

Conversations With the Experts: Management of Iron Overload

Chair:

John B. Porter, MA, MD, FRCP

Panel:

Pierre Brissot, MD

Aristoteles A.N. Giagounidis, MD

Ali T. Taher, MD

Recent information on the pathophysiology of iron overload and its clinical consequences, coupled with the availability of new therapeutic agents, has led to a greater understanding of the need to manage iron overload and an increased recognition of the benefits of iron chelation therapy in terms of extended survival and improved quality of life. The application of these advances to the treatment of iron overload in patients with thalassaemia, myelodysplastic syndromes (MDS), rare anaemias, sickle cell disease (SCD), and hereditary haemochromatosis (HH) was the focus of a round table discussion among four international experts in these fields.

Thalassaemia major and thalassaemia intermedia differ primarily in the age at which a patient begins transfusions and the frequency of these transfusions. Most thalassaemia intermedia patients escape the need for regular blood transfusion, while some become transfusion dependent in their 20s or 30s. For those intermedia patients who have begun receiving regular transfusions, the clinical risks of iron overload are generally similar to that of thalassaemia major patients. It is important to note that thalassaemia intermedia patients can develop iron overload even if they are not transfused. In such cases, there are important differences between the distribution of iron overload from that of thalassaemia major. In a recent study in patients with thalassaemia intermedia, a discrepancy was observed between serum ferritin levels and liver iron concentration, indicating that serum ferritin is not a good marker for iron overload in patients with this form of thalassaemia. In addition, for reasons that are not yet understood, patients with thalassaemia intermedia who are not regularly transfused, do not accumulate iron in the heart despite high liver iron levels. With respect to iron removal from the heart, two studies presented at this EHA meeting in patients with thalassaemia major found that

treatment with deferasirox at 30 mg/kg/day improved T2* measures of cardiac iron. In the second, a prospective trial, improvements in myocardial T2* were seen in most thalassaemia major patients at 30 mg/kg/day at 6 months of treatment. In patients who did not experience an improvement in T2*, an increased dosage of 40 mg/kg/day was given for and the results at 1 year are awaited.

Although previously, iron overload was not generally discussed as part of supportive therapy for patients with MDS, now—based on the results of studies suggesting benefits in terms of survival and perhaps enhanced erythropoiesis—it has become an important issue in treatment. This indirect evidence comes from several sources, including a study showing a relationship between survival and transfusion dependency/independency in MDS patients, irrespective of risk group, and the observation of a correlation between serum ferritin and outcomes in different MDS risk groups. MDS patients who can benefit from iron chelation include low-risk transfusion-dependent patients with serum ferritin above 1000 to 2000 ng/mL and high-risk patients undergoing curative therapy. With the exception of the latter, high-risk patients generally do not have an expected survival long enough to warrant chelation therapy.

Recently, there have been some investigations examining the response to chelation in patients with various rare anemias, such as Blackfan anaemia, compared with the response in patients with thalassaemia major and MDS. In these conditions, in which the source of iron overload is transfusion, the change in liver iron in relation to the change in ferritin was similar across groups, unlike the discrepancy observed in this relationship in patients with thalassaemia intermedia, in which the source of iron overload is the gut. In addition, the response to chelation in the groups studied was related to the rate of transfusion, with a greater frequency of transfusion requiring more chelation therapy.

There has been some question as to whether SCD is fundamentally different from thalassaemia, particularly in terms of a lower risk of cardiac iron. Until age-matched controlled studies are available, however, this issue remains unresolved.

The specific mechanism of iron overload in the different types of HH bears a direct relationship to appropriate iron chelation therapy in patients with these disorders. Types 1, 2, and 3 are characterized by a deficiency in hepcidin, resulting in an increased release of iron from enterocytes or macrophages into the serum and from there into the parenchymal cells. On the other hand, type 4 is the result of a mutation in ferroportin, resulting in a ferroportin deficiency with an accompanying decreased mobilization of iron/decreased exit of iron from the cell into the serum. Thus, while venesection is an effective means of reducing iron overload in the hepcidin-deficient types 1, 2, and 3, it is not as useful in treating iron overload in the ferroportin-deficit type 4. In contrast, iron chelators can be beneficial in type 4 HH and in occasional cases of types 1, 2, and 3 HH when venesection is not feasible due to psychological resistance or impaired venous status, or as adjunctive therapy when there is a need for rapid reduction of massive iron overload.