Anemia related to cancer treatment has multiple etiologies, including bleeding, marrow infiltration, anemia of chronic disease, and the effects of chemotherapy and/or radiation therapy on bone marrow function or renal function. Although the incidence of anemia in patients with solid tumors and lymphoma may be as high as 60%, the incidence is even higher (70%–90%) in patients receiving myelosuppressive chemotherapy, radiation therapy, or both. Anemia can lead to a multitude of symptoms (eg, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness) and it may also have an adverse impact on comorbid conditions such as cardiac and pulmonary disease. This article provides a comprehensive discussion of the risk factors, consequences, and management of chemotherapy-induced anemia. Much research is being conducted on identification of certain risk factors that may be used to predict development of chemotherapy-induced anemia prior to administration of chemotherapy. Additionally, several treatment guidelines offer direction on proper assessment of chemotherapy-induced anemia and use of appropriate therapeutic strategies, including transfusions and erythropoietic agents. The judicious use of erythropoietic agents, the latest update on potential adverse effects, and the role of iron therapy are also discussed in this article.


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or bisulfan) or in those who have undergone high-dose chemotherapy with stem-cell support or radiotherapy to the marrow compartment.5

The contribution of ACD, which is mediated by inflammatory cytokines that directly suppress erythropoiesis and erythropoietin production, has been underappreciated. Patients with ACD have low serum iron levels, but the bone marrow is replete with iron, suggesting an iron utilization defect (termed functional iron deficiency) rather than a deficiency.1 Serum ferritin levels may sometimes be elevated in patients with cancer as a result of inflammation and may not always be reflective of iron stores. Despite the limitations of measuring serum iron parameters, a functional iron deficiency has been generally characterized by a serum ferritin level less than 100 ng/mL or a transferrin saturation (TSAT) level less than 20%.1

Although the incidence of anemia in patients with solid tumors and lymphoma may be as high as 60%, the incidence is even higher (70%-90%) in patients receiving myelosuppressive chemotherapy and/or radiation therapy.2 The incidence and severity of CIA depend on a variety of factors, including the type, schedule, and intensity of chemotherapy administered, and whether the patient has received prior myelosuppressive chemotherapy and/or radiation therapy.4 Symptom severity depends on the degree of anemia, the type of underlying malignancy, and the patient's pulmonary and cardiovascular function.4 Comorbid conditions, which are particularly prevalent in the elderly, may increase susceptibility to anemia and a patient's ability to tolerate the symptoms associated with anemia.2 Elderly patients with cancer frequently manifest clinical symptoms of anemia at higher hemoglobin (Hgb) levels than do anemic patients without cancer.

In characterizing and documenting the risk of CIA in adults with nonmyeloid malignancies, one group of investigators undertook a comprehensive review of published chemotherapy trials of the most common single agents and combination chemotherapy regimens.4 As seen in other studies, the highest frequency of anemia that required RBC transfusions was observed in patients who received cytotoxic therapy for lymphomas, lung tumors, and gynecologic (ovarian or genitourinary) tumors.5,6 Platinum-based therapies (eg, cisplatin and carboplatin)—which continue to play a major role in the treatment of lung, ovarian, and head and neck malignancies—in addition to the new generation of chemotherapeutic agents—particularly antimicrotubular agents (eg, taxanes and vinorelbine) and camptothecins (eg, irinotecan and topotecan)—were observed to be particularly myelosuppressive.1 Dose intensity, the practice of administering higher doses of chemotherapy over a shorter period of time, is also associated with an increased risk of myelosuppression (ie, neutropenia, thrombocytopenia, and 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 cancer patients.

In an effort to potentially circumvent the complication with timely treatment, researchers have attempted to identify certain risk factors that may be used to predict the development of anemia prior to administration of chemotherapy.6 In one study, 6 variables were found to be statistically significant for anemia prediction, including lower baseline Hgb (Hgb ≤12.9 g/dL in females and ≤13.4 g/dL in males), cancer type (lung or gynecologic cancer vs other malignancies), treatment with platinum versus nonplatinum therapy, and female gender.6

**Consequences of Anemia**

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.4 The latter complication is considered much more debilitating than acute fatigue, which occurs in response to exercise or everyday exertion.

Recent advances in assessing the relationships between anemia and certain clinical symptoms, such as fatigue, in cancer patients are providing new insights into these closely related factors.2 In one survey of 379 patients undergoing chemotherapy with or without radiation, 301 patients reported experiencing fatigue at least a few days each month during their most recent chemotherapy treatment.7 In the majority of patients, fatigue was considered the side effect or symptom that affected everyday life the most, leading to changes in employment status and increased caregiver requirements. Another analysis of 5 randomized trials found that an increase in Hgb concentration of at least 2 g/dL was associated with an improvement in
fatigue, which led to improvements in energy, ability to perform usual activities, and overall health.8

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 cancer patients with anemia, compared with cancer patients without anemia.6 The increased relative risk of death was particularly evident in patients with head and neck cancer (75%), a finding that is supported by other retrospective studies as well. Tumor hypoxia, resulting from the reduced oxygen-carrying capacity of blood in anemic patients, 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.10 However, the effects of erythropoietic therapy on survival of cancer patients are less clear.

EARLY ASSESSMENT AND APPROPRIATE TREATMENT STRATEGIES

The National Cancer Institute considers normal Hgb levels to be 12 g/dL to 16 g/dL for women and 14 g/dL to 18 g/dL for men. The World Health Organization and National Cancer Institute have provided 2 of the most commonly used toxicity scales for correlating levels of Hgb with different grades (severity) of anemia (Table 1).4 Although the scales are the same in their classification of more severe grades of anemia, they differ slightly in their classification of lesser grades.

The frequency of anemia assessment should be sufficient enough to detect anemia before it becomes severe. Clinicians will typically check Hgb levels prior to administration of chemotherapy and at each scheduled clinic visit. Baseline laboratory studies should include a complete blood count, serum iron, folate, ferritin, and vitamin B12 concentrations. Patients should be screened for occult blood in the stool and for possible sites of chronic or acute blood loss (ie, gastrointestinal or genitourinary tract).11 A complete assessment should rule out any causes of anemia that can be managed with standard therapy. These causes may include iron-deficiency anemia (microcytic), B12-deficient anemia (megaloblastic), or anemias caused by hemolysis, hemorrhage, or occult bleeds. Once anemia is identified (Hgb levels ≤11 g/dL), an initial risk assessment should include the severity of anemia, consideration of symptoms such as chest pain or dyspnea, and comorbidities. If the anemia is identified as CIA, then management is based mostly on severity, with therapeutic options being colloidal fluids, RBC transfusions, erythropoietic agents, and iron supplementation.1 Patients with symptomatic but transient anemia resulting from acute blood loss, or those with symptomatic chronic anemia, should receive crystalloids to replace intravascular volume.

TRANSFUSIONS

RBC transfusions are indicated in patients with cancer who have acute anemia following acute blood loss when crystalloid infusions do not adequately correct intravascular volume, in those with chronic symptomatic anemia unresponsive to iron replacement, and in those in whom medical necessity does not allow adequate time for erythropoietic therapy to be effective.4 A single unit of packed RBCs increases Hgb concentration by 1 g/dL and hematocrit by 3%, if there is no active bleeding. Prior to development of erythropoietic agents, transfusions were used widely in patients with cancer, often at a significantly higher Hgb concentration threshold (10 mg/dL) than that of today’s levels (7–8 g/dL). Allogenic blood transfusions are notoriously associated with a multitude of problems, including the potential for transmission of infection, in addition to immune-mediated (eg, alloimmunization) and nonimmunologic (eg, circulatory overload) reactions.11 Although the blood supply is now carefully screened and the risk of HIV transmission is negligible, other infectious agents (eg, hepatitis viruses, cytomegalovirus, and Epstein-Barr virus) remain a concern. Transfusions have also been associated with shorter survival times and higher

<table>
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<tr>
<th>Grade</th>
<th>Severity</th>
<th>NCI Scale</th>
<th>WHO Scale</th>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>Normal limits*</td>
<td>&gt;11</td>
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<tr>
<td>1</td>
<td>Mild</td>
<td>10–normal</td>
<td>9.5–10</td>
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<tr>
<td>2</td>
<td>Moderate</td>
<td>8–10</td>
<td>8–9.4</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>6.5–7.9</td>
<td>6.5–7.9</td>
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<tr>
<td>4</td>
<td>Life-threatening</td>
<td>&lt;6.5</td>
<td>&lt;6.5</td>
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* 14–18 g/dL for men, 12–16 g/dL for women. NCI = National Cancer Institute; WHO = World Health Organization. Adapted with permission from Groopman et al. JNCI. 1999;91:1616-1634.
recurrence rates in patients with soft-tissue sarcoma or cancers of the colon, rectum, or lung. However, these negative outcomes may have been confounded by advanced stage malignancies, the need for more extensive surgery, or greater perioperative blood loss.3

In 1996, the Serious Hazards of Transfusion (SHOT) scheme for monitoring the safety of blood transfusions was implemented in the United Kingdom, where hematologists were invited confidentially to report deaths and major complications following blood transfusion.11,12 An analysis of 6 years of SHOT data revealed that 64% of more than 1600 adverse events associated with blood transfusions involved an incorrect blood component. Other commonly reported adverse events included acute and delayed transfusion reactions and acute lung injury. Concern over the safety of the blood supply led to a reduction in blood donation rates during the 1980s. Although collections have increased in the 1990s, the blood supply continues to be strained because of an increase in demand.

Erythropoietic Therapies

Although treatment guidelines differ somewhat on the Hgb concentration at which erythropoietin should be administered, there is general consensus that patients with an Hgb level of less than or equal to 10 g/dL, with or without accompanying symptoms, should receive therapy.11 Patients with Hgb levels of 10 g/dL to 12 g/dL should receive erythropoietic therapy if they suffer from significant symptoms of anemia and/or have progressively decreasing Hgb values.13

Erythropoietin is a hematologic growth factor that regulates the proliferation, maturation, and differentiation of RBCs. Erythropoietin is produced by the kidney and released into the bloodstream in response to hypoxia, at which point it interacts with progenitor stem cells to increase RBC production. Several large, prospective, placebo-controlled studies have demonstrated the value of epoetin alfa, the human recombinant form of erythropoietin, for the treatment of anemia in cancer patients. One large study included 413 patients, 68% of whom had solid tumors.14 Patients were grouped according to treatment regimen (no chemotherapy, non–cisplatin-containing chemotherapy, and cisplatin-containing chemotherapy) and randomly assigned to receive placebo or epoetin alfa. In all 3 groups, patients receiving epoetin alfa had a statistically significant increase in hematocrit compared with placebo-treated patients, and those receiving chemotherapy had a reduction in transfusion rates. Compared with patients who received placebo, those treated with epoetin alfa and who had an increase in hematocrit of at least 6% also had statistically significant improvements in energy level and the ability to perform daily activities. Improvements in some anemia-related symptoms appear to be significantly greater in patients with an increase from baseline in Hgb concentrations of greater than or equal to 2 g/dL than in those with smaller Hgb increases.2

Produced by recombinant DNA technology, the 2 currently available erythropoietic agents, epoetin alfa and darbepoetin alfa, are approved by the US Food and Drug Administration (FDA) for the treatment of CIA in patients with nonmyeloid malignancies. Epoetin is approved for initial drug administration at 40 000 U once weekly (QW) or 150 U/kg thrice weekly (TIW). Darbepoetin, which has a 3-fold longer serum half-life than epoetin alfa, is approved for administration at 500 µg once every 3 weeks or 2.25 µg/kg QW.15,16 The results of recent clinical trials and the accumulation of clinical experience have prompted a variety of dosing schedules for these erythropoietin agents (eg, QW or once every 2 or 3 weeks). The findings suggest comparable efficacy (in regard to transfusion requirements and tolerability) between darbepoetin (2.25 µg/kg QW) and epoetin (40 000 U QW), regardless of tumor type or degree of anemia at baseline.1 The most common epoetin dose and schedule evaluated in clinical trials was 150 U/kg TIW or 10 000 U TIW subcutaneously (SC), and large-scale, community-based trials with more than 3000 patients have documented the equivalent effectiveness of the 40 000 U QW dosing regimen.1,17 Erythropoietic dosing regimens involving higher starting doses are also being explored for their potential to improve response time to therapy and the proportion of responding patients. In one pilot study, higher initial dosing of epoetin (40 000 U for 3 consecutive days) conferred higher response rates than standard doses in patients with solid tumors who had Hgb levels of less than 11 g/dL.18

In regard to optimal therapeutic regimens, guidelines from the American Society of Clinical Oncology and the American Society of Hematology consider the use of epoetin at 150 U/kg TIW SC to be supported by "good evidence" from clinical trials (Table 2).19 The use of alter-
native weekly (40 000 U/wk) dosing regimens, however, is supported by “less strong evidence,” based on common clinical practice. Guidelines from the National Comprehensive Cancer Network refer to a “final report” indicating greater Hgb increases with epoetin 40 000 U QW versus darbepoetin 200 µg every 2 weeks.1,20

**Assessing Response**

The clinical response to erythropoietic therapy depends on various factors, including the type of malignancy, disease stage, and the patient’s condition. Lower baseline serum levels of erythropoietin and ferritin may increase the likelihood of response.3 Once erythropoietin therapy is initiated, changes in Hgb levels are commonly used to characterize response and make dosage titrations. The National Comprehensive Cancer Network guidelines, for example, consider an increase in Hgb levels of 1 g/dL to be the distinguishing factor between patients with a response versus those with no response to erythropoietic therapy.1 In patients with a response, the guidelines recommend that erythropoietin be continued to maintain an optimal Hgb (12 g/dL); higher levels are associated with adverse effects. Assessment of patients with no response to therapy should be performed at 4 weeks for epoetin alfa and 6 weeks for darbepoetin alfa. If no response is detected, a dose increase is recommended, with or without iron supplementation.5 If the Hgb

<table>
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<th>Table 2. American Society of Clinical Oncology/American Society of Hematology Guidelines: Summary of Recommendations</th>
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<tr>
<td>1. The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level ≤10 g/dL. RBC transfusion is also an option, depending upon the severity of anemia or clinical circumstances.</td>
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<tr>
<td>2. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration &lt;12 g/dL, but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions.</td>
</tr>
<tr>
<td>3. The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial close. Although supported by less strong evidence, an alternative weekly dosing regimen (40 000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.</td>
</tr>
<tr>
<td>4. Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, &lt;1–2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.</td>
</tr>
<tr>
<td>5. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the “normalization” of hemoglobin levels to above 12 g/dL.</td>
</tr>
<tr>
<td>6. Baseline and periodic monitoring of iron, total iron-binding capacity, transferring saturation, ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.</td>
</tr>
<tr>
<td>7. There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are not published high-quality studies to support its use in anemic myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.</td>
</tr>
<tr>
<td>8. Physicians caring for patients with myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.</td>
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level increases by 1 g/dL at 8 to 12 weeks of therapy, then a dosage titration should be performed to maintain an optimal Hgb level of 12 g/dL. Erythropoietic therapy should be discontinued and transfusion initiated if there is no Hgb response at 8 to 12 weeks of therapy. Iron level and other anemia-specific causes should be checked if Hgb levels decrease. If Hgb level increases by more than 1 g/dL in a 2-week period, the dose should be reduced by 25%. If Hgb level exceeds 12 g/dL, therapy should be discontinued. Patients who experience a fall in Hgb level below 12 g/dL should have therapy reinitiated at a 25% dose reduction of the prior dose.1

In an attempt to optimize the course of erythropoietic therapy, researchers are evaluating different measures of and times to response. For example, the use of traditional, single time-point endpoints (eg, hematopoietic response) to assess erythropoietic therapy has been criticized for its failure to reflect clinical benefits over the entire therapy course. As a result, area under the Hgb change curve (Hgb area under curve) was introduced as an alternative measure and was found to better quantify clinical benefits of erythropoietic agents.2 In regard to response time, ongoing research indicates that early responders, those with a greater than or equal to 1 g/dL rise in Hgb at week 4, experience better clinical outcomes than those who have less than a 1 g/dL rise in Hgb at week 4 or week 8.2 Furthermore, early responders have a superior hematological profile (assessed by area under curve), compared with patients who experience a 1 g/dL or greater rise in Hgb at week 8 but not at week 4.22

IRON THERAPY

Stimulation of erythropoiesis by erythropoietin increases the need for iron by developing RBCs. Initially, this iron is provided by the 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 erythropoiesis. As a result, functional iron deficiency (serum ferritin levels <100 ng/mL or TSAT levels <20%) usually develops in patients who are not supplemented with iron; it is the most common cause of inadequate response to erythropoietic therapy.3

A variety of oral iron products are available containing ferrous sulfate, ferrous fumarate, or ferrous gluconate.4 Immediate-release products are taken 3 to 4 times daily and are commonly associated with abdominal pain, nausea, vomiting, and constipation. Extended-release formulations are reported to cause less gastrointestinal complaints, but iron absorption may be diminished. Parenteral iron products (eg, iron dextran, sodium ferric gluconate, and iron sucrose) are helpful in treating functional iron deficiency in patients intolerant or unresponsive to oral iron therapy. Compared with oral supplements, intravenous iron has been found to be more effective in providing iron at the rate needed for erythropoietin-stimulated erythropoiesis.5 Because intravenous iron is associated with sensitivity reactions, small test doses by slow infusion are recommended and patients should receive pre-treatment with diphenhydramine and acetaminophen to minimize adverse events.1,3

ADVERSE EFFECTS OF ERYTHROPOIETIC THERAPY

Hypertension/seizures, thrombosis, and pure red cell aplasia (PRCA) are among the adverse effects that are associated with erythropoietic therapy.1 Between 1998 and 2004, almost 200 cases of PRCA were reported in patients treated with erythropoietin. However, more than 90% of these cases occurred with Eprex (Janssen Pharmaceutica; Berchem, Belgium), an epoetin alfa product used outside of the United States.1 The majority of complications seem to be associated with Hgb concentrations of greater than 12 g/dL, as observed in a large study of patients receiving erythropoietin for anemia of chronic kidney disease. Titration of erythropoietin therapy to an Hgb level of 13.5 g/dL versus 11.3 g/dL was associated with an increased risk of death and cardiac complications, with no incremental improvement in anemia-related symptoms.23 This data reinforced the recommendation that Hgb levels be targeted between 11 g/dL to 12 g/dL. Blood pressure should be controlled in all patients prior to initiating erythropoietic therapy and it must be monitored regularly in treated patients. Those who develop a loss of response to erythropoietic drugs should be evaluated for possible PRCA, and if present, therapy should be discontinued.1

Although previous studies have suggested that erythropoietic therapy may improve survival or have no negative effects on survival, several recent studies have raised concerns over potential negative effects on survival, particularly in patients with cancer-related anemia as opposed to CIA. Only the latter is a US
FDA-approved indication for erythropoietic therapy. Thus far, the use of erythropoietic therapy to a target Hgb level greater than 12 g/dL has been associated with: a shortened time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy; shortened overall survival and increased deaths attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy; and an increased risk of death in patients with active malignant disease receiving neither chemotherapy nor radiation therapy.24-26

In light of the recent findings, the US FDA has announced that it will re-evaluate the safety of erythropoietic therapy and, in the meantime, has issued a public health advisory warning that higher doses of erythropoietic therapy were associated with “an increased risk of death, blood clots, strokes, and heart attacks,” specifically in patients with chronic kidney failure.27 The US FDA also noted that in studies where erythropoietic therapy was given at recommended doses, an increased risk of death was reported in patients with cancer who were not receiving chemotherapy and an increased risk of blood clots was observed in patients following orthopedic surgery.28 The US FDA and the manufacturer of erythropoietic products have agreed on revised product labeling that includes updated warnings, a new boxed warning, and modifications to the dosing instructions. The new boxed warning advises physicians to adjust erythropoietic doses to maintain the lowest Hgb level needed to avoid the need for blood transfusions. Medicare has also announced that as of March 9, 2007, it will not reimburse the use of erythropoietic stimulating agents for the treatment of anemia of cancer; it will continue to reimburse therapy for “anemia secondary to chemotherapy.”29

CONCLUSIONS

The negative impact of anemia on the morbidity and mortality of patients with cancer who are receiving chemotherapy is well documented. The burden of cancer and its treatment should not be compounded by this disabling complication. Treatment of CIA involves an assessment of pertinent laboratory values, symptoms, and risk factors, in addition to judicious use of available therapies. Through proper evaluation and individualized treatment, clinicians can safely correct anemia and improve the well-being of patients.

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