MANAGING PATIENTS WITH CHEMOTHERAPY-INDUCED ANEMIA

George M. Rodgers, III, MD, PhD*

ABSTRACT

Anemia is a relatively common condition in patients with cancer, with an incidence of 60% among patients with solid tumors/lymphoma and 70% to 90% among those receiving myelosuppressive chemotherapy and/or radiation therapy. This article offers a review of chemotherapy-induced anemia (CIA), as related to prevalence, etiology, patient outcomes, and the latest treatment strategy. The risks and benefits of current treatments (eg, packed red blood cell transfusions, erythropoiesis-stimulating agents (ESAs), and iron supplementation), as well therapeutic recommendations from several guidelines on the management of CIA, are discussed in detail. Current guidelines emphasize an ongoing risk assessment of the patient with CIA, which takes into account symptoms, risk factors, and pertinent laboratory values. Guideline recommendations regarding ESA therapy are quite detailed and highlight the need to dose ESAs conservatively (maintaining hemoglobin levels <12 g/dL), use them in appropriate settings (ie, anemia related to myelosuppressive chemotherapy; avoid in patients with cancer who are not receiving chemotherapy), and discontinue them after completion of chemotherapy. (Adv Stud Med. 2008;8(10):346-351)
known to induce anemia due to combined bone marrow and kidney toxicity. Antimicrotubular agents (eg, taxanes and vinorelbine) and camptothecins (eg, irinotecan and topotecan) are also considered particularly myelosuppressive.

Dose intensity, the increasingly widespread practice of administering higher doses of chemotherapy over a shorter period of time, is also associated with an increased risk of myelosuppression.

Many newer biologic agents are not cytotoxic or myelosuppressive in the traditional sense, but have nevertheless also contributed to the incidence of anemia. For example, almost 90% of patients treated with imatinib for gastrointestinal stromal tumors develop anemia, which is classified as grade 3 or 4 in 10% of patients. Likewise, patients with metastatic renal cell carcinoma who are treated with sunitinib monotherapy have a 26% rate of clinically significant anemia, and those given sirolimus have a 9% rate of grade 3 or 4 anemia. Because these agents and dose-intense regimens can be anticipated to play greater roles in the treatment of major solid tumors, anemia will continue to affect large numbers of patients with cancer.

**ETIOLOGY OF CIA**

Chemotherapy-induced anemia results from direct effects of cytotoxic agents on hematopoiesis (including synthesis of red blood cell [RBC] precursors) in the bone marrow or on renal function. For example, cisplatin, when administered over an extended period, causes progressive renal dysfunction, which ultimately leads to decreased renal production of endogenous erythropoietin and subsequently reduced production of RBCs. Chemotherapy may also impair erythropoiesis over the long term through damage to the stem-cell pool. Patients with breast cancer receiving adjuvant therapy with the combination of cyclophosphamide, methotrexate, and fluorouracil have experienced stem-cell impairment lasting as long as 5 years after treatment. This marrow suppression may last much longer in patients treated with more potent myelosuppressive agents or in those who have undergone high-dose chemotherapy with stem-cell support or radiotherapy to the marrow compartment.

In general, the myelosuppressive effects of particular cytotoxic agents are likely to accumulate with repeated cycles of therapy, as evidenced by a steady increase in rates and severity of anemia with additional chemotherapy cycles.

**CIA AND PATIENT OUTCOMES**

The association between uncorrected anemia before or during chemotherapy and poorer patient outcomes has been reported in several studies. Anemia can lead to a multitude of symptoms (eg, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness) and may also have an adverse impact on comorbid conditions, such as cardiac and pulmonary disease. The most common patient complaints are dyspnea on exertion and chronic fatigue, which may interfere with a patient's ability to perform normal daily activities.

A key differentiating characteristic of cancer-related fatigue versus fatigue in healthy individuals is its likelihood of persistence at rest. In various published surveys, fatigue has been represented as a symptom that has affected patients' everyday life the most and has been linked to changes in employment status among patients and even caregivers. The association between hemoglobin (Hb) levels and fatigue is well documented, with one analysis of 5 randomized trials linking an increase in Hb concentrations of at least 2 g/dL with an improvement in fatigue, and consequently, in energy, ability to perform usual activities, and overall health.

In looking at the impact of CIA on survival, a meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer and anemia compared with patients without anemia. The increased relative risk of death was particularly evident in patients with head and neck cancer (75%), a finding that also is supported by other retrospective studies. Tumor hypoxia, resulting from the reduced oxygen-carrying capacity of blood in patients with anemia, has been hypothesized to be a major contributor to reduced survival. Several studies have shown that tumor hypoxia also reduces the effectiveness of radiotherapy and chemotherapy, and is associated with tumor progression. The effects of erythropoiesis-stimulating agents (ESAs) on survival of patients with cancer are less clear and are discussed in the following sections.

**THERAPEUTIC OPTIONS FOR CIA**

Current treatments for CIA include packed RBC (PRBC) transfusions, ESAs, and iron supplementation, with the former 2 therapies accompanied by...
quite an extensive list of risks and benefits. The major benefit of transfusions is a rapid increase in Hb and hematocrit, with a single PRBC unit increasing Hb concentrations by 1 g/dL in a normal-sized adult who is not actively bleeding. Some studies have shown a survival benefit in oncology patients receiving transfusions, but most of the mortality data are conflicting. Risks associated with transfusions include infusion-related reactions, congestive heart failure, bacterial contamination, viral infections, and iron overload. There is also concern that full reliance on transfusions for the treatment of CIA would strain the US blood supply.

The most prominent benefits of ESAs (ie, epoetin alfa and darbepoetin alfa) are evident in studies demonstrating their ability to significantly raise Hb levels and reduce transfusion requirements. Based on the association between anemia, fatigue, and quality of life (QOL), it has been proposed by many experienced clinicians and researchers that, by raising Hb levels, ESAs may also improve functional status, productivity, and, ultimately, QOL. In some studies, ESAs have been shown to improve fatigue, and in one trial, an epoetin alfa-induced 6% increase in hematocrit led to improvements in patients’ energy levels and ability to perform daily activities. However, results of other studies have been less clear and, although the National Comprehensive Cancer Network (NCCN) anemia panel acknowledges the importance of examining QOL, it considers this end point to be more difficult to evaluate due to its subjectivity.

Hypertensive encephalopathy and seizures, thrombosis, and pure red cell aplasia are among the risks associated with ESAs, but the majority of these complications appear to be associated with Hb concentrations greater than 12 g/dL. The most concerning risk related to ESAs is the potential for increased mortality and tumor progression that has been observed in recent studies. In response to these emerging safety data, the US Food and Drug Administration called for inclusion of a “Black Box” warning in the current ESA labeling, the most recent of which emphasizes the increased risk of tumor progression and shortened survival in patients with advanced breast, head and neck, lymphoid, and non–small-cell lung cancer who are dosed with ESAs to achieve an Hb level 12 g/dL or greater. The Hb target in these studies has generally been 12 g/dL or greater—in fact, considerably higher than 12 g/dL in some cases. However, labeling warns that negative outcomes have not been excluded when ESAs are dosed to a target Hb level lower than 12 g/dL; therefore, the ESA dose should be adjusted to maintain the lowest Hb level needed to avoid the need for blood transfusions. In addition, revised labeling restricts the use of ESAs for treatment of anemia related to myelosuppressive chemotherapy and recommends discontinuing the agents after completion of chemotherapy. Just recently, further revisions to ESA product labels state that, among patients with cancer and CIA, ESAs should not be administered until Hb levels are lower than 10 g/dL and that ESAs should not be administered if chemotherapy is being given for curative intent.

In offering some perspective on the recent safety data, one article reviewed the various strengths and weaknesses of the studies and identified 3 important caveats. First, the use of ESAs in these trials did not reflect common use of the products in clinical practice—that is to treat, rather than to prevent, anemia in patients receiving chemotherapy, not radiation therapy. Second, the trials did not meet reasonable standards that should be used in designing optimal cancer progression or survival studies. Some of these ideal characteristics include minimal exposure to ESAs in controls, homogenous cancer type and treatment, baseline balance in known prognostic factors, and ESA use relevant to current clinical practice. Third, other studies that did not show a negative impact on tumor progression or survival were also published, albeit with similar shortcomings but should be considered nevertheless. The author of this article acknowledges the lack of definitive answers regarding the safety of ESAs, but does offer some apparent conclusions (Table 1). In the interim, clinicians await results of more definitive studies.

The importance of iron supplementation in the management of CIA cannot be overstated, because it may be valuable in limiting the need for ESA therapy, maximizing symptomatic improvement in anemia, and determining the reason for inadequate response to ESAs. Stimulation of erythropoiesis by erythropoietin increases the requirement for iron by developing RBCs. Initially, this iron is provided by circulating transferrin-bound iron and the labile iron pool in the reticuloendothelial cells. As these sources become depleted, the only remaining iron supply 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 optimal erythropoiesis. As a result, functional iron deficiency usually develops in patients after continued ESA use and is likely the most common cause of inadequate response to ESAs.3,22

Intravenous iron products are recommended for iron repletion in patients with cancer who have absolute iron deficiency (ferritin <30 ng/mL, transferrin saturation <15%) or in those receiving ESA therapy. Clinicians may actually limit ESA use by prescreening potential candidates for ESA therapy for absolute iron deficiency and attempting oral iron in individuals who have this condition.2 Iron can be administered in oral or parenteral form (eg, low–molecular-weight iron dextran, ferric gluconate, and iron sucrose), with parenteral iron being superior.2 Compared with oral supplements or no iron supplementation, intravenous iron has been found in various studies to be associated with fewer transfusions, a shorter time to reach target Hb levels, and an enhanced hematopoietic response to ESAs.23,24 Because most adverse effects (eg, hypotension, hypertension, bradycardia, nausea, and fever) are associated with high–molecular-weight iron dextran, the low–molecular-weight product is recommended. Because intravenous iron is associated with sensitivity reactions, small test doses by slow infusion are recommended.2

**CURRENT TREATMENT GUIDELINES**

Several organizations have released guidelines on the management of CIA, including the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the NCCN.2,14 The following section summarizes recommendations from these guidelines.

Although the guidelines differ somewhat in regard to Hb levels that dictate initiation and goals of therapy (Table 2), they appear similar in the general principles that govern overall management of CIA.2,14 Initial screening of anemia in patients with Hb levels lower than 11 g/dL includes a complete blood count, with indices and a review of the peripheral blood smear. Once other causes of anemia (eg, bleeding or renal dysfunction) have been ruled out, a risk assessment, including acuity and severity of anemia, cardiac and pulmonary symptoms, and presence of comorbidities (eg, cardiac history, chronic pulmonary disease, and cerebral vascular disease), should be used to determine which patients receiving myelosuppressive chemotherapy require immediate intervention with PRBC transfusion. Therapeutic

<table>
<thead>
<tr>
<th>Table 1. ESA Therapy in CIA: What We Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Increasing hemoglobin concentration to levels of ≥ 13 g/dL in an attempt to improve tumor oxygenation and response to treatment is a failed experiment and should not be done in routine clinical practice.</td>
</tr>
<tr>
<td>o The use of ESAs during radiotherapy for head and neck cancer cannot be regarded as safe and should not be a part of routine clinical practice.</td>
</tr>
<tr>
<td>o The use of ESAs in patients with cancer is associated with an increased risk of venous thrombosis and thromboembolism, especially in patients who have pelvic malignancies, are receiving radiotherapy, or are taking other medication (eg, hormones or thalidomide).</td>
</tr>
<tr>
<td>o Treatment of anemia of cancer with ESAs may be associated with a decrease in survival.</td>
</tr>
<tr>
<td>o There has not been a negative survival signal in trials addressing the most frequent use of ESAs in oncology, treatment of CIA.</td>
</tr>
<tr>
<td>o There is a paucity of well-designed and executed studies of the effect of ESAs on survival, particularly regarding their use to treat CIA.</td>
</tr>
</tbody>
</table>

**Table 2. Summary of International Evidence-Based Guidelines**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>ASCO/ASH</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate ESA therapy</td>
<td>Hb ≤ 10 g/dL (clinical decision if Hb &gt; 10 to ≤ 12 g/dL)</td>
<td>Hb ≤ 11 g/dL*</td>
</tr>
<tr>
<td>Goal of treatment</td>
<td>Maintain Hb at or near 12 g/dL</td>
<td>Maintain between 10–12 g/dL</td>
</tr>
</tbody>
</table>

*The NCCN guidelines recommend that a benefit-risk discussion be held with the patient regarding the use of ESA therapy vs transfusion. Topics to be considered include use of ESA in patients with curative vs non-curative tumors, thrombosis risk, and potential risk of ESA on tumor progression and survival.1 ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; NCCN = National Comprehensive Cancer Network. Data from National Comprehensive Cancer Network2 and Rizzo et al.14
decisions are heavily dependent on an ongoing risk assessment, which is outlined in an algorithmic format in the 2009 NCCN guidelines.\textsuperscript{2}

If patients require immediate correction of anemia, transfusions should be offered according to institutional policies.\textsuperscript{2} For patients who do not require immediate therapy, the decision of whom and when to treat has become rather complex as a result of the aforementioned evidence regarding the potential harm of using ESAs in patients with cancer. As a reflection of this safety data, one of the major updates to the 2009 NCCN guidelines is the inclusion of a recommendation calling for a benefit-risk evaluation based on curative versus non-curative goals of chemotherapy. For patients undergoing potentially curative chemotherapy, the risks of ESAs may outweigh the benefits, and transfusion is the recommended therapy. For patients undergoing non-curative chemotherapy, ESA therapy may be considered more appropriate, because there is less risk than with transfusion; however, a discussion on associated risks and benefits should still take place with the patient.\textsuperscript{2} Both the NCCN and ASCO/ASH guidelines caution against using ESAs in patients with cancer who are not receiving chemotherapy.

At this point, it is also necessary to perform a complete symptom assessment (independently of whether a patient has been transfused) to identify those patients for whom an initial or additional intervention is needed to correct anemia. Symptomatic patients not requiring immediate correction may be given transfusions or ESA therapy.\textsuperscript{2} For prevention of transfusion, the NCCN guidelines consider ESA therapy in symptomatic patients with Hb levels of 10 g/dL or lower and in those with Hb levels between 10 and 11 g/dL a class 1 recommendation (based on high-level evidence) and for those with less severe anemia (Hb >10 g/dL to <12 g/dL), they recommend determining the need for ESAs based on clinical circumstances (eg, elderly patients with limited cardiopulmonary reserve).\textsuperscript{14}

Asymptomatic patients should be further evaluated for risk factors that may result in development of symptomatic anemia, including low Hb levels, transfusion in the past 6 months, prior myelosuppressive therapy or radiotherapy, myelosuppressive potential of current therapy, and predisposing comorbidities.\textsuperscript{2} Whereas asymptomatic patients without risk factors should just be observed, asymptomatic patients with risk factors may be observed or treated with ESA therapy (if Hb levels are ≤10 g/dL).\textsuperscript{2} Compared with the ASCO/ASH guidelines, the NCCN guidelines are more conservative in regard to target Hb levels (Table 2), recommending ESA dose titrations that maintain Hb levels between 10 and 12 g/dL (see Table 3 for ESA dosing and titration).\textsuperscript{2,14} Serum iron parameters should be measured in patients receiving ESAs for consideration of supplementation. ESAs should be discontinued once chemotherapy is complete and anemia resolved, usually within 6 weeks.\textsuperscript{2}

**Conclusions**

In order to safely manage CIA and improve the well-being of patients, clinicians must be diligent in performing a thorough and ongoing assessment of patient-specific risks and symptoms. Judicious use of ESAs as recommended by consensus guidelines, and in combination with appropriate parenteral iron supplementation, will optimize benefits and minimize risks of therapy.
REFERENCES


