ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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New Intravenous Iron Replacement Therapies

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H&O How common is anemia in cancer patients?

MA Up to 70% of patients with cancer will develop clinically significant anemia during the course of their therapy. Anemia is more likely to develop in cancers associated with bleeding.

H&O Can anemia influence clinical outcome?

MA Anemia is associated with poorer outcomes, shorter survival, and increased relapse rates. Whether anemia is a contributing factor to these poorer outcomes is unknown. The association may exist because sicker patients are more likely to develop anemia. The treatment of anemia in cancer has not been associated with improved survival. Transfusions in cancer patients have always been associated with decreased survival. It is probable that anemia can influence clinical outcomes by causing patients to be more fatigued and to have poorer performance scores, which are associated with worse outcomes.

H&O What are the various formulations of iron replacement?

MA Oral iron has not been shown to be useful in oncology patients. Intramuscular iron should never be given. According to guidelines from the National Comprehensive Cancer Network (NCCN), if iron is to be given, it should be given intravenously.

There are 5 intravenous iron formulations. Two are iron dextrans: a low-molecular-weight formulation (INFeD, Watson) and a high-molecular-weight formulation (Dexferrum, American Regent). The low-molecular-weight iron dextran is associated with very few adverse events. The high-molecular-weight iron dextran has been shown—in a preponderance of literature—to be associated with a significantly higher adverse event rate than low-molecular-weight iron dextran.

There are 2 salts: ferric gluconate (Ferrlecit, Sanofi-Aventis) and iron sucrose (Venofer, American Regent). Neither of the salt preparations has any advantage over low-molecular-weight iron dextran. They cannot be given as complete replacement in a single setting, and neither has been approved in oncology. In my opinion, the salt formulations should not be used in oncology patients, except in those who are sensitive to iron dextran.

There is a new iron preparation called ferumoxytol (Feraheme, AMAG Pharmaceuticals). Half of a complete replacement dose can be given in 17 seconds, making it extremely convenient. This drug is reserved for anemia of chronic renal failure, and it seems to have a safety profile consistent with those of low-molecular-weight iron dextran, ferric gluconate, and iron sucrose. Currently, there is no complete replacement dosing data available for this agent, and it is much more expensive than the others. Studies are ongoing, and the data are eagerly awaited.

H&O Which patients would be likely to benefit from the use of intravenous iron replacement?

MA Intravenous iron replacement would be an option for patients who have absolute iron deficiency or functional iron deficiency (iron-restricted erythropoiesis). It should be considered in patients who have ferritin levels below 1,000 ng/mL and transferrin saturation (TSAT) levels below 50%, and who are hyporesponsive to erythropoiesis-stimulating agents (ESAs).

H&O How does intravenous iron compare to transfusion?

MA Intravenous iron is far safer than transfusion. There have been 9 studies in oncology, and they all showed that intravenous iron was associated with an improved hemoglobin response, as well as a decrease in the amount of ESA needed to reach the target hemoglobin.[1] Only 2 of the studies showed decrement in transfusion,[2,3] but they were also the only 2 powered to do so. Intravenous iron is much less expensive and much safer, and it is a more physiologic means of treating anemia.

H&O What do data suggest regarding the use of premedication, such as diphenhydramine, administered prior to the use of intravenous iron?

MA There are no data showing that the use of premedication is beneficial. In a 2000 study by Barton and colleagues of patients receiving premedication before intravenous iron dextran, somnolence due to diphenhydramine was the most frequent adverse reaction.[4] In addition, diphenhydramine can cause reactions that might be incorrectly attributed to iron replacement. For patients with an allergic diathesis or allergies to more than one drug, premedication with corticosteroids is prudent.

H&O What are some of the newer intravenous iron replacement therapies?

MA There are 2 new formulations that have been approved in Europe but not in the United States. Iron carboxymaltose (Ferinject, Syner-Med) is being used extensively in Europe in obstetrics/gynecology, inflammatory bowel disease, renal failure, and oncology. It can be given as a 1,000 mg infusion in 15 minutes. This drug was rejected by the US Food and Drug Administration (FDA) 2 years ago based on study data showing unexplained hypophosphatemia at 2 weeks and an increase in deaths and cardiovascular events in the treatment arm (although it is unknown whether those events were related to the iron). Iron carboxymaltose will probably be resubmitted to the FDA.

Iron isomaltoside (Monofer, Pharmacosmos A/S) is another compound that was recently approved in Europe. This drug can be given at 20 mg/kg in 15 minutes—in a 70 kg person, that would be administration of 1,400 mg. The safety and efficacy data appear to be consistent with those of low-molecular-weight iron dextran, iron sucrose, ferric gluconate, and ferumoxytol. We are awaiting more data for the use of this agent in oncology and other iron deficiency states.

H&O What are the future directions of intravenous iron replacement therapy?

MA Most people who receive a prescription for oral iron do not complete the entire regimen. Considering this lack of compliance, a better means of iron replacement should be considered. My colleagues and I will soon be publishing the results of a trial of 1,100 consecutive, nonselected, iron-deficient patients who received a gram of iron, which in most patients is full—or near full—replacement, in 1 hour. The data are compelling: Of the 1,100 patients, only 2 did not receive the full dose. With oral iron, it would be expected that a minimum of 700 patients would not complete the full dose.

The future of iron is to administer it more rapidly and safely at a full dose. Increased education is needed to clarify misunderstandings about the frequency and nature of adverse events. For the first time, there will be an educational session on the clinical use of intravenous iron at the American Society of Hematology meeting in December.

References

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