Role of Iron in Optimizing Responses of Anemic Cancer Patients to Erythropoietin

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Approximately 50% of cancer patients develop anemia. In the past, the only available treatment option for these patients was transfusion. Since the late 1980s, recombinant human erythropoietin (rHuEPO, epoetin alfa) therapy has been proven to be a safe, effective option in addition to, or instead of, red blood cell transfusions for the treatment of cancer-related anemia. However, at rHuEPO doses of 150 to 300 U/kg three times per week, only about 50% of cancer patients fully respond to therapy.

Introduction

Anemia is the most common hematologic abnormality seen in cancer patients, occurring in approximately 50% of this population. The incidence of anemia is higher in patients with advanced forms of cancer and in those undergoing chemotherapy or radiation.

A nationwide survey of cancer patients found that fatigue, a common symptom of anemia, has profound effects on patients, including their ability to work, meet family needs, and cope with their disease. This survey also concluded that fatigue, not pain, is the most common complaint of cancer patients and the one that is most likely to disrupt their lives. In addition, studies have shown that cancer patients with anemia have a higher relapse rate and mortality than patients with a similar stage of cancer who are not anemic. Despite these sequelae and risk factors, cancer-related anemia is frequently overlooked or undertreated. Since the late 1980s, recombinant human erythropoietin (rHuEPO, epoetin alfa [Epogen, Procrit]) therapy has been proven to be a safe, effective option in addition to, or instead of, red blood cell transfusions for the treatment of cancer-related anemia. However, at rHuEPO doses of 150 to 300 U/kg three times per week, only about 50% of cancer patients fully respond to therapy. The use of rHuEPO in the chronic renal failure population is seen as the best-case scenario for rHuEPO therapy and functional iron deficiency has been found to be the most common cause of inadequate response to rHuEPO in this population.

Causes of Cancer-Related Anemia

The development of anemia in patients with cancer may be attributed to various causes, including the anemia of chronic disease; certain malignancies; chemotherapy and radiation; deficiencies of iron, folic acid, or vitamin B12; malnutrition; infection; inflammation; and blood loss or hemolysis. The most common mechanism for the induction of anemia in this population is insufficient bone marrow response to erythropoietin.

Anemia of Chronic Disease

Anemia of chronic disease is common and often accompanies chronic infections, inflammatory disorders, and malignancies. Because this type of anemia results from an underlying illness, correcting the illness will improve the anemia.

The anemia of chronic disease is occasionally a microcytic, hypochromic type of anemia but can be morphologically variable. Changes in iron metabolism also occur, sometimes reflected specifically in a decreased concentration of serum iron, a reduction in total iron-binding capacity (TIBC), and a below-normal transferrin saturation (TSAT). This type of anemia is believed to be mediated by
inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and gamma interferon,[14-16] which have a direct inhibitory effect on erythropoiesis and may also inhibit production of erythropoietin.[17,18]

**Cancer Treatments**

Radiation and some forms of chemotherapy can have a direct myelosuppressive effect on the bone marrow. Most chemotherapeutic agents suppress rapidly proliferating marrow cells, while certain drugs also directly impair the process of erythropoiesis.[19] For example, when administered over an extended period, cisplatin (Platinol) causes early, progressive dysfunction of renal tubules. Cisplatin-induced renal toxicity is most likely caused by decreased renal production of endogenous erythropoietin, which leads to inadequate production of red blood cells.[20]

Chemotherapy also can impair erythropoiesis over the long term through damage to the stem-cell pool. Stem-cell impairment has been noted as late as 5 years after breast cancer patients received adjuvant therapy with the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF).[21] This damage may last much longer in patients treated with more potent stem-cell toxins (eg, nitrosoureas or busulfan [Myleran]) or in those who have undergone radiotherapy to the marrow compartment or high-dose chemotherapy with stem-cell support.

**Underproduction of Erythropoietin**

Inadequate production of erythropoietin is associated with the anemia of cancer. In one study, investigators compared serum erythropoietin concentrations in 74 cancer patients with concentrations in 24 patients with uncomplicated iron-deficiency anemia.[22] None of the cancer patients had hypoxemia or kidney failure.

An inverse linear relationship between hemoglobin and serum erythropoietin concentrations was seen in patients with iron-deficiency anemia but not in those with cancer-related anemia. At any hemoglobin concentration, serum erythropoietin concentrations were lower in the cancer patients than in patients with iron-deficiency anemia. Among patients with cancer-related anemia, serum erythropoietin concentrations were lower in those receiving chemotherapy than in those who had never received chemotherapy or in those who had not received chemotherapy during the previous 6 weeks.[22]

**Diagnosing Anemia**

Irrespective of cause, anemia results from an imbalance between the production and destruction of red blood cells. The consequence is a reduction in the circulating red blood cell mass, which is reflected in changes in hemoglobin level and, less directly, in hematocrit level. Hemoglobin concentration is a primary parameter that is measured directly and for which there is a recognized international standard.

In the United States, it has become common practice to substitute the direct measure of hemoglobin for an indirect measure, hematocrit. Although the hematocrit level will generally reflect the hemoglobin concentration, the former is not measured directly, and its derivation depends entirely on the validity of the algorithm and counting mechanism of an automated cell counter. Since many different types of cell counters are available, they will not all give the same value for the hematocrit at a given hemoglobin concentration.

Although the hemoglobin level at which a patient is deemed anemic is not exact, it usually ranges from 11 to 12 g/dL. When the hemoglobin concentration is 10 g/dL, a diagnosis of anemia is unequivocal. Red blood cells may initially be normochromic and normocytic but will usually become microcytic (mean corpuscular volume [MCV] < 84 fL; mean corpuscular hemoglobin [MCH] < 27 pg). Patients who are anemic due to iron deficiency usually have a serum ferritin concentration of ≤12 µg/L, while patients with anemia due to malignancy usually have a serum ferritin concentration > 20 µg/L.

**Benefits of Treating Anemia**

Anemia can have a substantial negative impact on the quality of life of cancer patients.[23] Conversely, the correction of anemia can result in a dramatic improvement in quality of life, reflected by increased energy and improved ability to perform daily activities. Because of these potential benefits, intervention for the correction of anemia should not be neglected in this patient population.

Furthermore, reversal of cancer-related anemia may enhance the therapeutic response in patients receiving radiation therapy. Adequate oxygenation at the tumor site is necessary for an optimal response to radiation therapy, and, therefore, anemia may prevent a successful therapeutic response.
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outcome.[24] In fact, observations in cancer patients receiving radiation therapy have shown a reduced rate of survival in the presence of anemia.[2] Treatment with rHuEPO has been reported to raise hematocrit and hemoglobin levels in anemic cancer patients undergoing radiation therapy.[25-27] However, the impact of the correction of anemia on disease outcome following radiation therapy has yet to be evaluated in a controlled, randomized trial.

Treatment Options for Cancer-Related Anemia

Several therapeutic options exist for treating the anemia of cancer; these include transfusion, rHuEPO, and supplemental iron. The immediate goal of treatment is to restore the patient’s hemoglobin or hematocrit to an adequate level. Relief of symptoms, such as fatigue and weakness, and prevention of complications in patients with coexisting disease are less quantitative, but equally important, goals.

Red Blood Cell Transfusions

In the past, red blood cell transfusions were the only therapeutic option available for the management of anemia in cancer patients. By inducing a rapid rise in hemoglobin, red blood cell transfusions are able to correct anemia more quickly than any other existing treatment. However, transfusions are associated with risks of complications that may limit their appropriateness for anemia treatment. The most widely recognized drawback is the potential for transmission of infection. The risk of transmitting the human immunodeficiency virus (HIV) by transfusion has decreased, but other common pathogens can still be transmitted. Other potential complications include transfusion reactions and iron overload from multiple transfusions. Red blood cell transfusions also have a significant impact on health care costs.[28] Furthermore, transfusion may have a negative impact on prognosis in cancer patients. Shorter survival times and higher recurrence rates have been reported following transfusion in patients with soft-tissue sarcoma or cancers of the colon, rectum, or lung. These effects may be caused by transfusion-induced immunosuppression, but the negative outcome may reflect a selection bias for more advanced stage of malignancy, the need for more extensive surgery, or greater perioperative blood loss.[29]

Patients occasionally refuse red blood cell transfusions because of personal or religious beliefs. Jehovah’s Witnesses do not accept autologous blood donation and storage or transfusion of whole blood or the three principal blood components.[30] While red blood cell transfusions are indispensable in certain cases, finding alternatives to transfusion that do not share its inherent risks has distinct advantages.

Recombinant Human Erythropoietin

Recombinant human erythropoietin can serve as an adjunct or alternative to transfusion for the treatment of cancer-related anemia. In 1989, rHuEPO was approved for the management of anemia in dialysis patients with chronic renal failure. Erythropoietin deficiency[31] and the absence of the usual inverse linear relationship between hemoglobin values and erythropoietin levels[19] were noted in chronic renal failure patients, suggesting the potential of exogenous erythropoietin to correct anemia in these patients. Clinical trials demonstrated that rHuEPO could correct anemia[32] and improve quality of life.[33]

The anemia of cancer is often associated with decreased erythropoietin levels and the lack of an inverse relationship between hemoglobin and erythropoietin levels,[22] which led to the investigational use of rHuEPO for the treatment of cancer-related anemia. Several clinical trials in cancer patients have found that rHuEPO therapy corrects anemia, increases hematocrit levels, and reduces the number of transfusions needed; also, in responding patients, rHuEPO treatment is associated with an improvement in quality of life.[8,23,24,34-36] The results of the major studies of rHuEPO in the oncology population are summarized in Table 1.

To assess the effectiveness of rHuEPO in treating cancer-related anemia in the community oncology setting, Glaspy and colleagues conducted a phase IV, open-label study. More than 500 community-based oncologists enrolled 2,342 cancer patients receiving cytotoxic chemotherapy. Patients were treated with rHuEPO (150 to 300 U/kg) administered subcutaneously three times per week for 4 months. Treatment with rHuEPO produced a significant increase in mean hemoglobin and a decrease in transfusion requirements, and was associated with significant increases in mean self-rated scores for energy level, activity level, and overall quality of life. The degree of improvement in each of these quality-of-life parameters correlated significantly with the increase in hemoglobin (Figure 1) and was unrelated to tumor response.[23]
The results of this study have been confirmed in a second phase IV study.[37] A similarly designed study in dialysis patients reported comparable findings.[38] Glaspy et al developed an algorithm for treating patient treated with cancer chemotherapy who develops anemia (Figure 2). The algorithm recommends that iron stores be assessed before and during rHuEPO therapy since almost all patients will eventually need iron supplementation to support rHuEPO-stimulated erythropoiesis.[23]

**Predicting rHuEPO Response**

Clinical trials have shown that many cancer patients do not respond to rHuEPO therapy with a significant increase in hemoglobin and/or a decrease in transfusion requirements. Treatment results may vary depending on the type of malignancy, disease stage, and patient's condition. The ability to predict responsiveness to rHuEPO would make this therapy more cost-effective by allowing clinicians to select the best candidates for therapy or to discontinue treatment early in nonresponders.[39] Although baseline characteristics seem to be of little value in predicting rHuEPO responsiveness,[39,40] certain changes in the early phase of therapy may be helpful. Approximately 4 to 5 weeks after rHuEPO therapy begins (the point at which most patients start to respond), the clinician should evaluate certain parameters to establish the patient's response.[19] In responding patients, transfusion requirements (if present) should decline and the hematocrit level should increase. In addition, a rise in the reticulocyte count of ≥ 40 × 10⁹/L after 1 month of rHuEPO therapy may significantly predict which patients will respond.[41,42]

Serum levels of erythropoietin and ferritin are also predictive of rHuEPO response. For example, cancer patients whose baseline erythropoietin levels are < 100 mU/mL are likely to respond to therapy. However, response is variable in patients with erythropoietin levels between 100 and 300 mU/mL and is unlikely in those with erythropoietin levels > 300 mU/mL. Although cancer patients with baseline serum ferritin levels < 400 ng/mL will probably respond to rHuEPO therapy, those with baseline ferritin levels > 400 ng/mL may not respond.[34,39,41] An algorithm to help predict response or resistance to rHuEPO in the anemic cancer patient is shown in Figure 3.

There are many causes of rHuEPO resistance in chronic renal failure patients, the most important being insufficient iron available for erythropoiesis.[10,12] The prevalence of iron deficiency in hemodialysis patients treated with rHuEPO has been estimated at 43% to 74%.[43-46] Therefore, careful monitoring of iron stores and treatment of iron deficiency are essential for optimizing rHuEPO therapy.

**Effect of rHuEPO Therapy on Iron Metabolism**

Experience with rHuEPO therapy in chronic renal failure patients[32,43,44,47] suggests that inadequate availability of iron may explain the lack of response to rHuEPO in at least some patients with cancer-related anemia. Treatment with rHuEPO places extreme demands on the erythropoietic system, and the rise in hemoglobin may be limited by the rate at which iron can be supplied to the erythrocyte precursors in the bone marrow.[48] In normal erythropoiesis, there is a steady production of red blood cells. However, when patients receive rHuEPO therapy, the rate of erythropoiesis increases two- to threefold.[31,32] These sudden bursts of erythropoietic activity induced by rHuEPO therapy cause iron to be swiftly mobilized from the reticuloendothelial cells to the erythroid marrow. As a result, patients develop absolute iron deficiency, which is characterized by both depleted iron stores and impaired iron delivery to the erythroid marrow.

A review of normal iron physiology and metabolism may be helpful in understanding the role of iron in erythropoiesis, especially in erythropoiesis stimulated by rHuEPO. In normal subjects, body iron is carefully conserved in a tightly balanced system, and iron moves back and forth from iron stores to red blood cell mass, with little day-to-day variation.

The usual total body iron content in humans is about 4 g. Approximately 3 g are contained in circulating red blood cells as hemoglobin, and 1 g is stored in reticuloendothelial cells. A very small amount of iron (only about 4 mg) is bound to transferrin, which is the circulating iron transport protein that carries iron between red blood cells and reticuloendothelial iron stores. Figure 4 illustrates the distribution of body iron and the processes of external iron exchange.[49] Iron released from red blood cells at the end of their life span provides iron for developing new red cells. The iron derived from these cells initially enters the labile iron pool in the reticuloendothelial cells, but it is rapidly returned to the circulation and delivered by transferrin to the erythroid marrow for incorporation into developing red blood cells.

In patients with anemia, the amount of iron needed by developing erythroid cells is reduced. Consequently, the iron released from red blood cells is diverted to iron stores in the reticuloendothelial cells.
Stimulation of erythropoiesis by rHuEPO therapy increases the need for iron by developing red blood cells. Initially, this iron is provided by circulating transferrin-bound iron and the labile iron pool in the reticuloendothelial cells.[48] As these sources are depleted, the only remaining supply of iron is the iron stores in the reticuloendothelial system. Iron mobilization from these stores is slow, and, despite adequate stores, iron cannot be provided fast enough to support erythropoiesis. This results in a phenomenon known as functional iron deficiency.

Functional iron deficiency has been shown to occur in many different populations receiving rHuEPO therapy, including chronic renal failure patients,[32,50] patients with anemia of chronic disease,[9,51] and autologous blood donors.[52,53] It has also been seen when normal volunteers with replete iron stores receive rHuEPO therapy,[31,54] based on the appearance of reticulocytes with reduced hemoglobin content.[54]

In patients with anemia of chronic disease, erythropoietic activity is suppressed due to production of inhibitory cytokines. As a result, patients develop a microcytic hypochromic anemia that is superficially similar to iron-deficiency anemia. However, in patients with anemia of chronic disease, iron stores (as reflected by serum ferritin) are raised, not lowered, because the iron circulating in the red blood cell mass is no longer required and, therefore, is deposited into the iron stores.

For every 1-g/dL decrease in the hemoglobin concentration, the serum ferritin concentration will increase by approximately 20 µg/L. Therefore, in patients whose hemoglobin drops by 4 g/dL, the expected rise in serum ferritin concentration will be approximately 80 µg/L. This condition has often been mistakenly referred to as an reticuloendothelial cell block; however, there are no valid data to demonstrate that the increase in iron stores that occurs in patients with anemia of chronic disease is due to the inability of reticuloendothelial cells to release iron.

### Assessment of Iron Deficiency

There are many markers that can be used for assessing different aspects of iron status ([Table 2][55]); however, no one test reflects them all. Currently, the two best tests of iron status available in the United States are TSAT and serum ferritin.[56] Transferrin saturation reflects iron that is readily available for erythropoiesis, while serum ferritin indicates the amount of iron stored in the reticuloendothelial cells of the liver, spleen, and bone marrow.[56]

When using TSAT and serum ferritin to evaluate iron deficiency, it is important to differentiate between absolute and functional iron deficiency.[55] In healthy subjects, absolute iron deficiency occurs when iron stores are depleted (serum ferritin level < 12 ng/mL)[57] and iron delivery to the erythroid marrow is impaired (TSAT level < 15%).[56,58] In chronic renal failure patients, absolute iron deficiency has been defined as a serum ferritin level < 100 ng/mL and a TSAT level < 20%. In contrast, functional iron deficiency occurs when there is not enough available iron in the bone marrow to support erythropoiesis, despite normal or elevated iron stores (ie, serum ferritin levels > 100 ng/mL).[56] Functional iron deficiency has even been seen in chronic renal failure patients with serum ferritin levels ≥ 500 ng/mL.[32]

Because no absolute level of TSAT or ferritin is diagnostic of functional iron deficiency, the diagnosis can be made by administering IV iron and monitoring the erythroid response.[56,59] If a patient’s hematocrit/hemoglobin level increases with a stable or falling rHuEPO dose following IV iron therapy, functional iron deficiency was most likely present.[59]

Unfortunately, both TSAT and serum ferritin are indirect tests that have limitations. The accuracy of the TSAT is limited by problems in both of the parameters (serum iron and TIBC) used in its calculation. The use of serum iron as a measurement is limited by interlaboratory variability[60] and by a marked diurnal variation.[61,62] Total iron-binding capacity typically increases with iron deficiency; however, in certain conditions (eg, chronic renal failure) it may decrease independent of iron status because of malnutrition.[63]

Serum ferritin increases independent of iron stores[64] in certain clinical states associated with inflammation,[65] such as infection, rheumatoid arthritis, malignancy,[66] and smoking.[67] In addition, serum ferritin levels may increase due to the release of intracellular ferritin from damaged cells (eg, in liver disease).[55]

Recently, the percentage of hypochromic red blood cells has emerged as a potentially useful measurement of functional iron deficiency. The percentage of hypochromic red blood cells is an indirect measurement of how much iron is actually entering the red blood cells, and is measured by an automated blood count analyzer that is not commonly available in the United States.[50] This test measures the proportion of red blood cells whose intracellular hemoglobin is < 28 g/dL; a level of > 10% has been shown to indicate functional iron deficiency in patients treated with rHuEPO.
Treating Iron Deficiency in Renal Failure Patients Receiving rHuEPO

The nephrology community has recently published evidence-based guidelines on optimizing the treatment of anemia in chronic renal failure patients. This 3-year initiative, known as the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) Clinical Practice Guidelines for the Treatment of Anemia of Chronic Renal Failure, involved a review of approximately 3,000 articles and includes a detailed section on iron management in chronic renal failure patients who are receiving rHuEPO.

The iron support section of these guidelines examines how to ensure that patients have sufficient iron to achieve and maintain a target hematocrit of 33% to 36% (hemoglobin, 11 to 12 g/dL). Table 3 summarizes the major recommendations regarding iron support in chronic renal failure patients who are receiving rHuEPO.[56]

Oral Iron Therapy

Although oral iron therapy is the initial approach for treating iron deficiency, it usually cannot provide iron at the rate needed for rHuEPO-stimulated erythropoiesis.[56] Numerous studies have shown that oral iron therapy fails to maintain adequate iron stores in hemodialysis patients receiving rHuEPO therapy,[68-70] as well as in normal subjects treated with rHuEPO.[54] This may be because oral iron is poorly absorbed in rHuEPO-treated patients,[71] especially when patients have normal or elevated serum ferritin levels (eg, > 100 ng/mL).[72] Oral iron therapy is also associated with a high incidence of gastrointestinal side effects (heartburn, nausea, and diarrhea) that affect patient compliance.

Intravenous Iron Therapy

In contrast, IV iron replenishes the labile iron pool in reticuloendothelial cells and has been found to be more effective in providing iron at the rate needed for rHuEPO-stimulated erythropoiesis. In a randomized study by Macdougall and colleagues, patients receiving IV iron dextran (250 mg/2 wk) were compared to patients receiving either oral ferrous sulfate (200 tid) or no iron therapy. At 16 weeks of follow-up, patients receiving IV iron therapy had the highest hemoglobin level (P < .005) vs the groups receiving oral iron or no iron, and there was no significant difference in hemoglobin between the oral iron group and the group receiving no iron (Figure 5a).[69]

Whereas serum ferritin levels were maintained in the group receiving IV iron, these levels decreased significantly in the oral-iron and no-iron groups (P < .0005 for IV iron vs oral iron and P < .005 for IV iron vs no iron) at 12 and 16 weeks (Figure 5b). In addition, the group receiving IV iron had the lowest rHuEPO dose requirements (P < .05 for IV iron vs no iron; Figure 5c).[69]

To date, several other studies have shown that IV iron therapy effectively provides sufficient iron for optimal erythropoiesis in rHuEPO-treated uremic patients with both absolute[12,73,74] and functional iron deficiency.[68,75-78] As demonstrated by increased hematocrit/hemoglobin levels (Table 4),[56] Intravenous iron administration has also been associated with a reduction in the dose of rHuEPO needed to maintain the target hematocrit/hemoglobin level.[12,68,73-78] A few studies have shown that administering IV iron, even without the use of rHuEPO therapy, can increase patients' hematocrit/hemoglobin levels (Table 4).[75,79]

The successful management of functional iron deficiency in patients with chronic renal failure by the administration of IV iron suggests that this approach might also increase the responsiveness of patients with cancer-related anemia to rHuEPO. Controlled clinical trials are currently underway to evaluate the effect of IV iron on the response to rHuEPO in this patient population.

Since normal iron stores are approximately 1,000 mg, the recommended IV iron regimen for treating absolute iron deficiency in chronic renal failure patients is a total dose of 1,000 mg administered as 100-mg doses over 10 successive hemodialysis sessions. For treatment of functional iron deficiency and maintenance of adequate iron stores during rHuEPO therapy in chronic renal failure patients, the recommended regimen is 25 to 100 mg of IV iron every week for 10 weeks.[56] The most appropriate and effective regimen for dosing IV iron in cancer patients is currently under study. Figure 6 provides a flowchart for the management of iron in chronic renal failure patients that may prove useful until a recommended dosing regimen for IV iron in cancer patients is available.[80] In the United States, IV iron is only available in the form of iron dextran.

Currently, two different iron dex-tran preparations are available for IV use in the United States: INFeD (USP/Schein Pharmaceutical, Inc.) and Dexferrum (USP/American Regent Laboratories, Inc.). It is important to note that these two products have different molecular weights (INFeD: 165,000[81]; Dexferrum: 267,000[82]) and are therefore not bioequivalent. Although one of these products, INFeD, is indicated for intramuscular injection, this route of administration is not recommended due to a number of clinical concerns, including discomfort, sarcoma formation, and staining at the
injection site.[83]

**Safety of IV Iron**

Some physicians have avoided prescribing iron dextran due to reports of serious allergic reactions, such as anaphylaxis. The safety of iron dextran has been tested in two studies. One study performed in nonuremic patients reported three immediate, serious reactions (0.1%) among 2,099 iron dextran injections (Imferon) in 481 patients.[84]

Another more recent study retrospectively examined the safety of iron dex-tran (INFeD) in 573 hemodialysis patients at four different centers over 2 years.[81] The most common adverse effects were dyspnea or wheezing and itching, each of which occurred in 1.5% of the study population. Four serious adverse events were reported (0.7% of patients treated), with no deaths or permanent disabilities. A history of multiple drug allergies was found to significantly correlate with adverse reactions to iron dextran.

Due to the potential for a serious adverse reaction, a test dose of 25 mg of IV iron dextran should be administered in all patients prior to the initiation of IV iron therapy. Appropriate therapy (such as epinephrine, diphenhydramine, steroids, and/or oxygen) should be on hand in case of the rare occurrence of a serious adverse reaction.[81]

Anxiety regarding IV iron preparations has been predicated on the experience with one particular iron dextran product, Imferon. Even though this product is no longer available, the memory of the anaphylactic reactions that it occasionally induced lingers. More recently developed IV iron preparations have sought to avoid the anaphylaxis associated with the dextran moiety of Imferon by using other molecules to coat and solubilize the ferric iron core.

Two other forms of IV iron used in Europe, iron saccharate and sodium ferric gluconate, have been found to be safe and efficacious in hemodialysis patients.[75,85,86] Reports from North American clinical trials have shown sodium ferric gluconate to be safe and effective[87]; this IV iron formulation may soon be available in the United States.

**Conclusions**

Cancer-related anemia affects a majority of patients at some point in their treatment and can have a substantial negative impact on quality of life. Correction of anemia by administration of rHuEPO can improve these patients' quality of life and, therefore, should not be neglected. A recent community-based study involving more than 2,000 cancer patients found that patients treated with rHuEPO experienced improvements in overall quality of life, exhibited increased activity and energy levels, and had decreased transfusion requirements.[23]

Studies have shown that only 50% of cancer patients respond to rHuEPO therapy.[7] The ability to predict which patients respond to rHuEPO would make this expensive therapy more cost-effective by allowing clinicians to select the best candidates for therapy or to discontinue treatment early in nonresponders.

In the chronic renal failure population, the most common cause of diminished response to rHuEPO therapy is iron deficiency. We believe that the persistence of anemia in at least some nonresponding cancer patients may be caused by a phenomenon known as functional iron deficiency. Functional iron deficiency has been observed in several different populations receiving rHuEPO therapy, including patients with anemia of chronic disease, chronic renal failure patients, individuals undergoing autologous blood donation, and normal subjects.

In a recent review of the use of rHuEPO in nonuremic patients, Cazzola and colleagues compared the bone marrow to a car engine, in which a [an adequate response to pushing on the accelerator (EPO) can be achieved only by a properly matched injection of fuel (iron).] According to Cazzola et al, the administration of rHuEPO in excess of functionally available iron will lead to iron-deficient erythropoiesis, diminished erythroid marrow response, and a waste of this costly drug.[9]

Increased iron stores are necessary to keep pace with the high rate of rHuEPO-induced erythropoiesis. Therefore, it is important to monitor iron status and correct iron deficiency prior to, and during rHuEPO therapy to optimize its response. The labeling for one brand of rHuEPO (Procrit)[88] recommends that patients should have a TSAT ≥ 20% and a serum ferritin ≥ 100 ng/mL, and notes that virtually all patients will require iron therapy.

Oral iron cannot always provide iron rapidly enough to support the accelerated erythropoiesis that occurs with rHuEPO therapy. Clinical data from chronic renal failure patients demonstrate that failed responsiveness to rHuEPO can be restored by administration of IV iron.[32] Intravenous iron can also reduce the rHuEPO dose required for the correction of anemia, increasing the cost-effectiveness of this expensive drug.[68]
Controlled clinical trials are currently underway to determine the effect of IV iron on improving rHuEPO response in cancer patients. In the meantime, the recently published NKF-DOQI Clinical Practice Guidelines for the Treatment of Anemia of Chronic Renal Failure provide some recommendations for the proper diagnosis and treatment of iron deficiency in patients receiving rHuEPO therapy.

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