Iron Chelation Therapy for Myelodysplastic Syndrome: If and When

AYALEW TEFFERI, MD

In November 2005, the US Food and Drug Administration approved deferasirox (Exjade, Novartis), an oral iron chelating agent, for use in transfusional hemosiderosis associated with hemoglobinopathies, rare anemias, and the myelodysplastic syndrome (MDS). Before this date, the only Food and Drug Administration–approved iron chelating agent in the United States was subcutaneously infused deferoxamine, the method of administration of which has been less than ideal, thus affecting compliance and maximal benefit. Therefore, the availability of an alternative oral agent is welcome news for patients. However, information on long-term toxicity and efficacy of deferasirox remains incomplete and is still being collected from ongoing phase 2 and phase 3 clinical trials. Furthermore, although there is little disagreement regarding the detrimental effect of iron overload and the therapeutic value of iron chelation in thalassemia major, the same is not true for MDS, in which survival and quality of life are primarily affected by leukemic transformation and infection. These are not trivial issues considering the relatively high cost associated with iron chelation therapy.

The MDS constitutes a stem cell–derived, ineffective clonal myeloproliferation that results in severe anemia and other cytopenia(s). Consequently, most patients with MDS are dependent on red blood cell (RBC) transfusions and thus are vulnerable to life-threatening end-organ damage from excess tissue iron deposition. However, it is well established that iron-related organ dysfunction develops after several years of chronic iron overload in both hereditary hemochromatosis and transfusional hemosiderosis from thalassemia major. Furthermore, in both these conditions, organ exposure to excess iron commences early in a person’s life. In contrast, the median age at diagnosis of MDS is older than 65 years, and overall survival is less than 5 years. Therefore, it is not surprising that practicing hematologists and oncologists infrequently encounter death and morbidity as a direct result of transfusional hemosiderosis in MDS. Similarly, no hard evidence implicates transfusional hemosiderosis as a major determinant of survival in MDS, and no controlled studies indicate that this particular complication can be avoided with iron chelation therapy. One recent retrospective report attempted to address the issue of iron overload and survival in MDS. The authors demonstrated a worse survival in the presence of RBC transfusion requirement and a serum ferritin level higher than 1000 µg/L. However, the value of such information is undermined by the fact that the specific adverse study parameters are expected to cluster with biologically advanced disease, and documentation was inadequate to suggest that the observed excess death was secondary to iron-related organ damage. Even if the latter was true, one still has to prove reversal of the particular complication by treatment intervention before recommending iron chelation therapy. Therefore, justification for iron chelation therapy in an individual patient with MDS requires a critical assessment of risk/cost-benefit ratio and likelihood of meaningful health outcomes as opposed to positive effects on surrogate laboratory values.

It is highly unlikely that iron chelation therapy would benefit patients with MDS whose median survival is estimated at less than 5 years. Included in this category are patients with a blast percentage of 5% or greater either in the bone marrow or in the peripheral blood and, in the presence of lower blast counts, those who display either multilineage dysplasia or chromosome 7 or complex cytogenetic abnormalities. According to the World Health Organization criteria, this constitutes the subclasses of refractory anemia with excess blast 1 and 2 and refractory cytopenia with multilineage dysplasia with or without ringed sideroblasts. Therefore, the key question is whether long-term survival patients with MDS who belong to the World Health Organization category of refractory anemia without or with ringed sideroblasts and those with isolated del(5q) cytogenetic abnormality (median survival, about 10 years) would benefit from iron chelation therapy if they have evidence of iron overload from RBC transfusions. In a proportion of such patients, the need for multiple transfusions is partially ameliorated by the therapeutic use of erythropoietin and other myeloid growth factors. The issue is further confounded by the prospect of an effective drug therapy (lenalidomide) for del(5q)-associated MDS, which would imply that phlebotomy might be the preferred and less expensive method of iron removal in that particular setting.
On the basis of the aforementioned discussion, it is reasonable to consider the possibility that chronic iron overload might be detrimental to a subset of RBC transfusion–dependent patients with MDS with refractory anemia without or with ringed sideroblasts or the del(5q) syndrome who are unresponsive to drug therapy.11,15 This is not, however, a treatment guideline but identification of a study population in whom a prospective randomized study would be appropriate. Moreover, considering the finite survival from the underlying hematologic malignancy, such a study should use clinically meaningful end points such as death and morbidity rather than laboratory surrogates such as serum ferritin and magnetic resonance imaging of the liver and heart. Controlled studies are also needed to address the intriguing possibility of alleviating ineffective hematopoiesis and improving cytopenias in MDS with iron chelation.18,19 Until then, the temptation to institute iron chelation therapy in MDS based on anxiety over either hyperferritinemia or frequency of RBC transfusions must be tempered by economical responsibility and current uncertainty regarding impact on overall health outcome.

REFERENCES