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In search of the optimal iron chelation therapy for patients with thalassemia major

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(Related Original Article on pages 41 and 48)

Despite the fact that iron chelation therapy has been available for more than forty years, iron cardiomyopathy is the most common cause of death in patients with transfusion dependent anemia.[1,2] In the last decade, however, such deaths have been significantly reduced.[2-5] This improvement has been attributed in part to greater iron chelation options and the ability to recognize pre-clinical cardiac iron deposition by Magnetic Resonance Imaging studies (MRI). Patients with low cardiac T2*, as measured by MRI, have a significant risk of developing overt heart failure over a 12-month period if changes to their chelation regime are not made (Figure 1).[6] Surrogate markers used in the past, such as ferritin and liver iron concentration for predicting cardiac risk, have been shown not to be particularly predictive of the degree of cardiac iron load (Figures 2A and B) with an r value of less than 0.5 for both.[7] This indicates how valuable MRI measurements are. Optimal chelation therapy remains a controversial topic. The article by Pepe *et al.*[8] published in this issue of the journal (MIOT Study), outlines results from a large Italian multicenter cross-sectional analysis on the MRI of patients who have received iron chelation ther-

apy for at least 12 months with monotherapy with deferasirox, deferiprone or desferrioxamine. The parameters analyzed include whole-heart T2*, cardiac function and liver T2*. The major innovation of this paper is that the MIOT (Myocardial Iron Overload in Thalassemia) project on behalf of the Society for Thalassemia and Hemoglobinopathies (SOSTE) has created a network of thalassemia centers throughout Italy that have agreed to standardize and share their cardiac MRI assessments. This type of network is extremely powerful and allows observational trials to be performed relatively easily. The novel aspects of the MRI analysis include the number of segments of the heart that had normal iron concentration. In the future, this latter analysis might show a relationship to the incidence of arrhythmias which are not necessarily related to the degree of cardiac iron loading as determined by cardiac T2*.[6]

The MIOT study shows that the group of patients on deferiprone had better cardiac T2* levels and better cardiac function, including right ventricular ejection fraction, than those taking either desferrioxamine or deferasirox. In addition, the hearts from patients on deferiprone also had more segments with normal T2*. The study had three key limitations. First, there was considerable selection bias. Patients who remained on desferrioxamine or deferiprone were likely to have had established an acceptance of their therapies, while patients using the newest chelator, deferasirox were inherently less happy with their prior treatment. Secondly, treatment duration was at least half as long for deferasirox therapy compared with the other two chelators; cardiac iron removal is known to be a very slow process. Thirdly, cardiac iron levels were only characterized at the end of the observation interval. Even though ferritin levels were similar between the deferiprone and deferasirox groups, it does not preclude the possibility that the starting cardiac T2* was higher in the deferiprone group, particularly given the greater duration of deferiprone therapy.

Irrespective of these caveats, the results are meaningful and worthy of attention. The first publication suggesting cardiac protection of deferiprone[9] came from the group that first developed the methodology for assessing cardiac iron load indirectly using the T2* evaluation of the heart.[10] Subsequent studies showed similar outcomes.[11, 12] In a pivotal randomized study, deferiprone was superior to desferrioxamine in removing iron from the heart and showed a significantly greater improvement in left ventricular ejection fraction (LVEF).[13] A large Italian study showed no new cardiac events in 157 patients who changed to deferiprone compared to 57 cardiac events and 15 cardiac related deaths in the 359 patients who had continued on desferrioxamine.[14] A study from Athens with similar results has also been recently published. In addition, in patients with cardiac dysfunction, this latter study showed more patients achieved reversal of cardiac dysfunction on deferiprone than those who remained on desferrioxamine.[15] The data from this MIOT study are also very consistent with results that were published from the same unit in Athens that showed superiority of deferiprone and combination of deferiprone and desferrioxamine over desferrioxamine and deferasirox with respect to clearance of

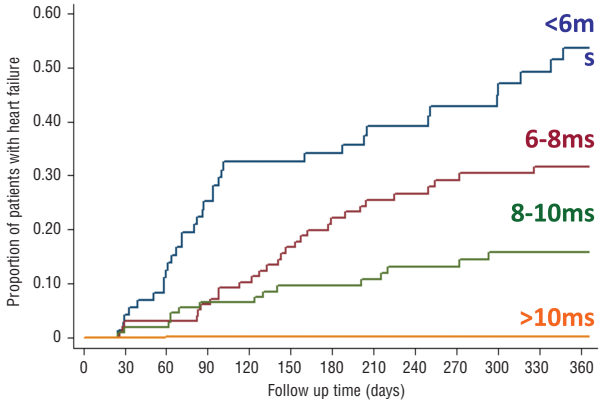

Figure 1. Kaplan-Meier curve showing the proportion of patients who developed overt cardiac failure over a 12-month period according to their baseline cardiac T2* value if no changes were made to their chelation regime. Reproduced with permission from Kirk P *et al.*[6]

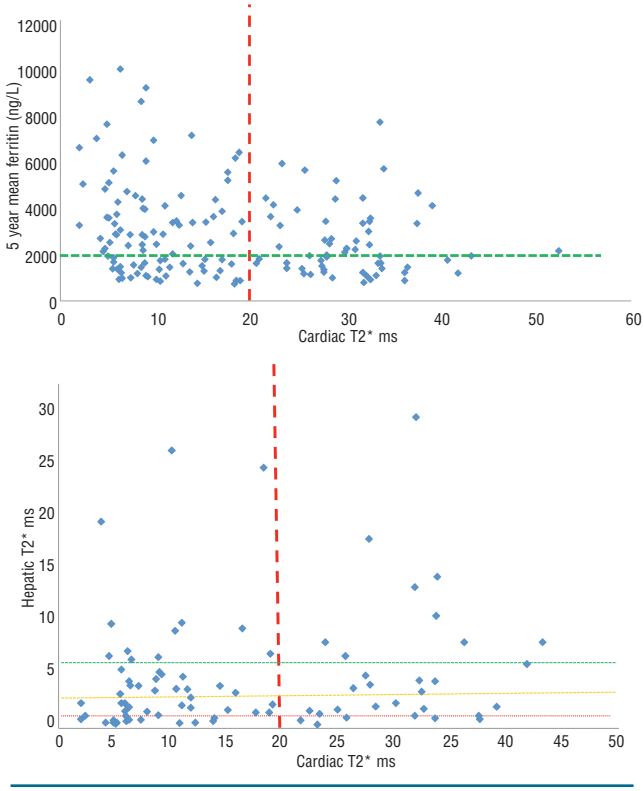

Figure 2. Cardiac magnetic resonance imaging T2* assessments and analysis of historical parameters in patients with transfusion-dependent thalassemia. (A) Scatter diagram and regression line of the 5-year ferritin compared to the Cardiac T2*. The vertical red dotted line indicates the T2* value below which cardiac iron is considered to be present. The horizontal green dotted line represents the mean ferritin value above which a patient is considered to be at risk of cardiac problems. (B) Scatter diagram of hepatic T2* compared to cardiac T2*. The three horizontal dotted lines indicate the divisions of hepatic T2* that are associated with acceptable (>5.2), (green) mild (2.5-5.2), (yellow) moderate (1-2.5 ms) and (fine dotted red) heavy (<1ms). The vertical red dotted line indicates the level of cardiac T2* that differentiates between a normal and an iron-loaded heart. Adapted from Aessopos *et al.*[7]

cardiac iron.[16] Another recent Italian study concluded that, when deferiprone is used, cardiac improvement is seen before there is a significant reduction in the total body iron.[17]

The theoretical mechanism for the cardiac protective effect of deferiprone is related to its chemical characteristics, including its small molecular weight. These characteristics allow it to promptly permeate cells, giving it access to and binding the free intracellular iron[18] that potentiates the formation of toxic free radicals. It, as well as the other two chelators, also reduces free plasma iron (labile plasma iron)[19] that is thought to enter many organs, including the heart and pancreas.

The cardiac profile of deferasirox is less well characterized. Three recent publications demonstrate that deferasirox at doses in the range of 40 mg/kg/d is capable of reducing cardiac iron, particularly in patients with mild to moderate hepatic and cardiac iron loading. In the US04 study, cardiac response was strongly associated with initial and final liver iron levels; reductions in liver iron were a prerequisite for cardiac response.[20] In the EPIC sub-studies, cardiac response was correlated with both initial cardiac T2* and changes in serum ferritin. Patients without cardiac iron overload, i.e. with T2* greater than 20 ms, did not accumulate iron in the heart over a one year period. Interestingly, these patients improved their left ventricular ejection fraction while patients having residual cardiac iron did not.[21] In the most recent of these studies, published in this issue of the journal,[22] continuous treatment with deferasirox for two years with a target dose of 40 mg/kg/d continued to remove iron from the heart of patients with β-thalassemia major and mild, moderate and severe cardiac siderosis.

Although the ability of a chelator to control cardiac iron is important, control of total body iron overload remains critical. By using all current information available today with respect to cardiac protection and achieving this, we will be able to pay greater attention to reducing deaths from infection and hepatic cancer and cirrhosis. As patients are becoming older, the incidence of hepatic cancer and cirrhosis is increasing.[23] These complications are related to iron overload and viral infections of the liver. For patients with active hepatitis, appropriate management should be instituted with antiviral treatment. There is evidence that the success of the antiviral therapy is greater with low levels of liver iron.[24] There are, therefore, two arms to chelation for liver iron. The first is to prevent it, so that the risk of iron induced malignancy is reduced, and the second is to clear the liver of iron both for reduced risk of malignancy and to improve the effect of antiviral treatment.

The challenges that face us today with respect to iron chelation are:

- when should we start chelation, and with what, in order to maintain children at normal levels of iron stores, thereby reducing the incidence of cardiac disease, growth failure and endocrine dysfunction;
- how low can we maintain total body iron without side effects from over-chelation of iron;
- keeping patients committed to their chelation regimes that may be complicated and even cumbersome;
- develop new efficient iron chelators that may have acceptable side effects and be available to patients who for any reason cannot have current chelators;
- assess the efficacy and safety of the other combinations of the chelators, and in particular the use of deferasirox and deferiprone, so that injectable chelation will no longer be necessary. In particular, as randomized clinical trials are prohibitively expensive and cumbersome to perform, networks, such as that of the MIOT, are likely to provide such information.

With the large numbers of patients included in its data base, the MIOT network is ideally situated to provide clearer outcomes with respect to these questions, particularly changes in cardiac T2*, ventricular function and liver iron concentration according to the chelation regime. In addition to characterizing combination desferrioxamine-deferiprone therapy, the MIOT network could provide firm data on the outcomes with other combinations that will be used in the future. The availability of three chelators in many countries allows informed choices to be made for patients according to the MRI findings. Follow-up studies from the MIOT network will provide invaluable clinical guidance to centers with and without MRI capability. The ability to reduce cardiac T2* to normal and maintain it, should mean that deaths from cardiac failure will become of historical interest. Maintaining low iron burden in the liver and other organs should also reduce the common morbidities[25] and mortality even further.

Dr. Berdoukas is a pediatrician who has worked in the field of talassemia sindrome and hemoglobinopathies for almost 40 years. He conducted studies comparing deferiprone to desferrioxamine in their respective ability to remove excess cardiac iron. Dr. Wood is a pediatric cardiologist who studies the cardiovascular and endocrine consequences of hemoglobinopathies and their therapies.

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Prognostic relevance of anemia and transfusion dependency in myelodysplastic syndromes and primary myelofibrosis

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(Related Original Article on page 167)

Anemia is a cardinal manifestation of myelodysplastic syndromes (MDS) and primary myelofibrosis (PMF). Over half (54%) of the patients with *de novo* untreated myelodysplastic syndromes, in the International Prognostic Scoring System (IPSS) cohort, presented with hemoglobin levels of less than 10 g/dL.[1] In another independent cohort with IPSS low or intermediate-1 risk myelodysplastic syndromes, an almost identical proportion (55%) of patients presented with a similar degree of anemia.[2] Similarly, most patients with primary myelofibrosis are anemic at presentation and the hemoglobin level was less than 10 g/dL in 35% to 54% of patients in some studies.[3,4]

The pathogenesis of anemia in both myelodysplastic syndromes and primary myelofibrosis is poorly understood and is attributed to "ineffective erythropoiesis" for convenience. Because both disorders are markedly heterogeneous in their molecular and biological features, it is reasonable to assume that multiple factors contribute to the associated erythropoietic defect. In myelodysplastic syndromes, these include haploinsufficiency of genes and microRNAs in commonly deleted chromosomal regions, mitochondrial dysfunction, acquired abnormalities of hemoglobin synthesis, and abnormal expression of proinflammatory cytokines and other growth factors.[5] The latter has also been implicated in PMF-associated ineffective hematopoiesis;[6] additional contributing factors to MF-associated anemia include mutation profile (presence of *JAK2*V617F[7] might be favorable and *MPL*[8] and *TET2*[9] mutations unfavorable in this regard),[10] bone marrow stromal changes, hypersplenism and chronic low grade hemolysis.[11]

Anemia has long been recognized as an adverse prognostic factor for overall survival in myelodysplastic syndromes.[1,12,13] With the introduction of the World Health Organization (WHO) classification system there has been a re-examination of prognostic factors in myelodysplastic syndromes.[14,15] In a study of 467 *de novo* MDS patients, the development of red blood cell transfusion need was associated with significantly shorter overall and leukemia-free survival in myelodysplastic syndromes without excess blasts.[16] Subsequently, a dynamic prognostic model that