ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Treatment of Chemotherapy-Induced Anemia

George M. Rodgers, III, MD, PhD
Professor, Divisions of Hematology and Oncology
Department of Internal Medicine
Huntsman Cancer Institute
University of Utah
Salt Lake City, Utah

H&O Could you describe the etiology of chemotherapy-induced anemia?

GR The etiology of chemotherapy-induced anemia is multifactorial; primary causes are the underlying cancer and the effects of chemotherapy. Anemia resulting from the underlying cancer—known as the *anemia of inflammation*—causes cytokine release in the patient, which leads to decreased erythropoietin production by the kidney, as well as restricted availability of iron. This process results in the condition known as *functional iron deficiency*.

Anemia due to chemotherapy is often caused by myelosuppression. In addition, certain chemotherapeutic agents, especially platinum, can result in renal dysfunction, which can further decrease erythropoietin production.

H&O Does anemia influence outcomes in cancer patients?

GR There is reasonable evidence that anemia adversely affects outcomes in cancer patients. Several studies over the past 10 years have identified anemia as a poor prognostic factor. For cancer patients who have solid tumors or hematologic malignancies, anemia appears to be an independent risk factor for survival. Other studies have found that the hemoglobin level can predict cancer relapse and response to treatment. We do not know whether correction of anemia would improve survival.

H&O Which chemotherapy agents are associated with a higher risk of anemia?

GR Chemotherapy regimens that contain cisplatin, used to treat lung and ovarian cancer, can be associated with significant anemia in 30% or more of treated patients. Platinum-containing compounds are notorious for causing bone marrow suppression and kidney toxicity. Chemotherapy agents such as docetaxel are also strongly associated with chemotherapy-induced anemia. Chemotherapy agents that are less myelosuppressive and less nephrotoxic are less likely to be associated with anemia.

H&O Should a cancer patient with anemia undergo screening?

GR The clinician should look for multiple reasons for anemia, including bleeding, which can occur in cancer patients who have undergone surgery or who have tumors that invade blood vessels. Clinicians should suspect renal disease and deficiencies in nutrients such as vitamin B_{12} or folate; at-risk patients should undergo a complete blood count, iron studies, and assessment of vitamin levels. The National Comprehensive Cancer Network Cancer- and Chemotherapy-Induced Anemia Panel recommends that if all other reasons for anemia—such as bleeding, vitamin deficiency, and hemolysis—have been excluded, then a cancer patient who develops anemia after chemotherapy should be diagnosed with chemotherapy-induced anemia and treated accordingly.

H&O Are there ways to prevent chemotherapy-induced anemia?

GR Ideally, before the patient receives chemotherapy, pre-existing anemia should be treated. For example, a young breast cancer patient with iron-deficiency anemia due to heavy menstrual periods should probably undergo treatment for iron deficiency before she receives chemotherapy. This approach could help avoid treatment of chemotherapy-induced anemia. Pre-existing anemia could be caused by iron deficiency or underlying preexisting renal disease, which could be addressed with erythropoietin therapy.

H&O Which patients with chemotherapy-induced anemia should receive treatment for it?

GR The major determinant would be patient symptoms and comorbidities, such as underlying cardiovascular disease or pulmonary disease. Age could also be a factor. At one extreme would be a young cancer patient who is otherwise healthy, and who develops chemotherapy-induced anemia—perhaps a hemoglobin of 9 or 10 g/dL. This patient could probably tolerate these levels and not require treatment at all. In contrast would be an older lung cancer patient who requires oxygen for chronic hypoxemia and is receiving aggressive multiagent treatment. This patient might not be able to tolerate a hemoglobin of 9 g/dL and probably should be treated for chemotherapy-induced anemia.

H&O What are the treatment options?

GR As I mentioned, one option may be to not treat at all, which might be appropriate for patients with mild anemia or patients who have moderate anemia but no symptoms or comorbidities. For symptomatic patients, the options would be red cell transfusion or erythropoietic growth factor therapy, with or without intravenous iron.

At my institution, we have a pharmacy-run anemia clinic that presents the advantages and disadvantages of each treatment option to the patient. For example, risks associated with erythropoietic growth factors include thrombosis and the potential for shortened patient survival and tumor progression. Benefits of erythropoietic growth factors are avoidance of transfusion and its complications, and a gradual improvement in fatigue symptoms. Benefits of red cell transfusion are rapid improvements in hemoglobin and fatigue. Risks include transfusion reactions, viruses, iron overload in patients who require chronic transfusions, and thrombosis. There may also be a mortality risk in patients who are transfused. We inform patients of the advantages and disadvantages of the various options and let them decide.

H&O What is next in the treatment of chemotherapy-induced anemia?

GR There is an increasing body of literature suggesting that patients who have anemia of inflammation, as cancer patients do, will achieve much better responses with intravenous iron. I would encourage readers to become familiar with that literature. Appropriate use of intravenous iron may minimize the need to use high doses of erythropoietin growth factors and thus avoid the potential risks associated with that treatment.

Suggested Readings

Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *ASH Education Program Book*. Washington, DC: American Society of Hematology; 2010:338-347.

Blohmer J-U, Dunst J, Harrison L, et al. Cancer-related anemia: biological findings, clinical implications and impact on quality of life. *Oncology*. 2005; 68(suppl 1):12-21.

Caro JJ, Saks M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer. *Cancer*. 2001;91:2214-2221.

Gilreath JA, Sageser DS, Jorgenson JA, Rodgers GM. Establishing an anemia clinic for optimal erythropoietic-stimulating agent use in hematology-oncology patients. J Natl Compr Canc Netw. 2008;6:577-584

Henry DH. Parenteral iron therapy in cancer-associated anemia. *ASH Education Program Book*. Washington, DC: American Society of Hematology; 2010:351-356.

Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis and mortality in hospitalized cancer patients. *Arch Int Med*. 2008;168:2377-2381.

Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med*. 2004;116(7A):11S-26S.

National Comprehensive Cancer Network Web site. *NCCN Guidelines for Cancer and Chemotherapy-induced Anemia*. Version 2.2011. nccn.org/epc-guideline/guideline/id/EDDAC6A8-9CDE-B334-F2EB-B9C9062EB883?jumpTo=false#. Accessed January 18, 2011.

Rizzo JD, Brouwers M, Hurley P, et al. ASCO/ASH clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol*. 2010;28:4996-5010.

(Clinical Update, continued from page 146)

pneumonitis. The latter toxicity is very unusual, but is something that doctors should be aware of when using this class of drugs. A similar spectrum of side effects has been previously seen across the board with virtually all of the available mTOR inhibitors.

H&O What is the future for mTOR inhibitors in sarcoma?

GD The goal of medical oncology and therapeutic development is to make cancer therapies better. If we are able to intensify the effects of molecular targeting or the effects of chemotherapy or radiation therapy by blocking the mTOR pathway, then we might be able to improve outcomes in sarcoma patients. The current crop of mTOR inhibitors are "first generation," meaning they shut down TOR complex 1 (TORC1). However, the development of new TORC1/TORC2 combination drugs is rapidly moving forward. That being said, we do not know the possible side effects that might be seen with inhibition of both TORC1 and TORC2. Thus, as in all oncology, it will be necessary to find a balance between toxicities and the possible benefits from future mTOR inhibitors, as well as from combinations of mTOR inhibitors with other targeted and nontargeted systemic anticancer therapies.