RE: Adding Epoetin Alfa to Intense Dose-Dense Adjuvant Chemotherapy for Breast Cancer: Randomized Clinical Trial

Moebus et al. (1) reported that erythropoiesis stimulating agents (ESAs) can treat chemotherapy-induced anemia (CIA) in breast cancer patients receiving adjuvant chemotherapy with no effect on overall survival, relapse-free survival, or intramammary relapse. They also conclude that epoetin increased thrombosis. Their treatment protocol did not include adequate iron replacement. Although iron studies were not reported, patients received 200 mg/day oral iron. Many may have been iron deficient or functionally iron deficient (FID) at enrollment. A substantial percentage undoubtedly became FID after enrollment because of treatment with an ESA because oral iron is ineffective therapy when an inflammatory process is present, especially malignancy being treated with chemotherapy. The preponderance of published evidence supports use of intravenous, not oral, iron in this setting (2). The National Comprehensive Cancer Network guidelines recommend intravenous iron when iron is indicated in CIA. With all the dietary perturbations present in CIA, oral iron may be ill-considered.

Failure to include adequate iron replacement as part of ESA study protocols is surprising. In a recent meta-analysis of intravenous iron supplementation for the treatment of chemotherapy-induced anemia, Gafter-Gvilli et al. (3) concluded that intravenous iron significantly increased the hematopoietic response rate, decreased the ESA dose required to achieve the same hematopoietic response, and decreased transfusions in trials with and without ESA. In fact, Steinmetz et al. (4) demonstrated that intravenous iron alone in the treatment of cancer-associated anemia (CAA) and CIA resulted in a substantial hemoglobin increase and stabilization at 11 to 12 g/dL. These findings suggest that adequate iron replacement and correction of FID with both cancer and ESA treatment may be the critical factor in maintaining hemoglobin and quality of life and reducing transfusions (currently the only US Food and Drug Administration-approved indication for ESAs).

Iron deficiency, including FID, may contribute to the increased thrombosis risk associated with ESAs. Although an increase in thrombotic events (TEs) is consistent in studies where an ESA is used to treat anemia, including chronic kidney disease, CAA, and CIA, unfortunately so is the lack of adequate iron replacement (3). High target hemoglobin may contribute to the increased risk of TEs, especially in combination with thrombocytosis associated with iron deficiency. Two publications reported decreased platelet counts and decrements in TEs when intravenous iron was added to the treatment paradigm compared with ESA alone (5, 6).

Although it is encouraging that ESA use reduced transfusion with no effect on overall survival and relapse, conclusions on thrombotic complications with the use of ESAs in this study may be flawed by lack of adequate iron replacement therapy and target hemoglobins of 12.5 to 13 g/dL. Until investigators incorporate adequate iron replacement into protocols, the true thrombotic risk of ESAs in the treatment of CAA and CIA remains unanswered. We urge American Society of Hematology and American Society of Clinical Oncology to revisit the guidelines for routine use of intravenous iron as an adjunct to ESAs in CIA and CAA and investigators to incorporate initial and ongoing assessment of iron parameters with adequate intravenous iron replacement in any study of ESAs for CIA or CAA.

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References

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