Hematopoietic response rates were higher in the i.v. iron group (86%) than in the standard care group (73%) (difference of 13%; 95% CI, 3–23%;  $p = 0.011$ ). More red blood cell transfusions were required in the standard care group (20%) compared with the i.v. iron group (9%) ( $p = 0.005$ ) (Figure 2).

These studies demonstrated that patients receiving i.v. iron had a greater hematopoietic response compared to those receiving oral iron.<sup>23,24,33,34</sup> However, Steensma et al.<sup>35</sup> reported that i.v. iron did not improve treatment response compared to oral supplementation or placebo in patients ( $n = 502$ ) with chemotherapy-associated anemia, hemoglobin concentrations of <11 g/dL, ferritin concentrations of >20 ng/mL, TSAT values of <60%, and

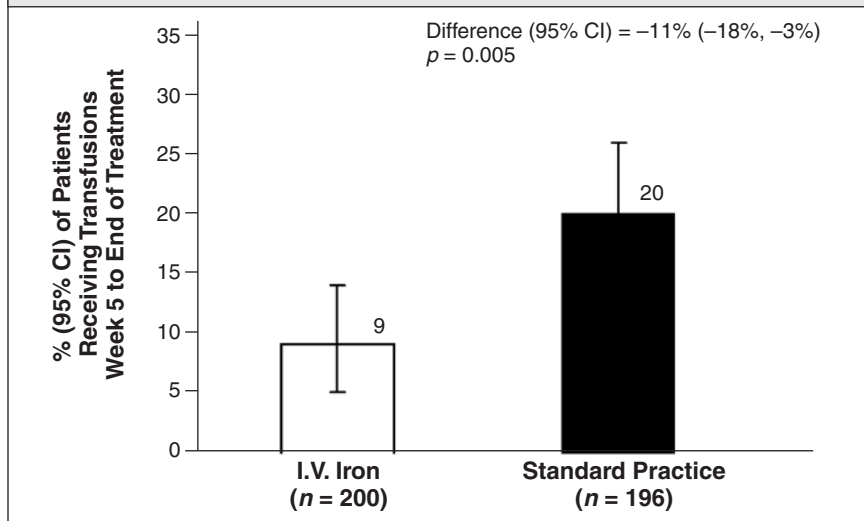
**Figure 1.** Kaplan-Meier time to target hemoglobin (Hb) levels ( $\geq 11$  g/dL) by i.v. iron usage. Reprinted from reference 34, with permission. Copyright © 2010 Wiley. All rights reserved.



a Zubrod performance score of  $>2$ . The study met an early stopping rule due to a perceived increase in combined grade 3 or higher adverse events in patients receiving i.v. iron (54% versus 44% in the oral iron group and 46% in the oral placebo group,  $p = 0.16$ ). Premedication with diphenhydramine was permitted at the discretion of the investigators, which may have been responsible for the perceived differences in reported adverse events. All principal outcomes were similar between groups, including hemoglobin response, changes in hemoglobin levels, improvements in quality of life, and transfusion requirements. It should be noted that the administered doses of i.v. iron were significantly lower (by approximately 400 mg) than in other published trials. No explanation for the less-than-planned dosing was provided in the paper.

Despite evidence supporting the use of i.v. iron, it remains underused in the oncology setting, particularly compared to its use among nephrol-

**Figure 2.** Kaplan-Meier proportion patients with chemotherapy-induced anemia who received transfusions during randomized, multicenter, controlled trial comparing the safety and efficacy of darbepoetin alfa administered every three weeks with or without i.v. iron.<sup>24</sup> Results are reported for patients enrolled in the study for at least 29 days. CI = confidence interval. Reprinted from reference 24, with permission. Copyright © 2008 American Society of Clinical Oncology. All rights reserved.



ogists. In a retrospective chart review of 50 patients with hemoglobin concentrations of  $<11$  g/dL who were receiving chemotherapy for a nonmy-

eloid malignancy, iron indices were measured in only 40% ( $n = 20$ ).<sup>36</sup> Fourteen of these 20 patients were candidates for iron supplementation.

Of 5 patients receiving a prescription for oral iron supplementation, 3 were considered candidates and 2 were not. Although this was a small, retrospective, single-center chart review, none of the patients received i.v. iron therapy.

**Safety of i.v. iron preparations**

Prior to 1992, HMW iron dextran (Imferon, Fisons, no longer marketed) was the only i.v. iron product available to treat iron deficiency in the United States.<sup>15</sup> In 1980, Hamstra et al.<sup>37</sup> reported the results of a pro-

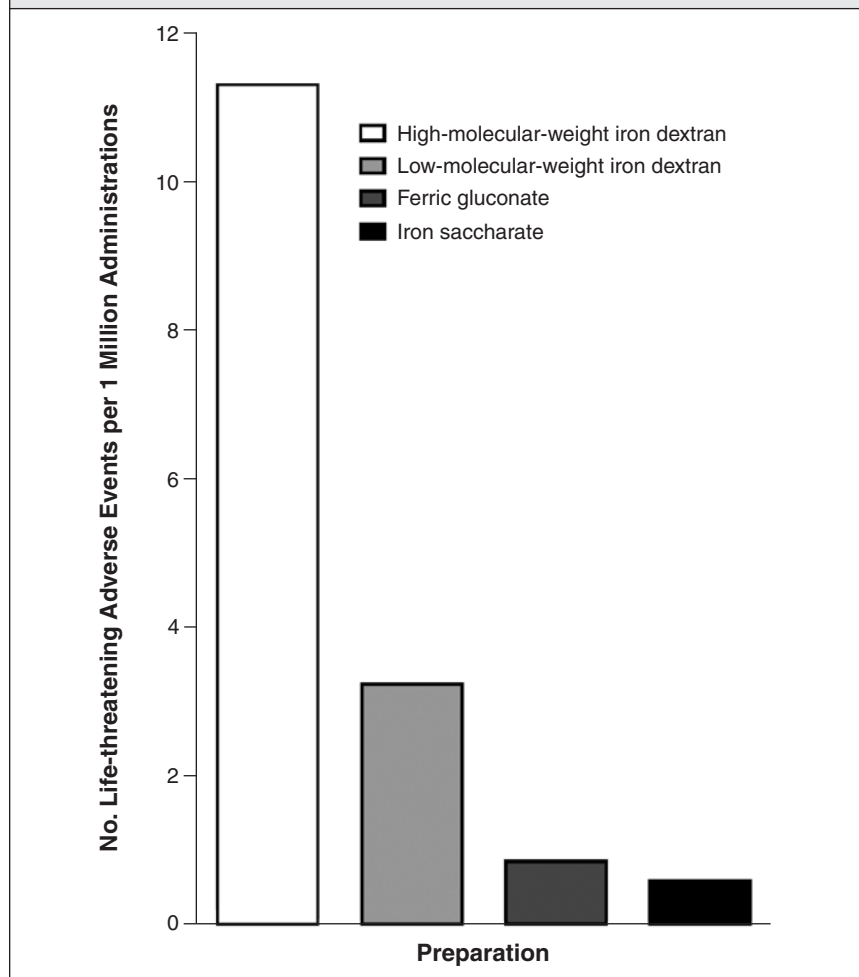
spective trial with i.v. iron dextran that included 471 patients. Whereas virtually all patients achieved clinical benefit, three serious acute and eight delayed adverse events occurred. All acute reactions were characterized as anaphylactoid. The authors concluded that i.v. iron should be reserved for those extreme clinical situations where oral iron was ineffective or poorly tolerated. In 1991, that iron dextran product (Imferon) became unavailable but, at the same time, LMW iron dextran (INFeD, Watson, Corona, CA) was marketed, and in

1996, a second HMW iron dextran (DexFerrum, American Regent, Shirley, NY) became available for use in patients undergoing dialysis and receiving ESAs.

In 1999 and 2000, two iron salts, sodium ferric gluconate (Ferrlecit, Sanofi-Aventis, Bridgewater, NJ) and iron sucrose (Venofer, American Regent) rapidly replaced iron dextran in the nephrology population, ostensibly due to increased safety.<sup>38,39</sup> An analysis of spontaneous reports of serious reactions to the iron dextran products and non-iron dextran products to FDA and European drug agencies found a significantly higher rate of reactions with the iron dextran products, as well as 31 deaths attributed to iron dextran and no deaths attributed to the other i.v. iron products.<sup>40</sup> Michael et al.<sup>38</sup> also found a low rate of reactions with sodium ferric gluconate in 2534 hemodialysis patients in a double-blind controlled study. Investigators then compared the observed rate to that of a historical control, obtained from a meta-analysis of four publications evaluating iron dextran. Compared to the historical control of patients who received iron dextran, sodium ferric gluconate was associated with a 93% risk reduction in life-threatening adverse reactions. These analyses did not attempt to differentiate the rate of reactions with HMW iron dextran compared with that of LMW iron dextran.<sup>15</sup>

However, analyses conducted by Chertow and colleagues<sup>41,42</sup> to evaluate FDA adverse drug event reporting data for reactions associated with all iron products indicated that HMW iron dextran products were involved in the majority of serious adverse events (Figure 3). These analyses included both currently available iron dextran products as well as the first iron dextran product (Imferon), which is no longer available. There were no significant differences in life-threatening or fatal serious adverse events when LMW iron dextran

**Figure 3.** Relative rates of reported serious adverse events with the four different parenteral iron preparations. From FDA Medwatch reports (2001–2003), Chertow et al.<sup>41,42</sup> reported that high-molecular-weight iron dextran was associated with a 3.2-fold increase in odds of an adverse drug event and a 3.4-fold increase in odds of a life-threatening event. Reprinted from reference 11, with permission. Copyright © 2007 Elsevier. All rights reserved.



was compared with sodium ferric gluconate and iron sucrose.<sup>42</sup> Of an estimated 30,063,800 doses of i.v. iron administered, the total number of iron-related adverse effects was 1,141 (approximately 38 per million doses).<sup>41</sup> When comparing LMW and HMW formulations of iron dextran, total and life-threatening adverse events were significantly more frequent with the use of HMW iron dextran than LMW iron dextran or non-dextran iron formulations. When excluding adverse events attributed to HMW iron dextran, the incidence of serious adverse events was less than 1 in 200,000 doses. However, Wysowski et al.<sup>43</sup> concluded that using the current mechanisms in place to evaluate risk, it is impossible to differentiate relative rates of adverse events between any of the i.v. iron products. Nonetheless, based on the preponderance of published evidence, albeit retrospective and observational, it appears prudent to use HMW iron dextran with caution.

Two subsequent studies and one meta-analysis prospectively compared the efficacy and safety of LMW iron dextran and iron sucrose, and found no differences in either efficacy or safety, but revealed cost and convenience advantages for LMW iron dextran.<sup>44-46</sup> These results conflict with those of previous reports of lower reaction rates to non-dextran iron based on historical controls.<sup>15,44-47</sup>

Nonetheless, serious acute adverse events with i.v. iron can be a concern. Although they occur infrequently, acute myalgias (specifically chest and back tightness) without tachycardia, hypotension, wheezing, stridor, or periorbital edema have been reported.<sup>11</sup> Patients who experience these symptoms are often mistakenly thought to be experiencing anaphylaxis. Acute myalgias resolve spontaneously, do not require treatment with antihistamines or pressors, and rarely recur with rechallenge.<sup>11</sup> Antihistamines can cause sedation

and vasoactive adverse effects (hypotension, flushing, and tachycardia), which may in turn be attributed to i.v. iron, resulting in inappropriate intervention and converting a harmless reaction to a more serious one.<sup>11,48</sup> Consequently, routine premedication is not recommended.

### Current status of i.v. iron in cancer care

Currently, the only i.v. iron product with FDA-approved labeling for use in oncology populations is iron dextran. Practitioners may avoid the use of any iron product for fear of serious adverse reactions. This fear may result in less-frequent use of i.v. iron in cancer-related anemia than in nephrology patients (Figure 4).<sup>49,50</sup> A recent review by Glaspy<sup>51</sup> suggested that oncologists use three times the amount of ESAs to achieve 50–60% of the benefit in transfusion reduction that is achieved by nephrologists treating dialysis-associated anemia. This marked difference in response rates is likely to be at least in part due to the near-universal use of iron supplementation in nephrology patients taking ESAs.<sup>28</sup> The National Kidney Foundation KDOQI guidelines suggest that chronic kidney disease patients undergoing dialysis be treated with iron and ESAs to reach a hemoglobin concentration between 11 and 12 g/dL,<sup>52</sup> while the Centers for Medicare and Medicaid Services (CMS) determined that ESA therapy should be discontinued in chemotherapy-induced anemia at 10 g/dL.<sup>53</sup> In 2007, after reviewing evidence on safety concerns related to ESA use, such as thrombosis, cardiovascular events, tumor progression, and reduced survival, CMS concluded that cancer-related anemia is no longer an indication for ESA use.

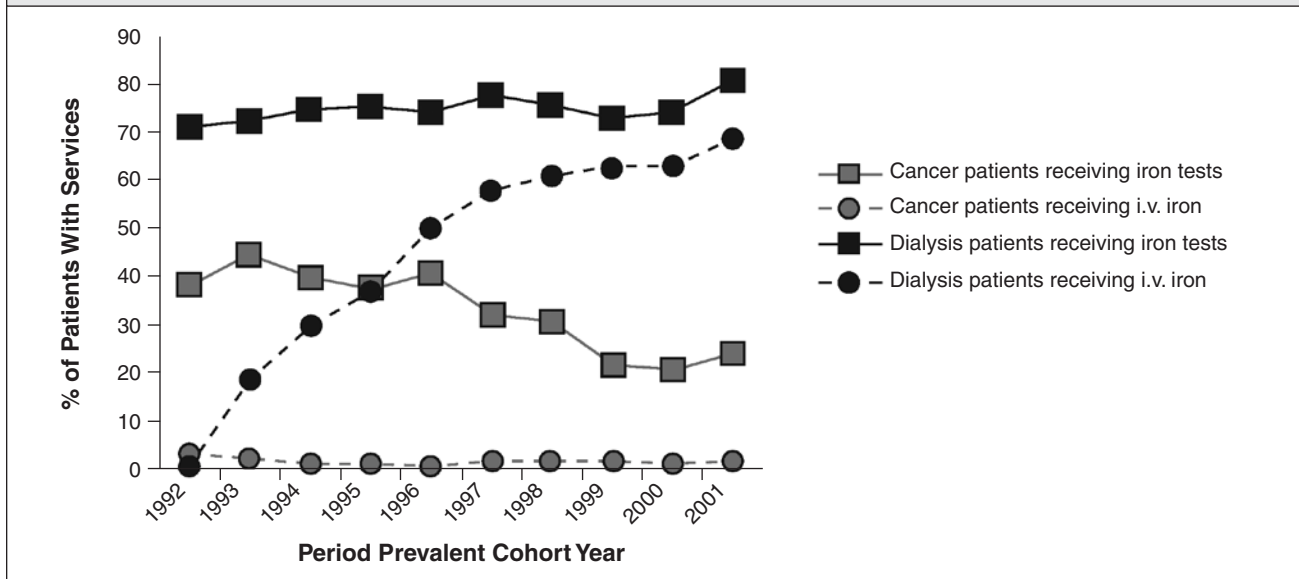
These recommendations are reflected in the 2010 NCCN guidelines for managing cancer-induced and chemotherapy-induced anemia,<sup>5</sup> and may have significant public health consequences. Vekeman et

al.<sup>54</sup> evaluated the potential impact of a reduction in ESA use for treating chemotherapy-induced anemia on blood supply. Results from this modeling simulation indicated that limiting ESA use in patients with chemotherapy-induced anemia would place considerable pressure on the U.S. blood supply. In fact, the model predicted that a 50–75% reduction in ESA use would prompt the use of 17–21% of the available 2008 marginal blood supply (the margin between blood screened and blood demand). Concerns regarding ESA use and morbidity and mortality have not yet prompted similar recommendations in patients on dialysis. In fact, research on the use of ESAs in dialysis patients has provided historical evidence that higher ESA dosing is responsible for increased morbidity and mortality in hemodialysis patients, even after adjustment for hematocrit values.<sup>55</sup> However, in all studies published, addition of parenteral iron has decreased quantities of ESAs necessary for therapeutic response.

### Emerging i.v. iron products

Ferumoxytol (Feraheme, AMAG, Lexington, MA) is a novel i.v. iron with labeling approved by FDA in June 2009 for use in chronic kidney disease patients with anemia. The carbohydrate-coated, superparamagnetic iron oxide nanoparticle formulation includes little free iron, allowing for large doses (510 mg) to be administered in as little as 17 seconds.<sup>56</sup> A second dose is required three to eight days following the first dose. Clinical trials have demonstrated the improved efficacy of ferumoxytol compared with oral iron therapy in patients with chronic kidney disease.<sup>57,58</sup> Adverse effects were similar to i.v. 0.9% sodium chloride injection and no cases of anaphylaxis were reported.<sup>56</sup> However, on November 29, 2010, an announcement from the manufacturer updated the product labeling to include bolded

**Figure 4.** Trends in iron testing and i.v. iron dosing in cancer patients receiving chemotherapy and an erythropoiesis-stimulating agent compared to patients on dialysis; estimates are based on a 5% sample of general Medicare patients.<sup>50</sup> Copyright © 2003. Reproduced with permission of the American Society of Hematology via the Copyright Clearance Center.



warnings and precautions that describe events that have been reported after administration in the post-marketing environment, including life-threatening hypersensitivity reactions and clinically significant hypotension.<sup>27,59</sup> Accompanying these warnings was a mandated increase in the observation period following administration from 30 minutes to 60 minutes to observe patients for signs and symptoms of hypersensitivity.

Iron carboxymaltose (Injectafer, Luitpold, Shirley, NY) and iron isomaltoside (MonoFer, Pharmacosmos A/S, Holbaek, Denmark) are currently in development in the United States and are marketed in Europe for the treatment of iron deficiency.<sup>28,60</sup> However, two years ago, FDA delayed approval of iron carboxymaltose due to concerns over observed hypophosphatemia at two weeks following administration and an imbalance in cardiovascular events and deaths in the treatment group compared with placebo. Further safety studies are currently under way.

**Conclusion**

Although i.v. iron is used almost

universally in patients with dialysis-associated anemia who are being treated with ESAs, its use in ESA-treated patients with cancer-related anemia is limited, despite evidence demonstrating improved outcomes in these patients. Studies of i.v. iron supplementation during ESA therapy continue to demonstrate benefits on hematopoietic responses, including improved hemoglobin levels, improved time to hemoglobin response, reduced ESA requirements, and reduced ESA costs, without significant toxicity. Intravenous iron may also reduce the need for transfusions.

A greater awareness of the benefits of i.v. iron use, as well as the relative safety differences among the available formulations, may result in a more widespread use of i.v. iron.

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■ SYMPOSIUM Iron replacement therapy

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## Iron replacement therapy in cancer-related anemia

Article 204-999-11-001-H01P

Knowledge-based activity

Qualifies for 1.5 hours (0.15 CEU) of continuing-education credit

### Learning objectives

After studying these articles, the reader should be able to

1. Summarize recent clinical findings that highlight the importance of treating iron deficiency.
2. Identify cancer patients who would benefit the most from iron replacement therapy.
3. Discuss current oral and i.v. iron replacement therapies for cancer-related anemia.
4. Discuss monitoring parameters and adverse effects associated with iron replacement therapy.

### Self-assessment questions

For each question there is only one best answer.

1. Anemia is defined by the World Health Organization as a hemoglobin concentration of
  - a. <13 g/dL in women, <12 g/dL in men.
  - b. <13 g/dL in men, <12 g/dL in women.
  - c. <12 g/dL in men, <12 g/dL in women.
  - d. <13 g/dL in men, <13 g/dL in women.
2. In patients with cancer, the prevalence of anemia is
  - a. 10–30%.
  - b. 20–60%.
  - c. 30–60%.
  - d. 30–90%.
3. Which of the following may contribute to cancer-related anemia?
  - a. Chemotherapy.
  - b. Radiation.
  - c. Nutritional deficiencies.
  - d. All of the above.
4. Cancer-related anemia can be caused by which of the following?
  - a. Blood loss.
  - b. Hemolysis.
  - c. Impaired production of red blood cells.
  - d. A combination of the above mechanisms.
5. Patients presenting with anemia may experience all of the following *except*
  - a. Fatigue.
  - b. Pallor.
  - c. Bradycardia.
  - d. Shortness of breath.
6. According to National Comprehensive Cancer Network (NCCN) treatment guidelines, patients with anemia and cancer should receive erythropoiesis-stimulating agents (ESAs) for only which of the following indications?
  - a. Chemotherapy-induced anemia where chemotherapy was given for a noncurative intent.
  - b. Significant blood loss.
  - c. Hemoglobin concentrations of <8 g/dL.
  - d. Metastatic breast, cervical, and head and neck cancers.
7. Which of the following tests is *not* a reliable indicator of iron stores in individuals with cancer?
  - a. Transferrin saturation (TSAT).
  - b. Serum ferritin.
  - c. Total iron-binding capacity (TIBC).
  - d. None of the above.
8. Absolute iron deficiency is characterized by all of the following *except*
  - a. Low serum ferritin concentration.
  - b. Low hemoglobin concentration.
  - c. Falsely elevated serum ferritin concentration.
  - d. Low TSAT value.
9. Functional iron deficiency is characterized by which of the following?
  - a. Hypoferremia.
  - b. Normal or decreased transferrin level.
  - c. Low TSAT value in the presence of normal ferritin levels.
  - d. All of the above.
10. Several trials have demonstrated that functional iron deficiency may be responsible for the suboptimal response to ESAs that often occurs in patients with cancer-related anemia.
  - a. True.
  - b. False.
11. For patients treated with ESAs with functional iron deficiency, the NCCN recommends oral iron supplementation as first-line treatment.
  - a. True.
  - b. False.
12. Which of the following formulations is *not* FDA-approved for managing cancer-related anemia in the absence of chronic kidney disease?
  - a. Low-molecular weight (LMW) iron dextran.

- b. Sodium ferric gluconate.
  - c. Iron sucrose.
  - d. B and C.
13. Intravenous iron administration in conjunction with ESAs
- a. Increases the risk of venous thromboembolism.
  - b. Decreases the risk of disease progression.
  - c. Increases ESA efficiency.
  - d. Does not improve outcomes.
14. In the clinical trials reviewed in this article, the addition of iron to ESA therapy demonstrated all of the following *except*
- a. More rapid improvement in hemoglobin levels.
  - b. Decreased need for blood transfusions.
  - c. Reduction in ESA dose required to produce response.
  - d. Increased total expenditures.
15. Which of the following i.v. iron preparations has been associated with the majority of reported serious adverse events?
- a. Sodium ferric gluconate.
  - b. Iron saccharate.
  - c. High-molecular weight (HMW) iron dextran.
  - d. LMW iron dextran.
16. Routine premedication with antihistamines
- a. Is routinely recommended.
  - b. May be associated with vasoactive adverse events, including flushing and tachycardia.
  - c. Increases the risk of anaphylaxis.
  - d. Improves hemoglobin response.
17. A recent analysis demonstrated that the rate of serious adverse events with parenteral iron, excluding those seen with HMW iron dextran, was approximately
- a. 1 in 100.
  - b. 1 in 1000.
  - c. 1 in 20,000.
  - d. 1 in 200,000.
18. How does ESA use differ between nephrologists and oncologists?
- a. Oncologists use 3 times the amount of ESAs as nephrologists.
  - b. Oncologists achieve 50% to 60% of the benefit in reducing transfusion requirements compared to nephrologists.

- c. Nephrologists practice near-universal iron supplementation with ESA use.
- d. All of the above.

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