In: Waters JH, Frank SM, eds.
Patient Blood Management: Multidisciplinary Approaches to Optimizing Care
Bethesda, MD: AABB Press/SABM, 2016

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Patient Blood Management Strategies to Treat Anemia and Thrombocytopenia in the Cancer Patient

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THIS CHAPTER OUTLINES strategies that optimize the use of erythropoietic agents and iron as well as other nonblood medical techniques to treat anemia and thrombocytopenia as they relate to the oncologic patient. Anywhere from 30% to 90% of cancer patients are found to be anemic, depending on cancer site, chemotherapy, and hemoglobin level used in defining anemia. Cancer-related anemia and thrombocytopenia are still frequently treated with either transfusion support or reduction and delay of radiation or chemotherapy, which may lead to suboptimal treatment and unnecessary complications.

The pathophysiology of anemia and thrombocytopenia directly caused by malignancy and subsequent treatment is multifactorial (see Table 5-1). The anemia of cancer is characterized, similar to the anemia of chronic disease, by reduced red cell production coupled with impaired iron regulation

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The authors have disclosed no conflicts of interest.

Table 5-1. Factors in Cancer-Related Anemia and Thrombocytopenia

Malignancy associated
- Marrow infiltration
- Humoral inhibitors of hematopoiesis
- Reduced levels of hematopoietic growth factors
- Nutritional deficiency
- Blood loss
- Hypersplenism
- Autoimmune hemolysis
- Disseminated intravascular coagulopathy

Therapy associated
- Marrow fibrosis or necrosis
- Committed progenitor cell death (short-term myelosuppression)
- Stem cell death (long-term myelosuppression)
- Blockage or delay of hematopoietic precursor proliferation
- Long-term myelodysplasia
- Immune-mediated destruction

Surgery associated
- Perioperative blood loss
- Reduced levels of hematopoietic growth factors after surgery

despite adequate stores of marrow iron, in part due to the recently discovered hepcidin and its role in metabolism. Malignant tumors also produce inflammatory cytokines, such as interleukin-1 and tumor necrosis factor, that directly suppress marrow function and impair iron absorption.

Avoidance of unnecessary blood transfusions would be desirable to avoid infections and further immunosuppression in individuals with cancer. Interventions to avoid anemia allow cancer therapy to be given on time, which may potentially decrease cancer recurrence[1,2] and improve quality of life.[3-5] This chapter's approach to anemia and thrombocytopenia focuses on simultaneous interventions to enhance hemostasis, stimulate erythropoiesis, and control ongoing blood losses.

Treatment of Anemia

Erythropoietic Agents

The evaluation of anemia and consideration of erythropoiesis-stimulating agents (ESAs) vs transfusion takes into account the benefits and risks of both. Benefits of transfusion include rapid improvement of hemoglobin and clinical improvement, with risks including transfusion reactions, circulatory and iron overload, viral infection, and development of antibodies. Regarding ESAs, the risks involved include thrombotic events, worse cancer outcomes, and potentially decreased survival. Randomized studies have shown the benefits of ESA, including improved hemoglobin and net reductions in transfusion requirements.[6]

Currently, the two recombinant ESAs that have been approved for the treatment of chemotherapy-induced anemia are epoetin and darbepoetin. Endogenous erythropoietin (EPO) is a glycoprotein that is produced in the kidney and that stimulates red cell production by exerting its effect on committed erythroid progenitors in the marrow. Epoetin alfa (epoetin) is a recombinant glycoprotein that contains the identical amino acid sequence biologically indistinguishable from EPO. Darbepoetin alfa (darbepoetin) is classified as a novel erythropoiesis-stimulating protein. It activates the same receptors as recombinant human erythropoietin but has a serum half-life that is two to three times longer, which has been attributed to its higher carbohydrate content, allowing for the potential for prolonged dosing intervals.

A thorough anemia evaluation should be performed at the initiation of therapy and again if an inadequate response occurs, as causes other than cancer treatment may coexist, including iron or vitamin deficiency, occult blood losses, or hemolysis. Baseline laboratory studies should include complete blood count (CBC) with review of the peripheral smear, reticulocyte count, EPO level, ferritin, vitamin B_{12}, folate levels, as well as a full metabolic panel to assess renal and liver function.

Administration of epoetin in subcutaneous weekly injections of 40,000 international units (IU) is frequently used, producing efficacy similar to the original three times per week dosing at 150 units/kg.[7,8] Weekly CBC and reticulocyte counts are obtained to assess response. In general, patients with lower baseline EPO levels have better responses; patients with anemia of malignancy usually have a serum EPO level inappropriately low for the degree of anemia, making them more likely to respond to an ESA.[9] A review of multiple studies showed an expected increase in hemoglobin after 4 weeks, ranging from 1.8-2.8 g/dL.[10] If there is no improvement at that point or the hemoglobin is still below 10 g/dL, dosages may be adjusted or additional iron administered. Subsequently, if there is no response in 8 weeks, administering more epoetin may not be beneficial and should therefore be discontinued. Once a target hemoglobin has been achieved, less frequent maintenance dosing can be attempted for patient safety, convenience, and cost-effectiveness.

Both ESAs appear to be equivalent with regard to efficacy and safety. For darbepoetin in cancer patients, the package insert recommends a starting dose of 2.25 μg/kg every week or 300 μg every 3 weeks with escalation to 500 μg if needed until completion of chemotherapy.[11] For inadequate responses (hemoglobin increases <1 g/dL), the dose can be increased to 4.5 μg/kg. No dosage adjustment is needed if administering darbepoetin with the triweekly dose.[11] Darbepoetin has been found to have a dose-response relationship, with greater efficacy seen with increasing doses.[3] Hemoglobin should be monitored weekly, and the erythropoietic agents should not be administered if the hemoglobin level is >11 g/dL.[5]

Both agents are well tolerated, although adverse effects such as constipation, edema, myalgia, headache, fever, pyrexia, vomiting, dyspnea, and pruritus have been reported. All erythropoietic agents are contraindicated in patients with hypersensitivity to albumin or other mammalian-derived products and in patients with uncontrolled hypertension. There does not appear to be any direct effect on blood pressure, but blood pressure can elevate during administration of epoetin and darbepoetin. Therefore, blood pressure should be adequately controlled before therapy and closely monitored throughout treatment. EPO receptors are expressed in various cancer cell lines, including breast and endometrial lines; however, it is not known if those receptors are functional or if they have any clinical implications.[12,13]

On November 8, 2007, the Food and Drug Administration (FDA) implemented new boxed warnings and other safety-related product labeling changes for the ESAs (Epogen, Procrit, and Aranesp) because of adverse occurrences in clinical trials. Patients with renal failure experienced greater risks for death and serious cardiovascular events when administered ESAs to attain higher hemoglobin levels.[14] Clinical studies have also shown that in patients receiving ESAs there is increased risk of serious thromboembolic events, stroke, and mortality.[15] ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small-cell malignancies.[16-18] In many of these trials, target hemoglobin levels were in the range of 13-15 g/dL, which may have contributed to the increased instances of events. A meta-analysis found no increase in mortality risk when ESA treatment is delayed until baseline hemoglobin level is <11 g/dL.[19]

To minimize these risks, published guidelines such as those from the American Society of Hematology (ASH) and the American

Society of Oncology (ASCO) should be followed.[20,21] The lowest dosage of ESA should be used that will gradually increase the hemoglobin concentration to the lowest level sufficient enough to avoid the need for red cell transfusion, and target hemoglobin level should be 10 g/dL to decrease risk of complications. In cancer patients, ESAs should be used only for treatment of anemia resulting from concomitant myelosuppressive chemotherapy and should be discontinued following the completion of a chemotherapy course. Modification of the dosage is also necessary if hemoglobin levels rise 1 g/dL in a 2-week period during the treatment.

Because of the potential risks regarding ESAs and to ensure patients are aware of these risks before beginning treatment, the FDA implemented a Risk Evaluation and Mitigation Strategy (REMS), requiring physicians to document their discussion with patients regarding the risks of such side effects as stroke, blood clots, heart attack and failure, tumor progression, and death before administering any ESAs.

Iron Therapy

Iron deficiency is categorized as being either "absolute," as evidenced by inadequate iron stores, or "functional," where the provision of iron is insufficient to meet the increased demands of erythropoiesis. There are numerous reasons for a high prevalence of the more commonly known absolute iron deficiency among cancer patients, including inadequate dietary intake, impaired iron reabsorption, occult blood loss, and phlebotomy. A diagnosis of absolute iron deficiency can be made when the ferritin level is <12 µg/dL; however, a level between 12-100 µg/L can be difficult to interpret in the context of underlying inflammatory processes such as malignancy.

Functional iron deficiency occurs when iron stores are adequate, yet there is an inability to mobilize iron into the marrow for erythropoiesis, in part due to the release of cytokines. Recently discovered is the importance of hepcidin, a peptide hormone produced by the liver and a key regulator of iron homeostasis. Its use in the treatment of anemic cancer patients can be analyzed and further developed as a novel agent in the treatment of anemia.

Concurrent administration of iron is essential with ESA therapy because the effectiveness of ESAs is limited when any degree of iron deficiency is present (ferritin <100 µg/L and transferrin saturation <20%). Although various oral iron formulations are available (most providing approximately 200 mg/day of elemental iron), their use is limited by intolerable gastrointestinal side effects and an inability to meet the demands of ESA-induced accelerated erythropoiesis. For instances in which oral iron therapy is desirable, tolerability can be improved by gradually escalating the dosage and administering it with meals. Taking oral iron in conjunction with vitamin C has the potential to increase absorption; iron and vitamin supplementation (folate, vitamin B complex, and vitamin C) necessary for red cell production should be started concurrently. Dietary goals should also be reviewed, as shown in Tables 5-2 and 5-3.

Some patients who do not respond to ESAs alone will respond when supplemental intravenous (IV) iron is added to the regimen compared to no or oral iron.[22,23] IV iron dextran [INFeD (Watson Pharma, Corona, CA)] has been available for decades, and two dextran-free preparations were then introduced in the United States: sodium ferric gluconate [Ferrlecit (Watson Nephrology, Morristown, NJ)] and iron sucrose [Venofer (American Regent, Shirley, NY)]. (See Table 5-4). More recently, two other supplemental intravenous irons have been approved: ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, MA) and ferric carboxymaltose (Injectafer, American Regent). Of the five IV iron formulations available in the United States, iron dextran is the only one that requires a test dose and premedications to help avoid anaphylactic reactions that have been attributed to the dextran component.