

Indications for Successful Iron Overload Treatment and Monitoring: Myelodysplastic Syndromes

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Myelodysplastic syndromes belong to the group of "iron loading anemias" which are characterized by ineffective erythropoiesis leading to increased duodenal iron uptake. Unrestrained iron absorption seems to be due to suppressed hepcidin production in the liver. Although this mechanism contributes to iron overload in MDS, it is not the main cause. Data from the Düsseldorf MDS Registry show that serum ferritin levels at the time of diagnosis are usually around 300-600 ng/ml, and rarely exceed 1000 ng/ml. The most important cause of iron overload in MDS is chronic transfusion therapy. At diagnosis, about 80% of patients have a hemoglobin of less than 10 g/dl, and the majority become transfusion-dependent. Many patients only temporarily respond to various MDS treatment approaches and therefore continue to require transfusions.

Chronic heart failure is probably the most relevant clinical complication of iron overload in MDS. In this elderly patient population, at least four factors contribute to cardiac disease – age, coronary-artery disease, the effects of chronic anemia, and myocardial iron overload. Recently, several groups have used magnetic resonance imaging to obtain evidence of cardiac iron overload in MDS. Their findings agree that it takes 75-100 units of packed red cells to produce T2* values of less than 20 ms, which are indicative of cardiac iron deposits. These findings suggest that there is a long latency period between the first accumulation of iron in the liver and the demonstration of iron in the myocardium. This is in accordance with a postmortem study from the pre-chelation era examining autopsy material from 131 patients with various types of leukemias and other anemias, excluding thalassemias and sickle cell disease. In this report, more than 75 units of blood were required to render the majority of these patients positive for cardiac iron overload. Grossly visible cardiac iron deposits were always associated with cardiac dysfunction and usually chronic heart failure. Iron chelation may have beneficial effects even in the absence of gross myocardial iron deposition, considering that elevated labile plasma iron, the toxic form of iron, can cause damage to the tissues, including the heart.

Other researchers have shown that transfusion dependency in MDS is associated with a decreased likelihood of survival, independent of patients' cytogenetic risk. Therefore,

transfusion dependency must reflect an unfavourable aspect of the disease which is not captured by the karyotype but may be related to unknown molecular genetic changes or iron overload. Two recent studies, one from Canada and one from France, suggest that iron chelation therapy has a beneficial effect on overall survival in patients with lower-risk MDS. Besides preventing iron-related organ damage, intensive chelation therapy may have the additional benefit of improving bone marrow function in MDS patients suffering from iron overload.

Not all patients with MDS are candidates for iron chelation therapy. Patients with high-risk MDS do not live long enough to experience the clinical complications of iron overload. The greatest benefit is expected in patients with lower-risk MDS (IPSS low and Int-1), characterized primarily by dyserythropoiesis. These patients have a favourable prognosis, implying several years of transfusion therapy. Patients with less favorable prognosis but documented stable disease may also benefit as well. Candidates for allogeneic stem cell transplantation should also be considered candidates for iron chelation in order to avoid iron-related organ damage that may increase the risk of transplant-related morbidity. Iron stores in patients with MDS should be assessed at diagnosis and at regular intervals thereafter. In patients for whom chelation therapy is appropriate, as defined above, treatment should begin when serum ferritin levels reach $>1,000 - 2,000$ ng/mL, and be continued as long as iron overload is clinically relevant.

Suggested Readings

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