Iron-chelating therapy for transfusional iron overload

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Supplementary Appendix:

Approach to Determining the Dose of an Iron-Chelating Agent

Iron-chelating therapy for iron overload in transfusion-dependent thalassemia is one of the most successful medical treatments, able to prevent death from iron toxicity in adolescence and make possible a life expectancy approaching normal.[1] The dramatic effect of deferoxamine on survival in transfusion-dependent thalassemia in Italy is shown in Supplementary Figure 1.[2] Continuing improvements in survival after the introduction of deferoxamine have resulted, in part, from advances in tailoring the doses of iron-chelating agents to the needs of individual patients.

The optimal dose of an iron-chelating agent is determined by three principal factors: the presence of cardiac iron overload, the body-iron burden and the rate of transfusional iron loading. Table 2 in the main article text shows an approach to using these factors to determine the doses of iron chelators likely to be needed for best management of patients with transfusional iron overload. The bioavailability of deferasirox may also affect the dose required.[3,4] In brief, if cardiac iron overload is present, ridding the heart of the excess iron becomes the critical therapeutic goal. In the absence of cardiac iron overload, the long-term objective is to maintain the body iron at a level that permits safe storage while avoiding chelator toxicity from administering excessive amounts relative to the body iron. The greater the rate of transfusional iron loading, the greater the dose of iron chelator that will be needed to control iron accumulation.

Cardiac Iron

The use of magnetic resonance imaging (MRI) methods to detect iron deposition in the heart, pituitary gland, pancreas and other organs has been a major advance in the management of transfusional iron overload.[5-7] In particular, measurements of the myocardial effective transverse relaxation time (T_2*) predict the risk of cardiac failure and arrhythmia in patients with thalassemia major.[8] If MRI evidence of myocardial iron deposition is found, eliminating excess iron from the heart becomes the dominant therapeutic objective (Table 2, main article text). Iron is removed from the heart much more slowly than from the liver, usually requiring years of intensive iron-chelating therapy. With continuous intravenous deferoxamine, one estimate is that the effective half-life for cardiac iron clearance is 13.5 months, while that for hepatic iron is 1.4 months.[7,9] As a consequence, in chelated patients, the hepatic iron concentration can not be used to predict the presence of cardiac iron. The liver iron can be within an optimal range despite severe cardiac iron overload. Nonetheless, sustained severe iron overload with high hepatic iron prospectively predicts cardiac iron loading.[10]

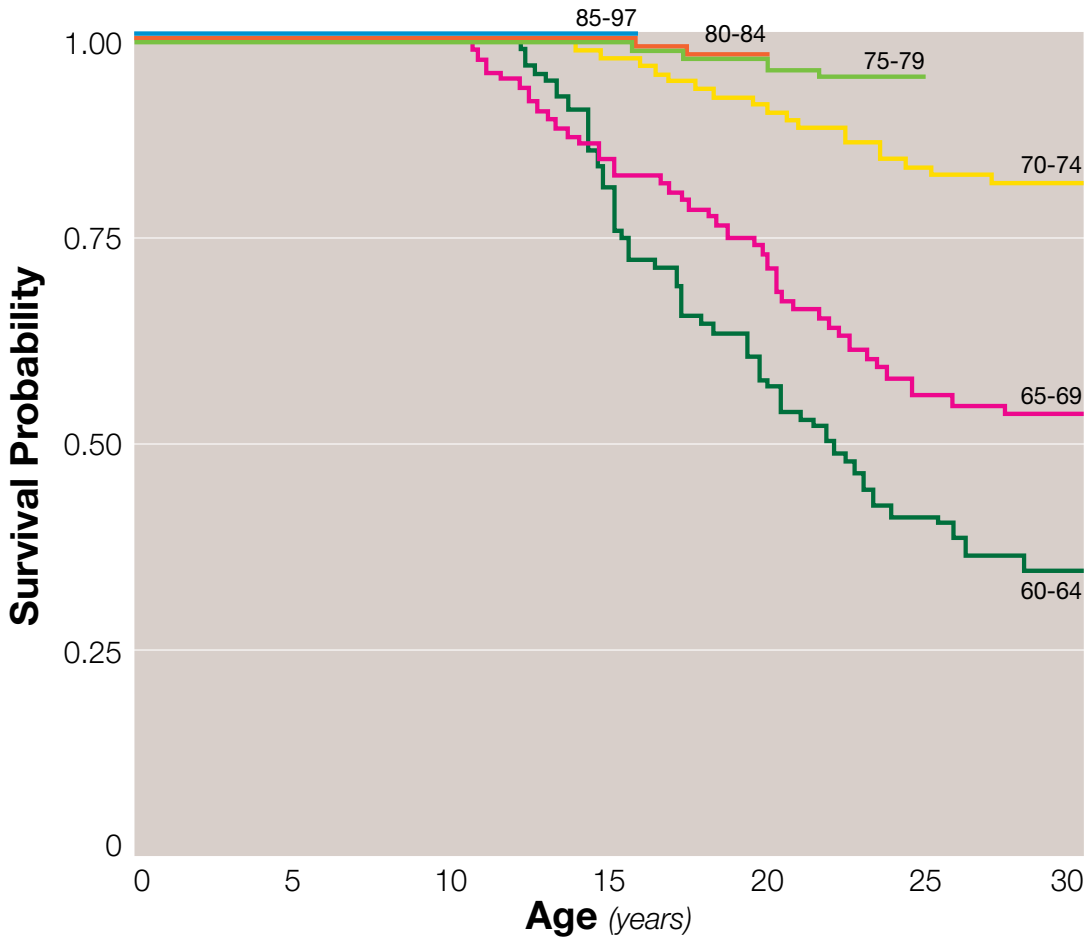
Body Iron

The best measure of the body iron load is the hepatic storage iron concentration,[11] which detects increases in both hepatocytes and reticuloendothelial macrophages (Kupffer cells). Chemical analysis of tissue obtained by biopsy is the reference method but, if properly calibrated, non-invasive MRI techniques can be used.[6,12-14] Commercial biomagnetic susceptometers using superconducting quantum interference device (SQUID) technology have had difficulties with calibration.[15-18] Serum ferritin should be used as the primary index of body iron only when other measures of liver iron are unavailable because concentrations are also influenced by a host of factors other than body iron, such as inflammation, infection, and liver disease, especially in sickle-cell

disease[19] (Supplementary Figure 2). The optimal body iron should minimize both the complications of iron overload and the adverse effects of iron chelators.[20] The hepatic iron concentrations corresponding to the optimal body iron, about 3 to 7 mg per gram of liver, dry weight, originally proposed for thalassemia major,[20] are conservative but seem generally applicable in transfusional iron overload despite differences in the pathophysiology of the underlying disorders. Liver iron concentrations greater than 15 mg/kg, approximately the transfusional iron load in a 60 kg individual given almost 50 units of blood, constitute severe iron overload, associated over the long-term with a greatly increased risk of liver and heart disease, diabetes and early death.[6,10,21,22] With severe iron overload, the rate of progression of hepatic fibrosis is proportional to the liver iron concentration.[6,21,22] In the absence of cardiac iron deposition, control of the liver iron burden becomes the predominant therapeutic aim.

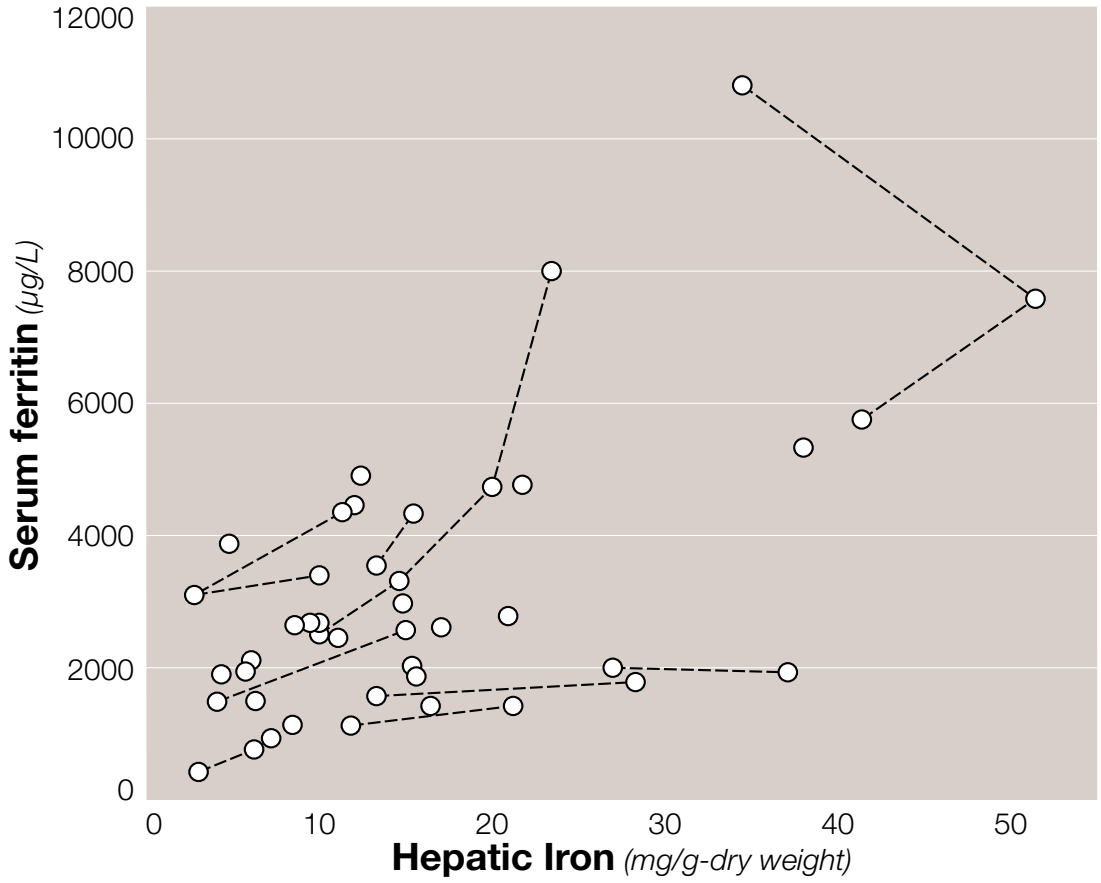
Rate of Transfusional Iron Loading

To maintain the iron load within an optimal range, chelator-induced iron excretion must match the rate of transfusional iron loading, or exceed the rate to reduce the body iron. Patients with sickle-cell disease who receive simple transfusions for prevention of stroke, as in the clinical vignette, will have rates of transfusional iron loading similar to those in thalassemia major. These rates of iron accumulation can rapidly increase the body iron to potentially toxic amounts (Supplementary Figure 3). With both deferoxamine and deferasirox, iron excretion increases linearly with dose,[23] so the higher the rate of iron loading, the greater the dose of these chelators that will be needed for optimal control of body iron (Table 2, main article text).



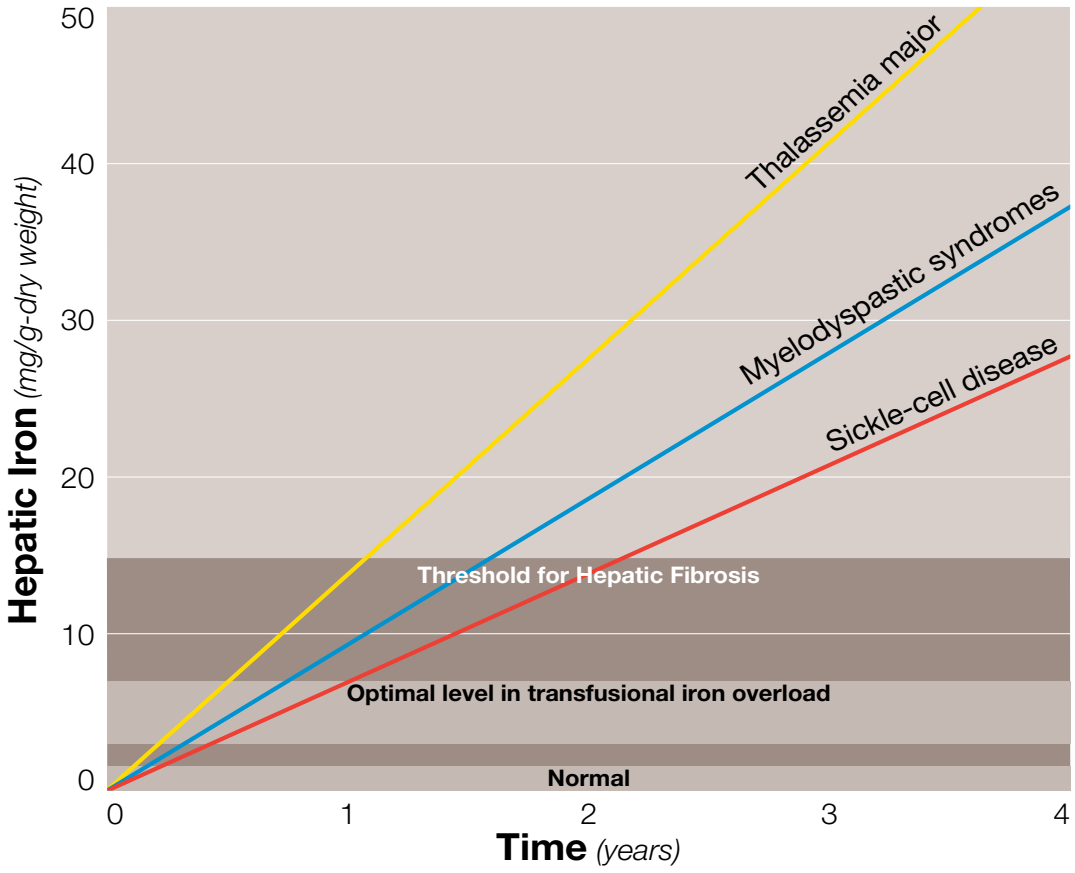
SUPPLEMENTARY FIGURE 1

FIGURE 2: Survival after the first decade of life in patients with thalassemia major in Italy. Kaplan-Meier probability of survival after the first decade of life for patients with thalassemia major since 1960, by 5-year birth cohorts. Deferoxamine use began as an intramuscular injection in 1975 and as a subcutaneous infusion in 1980. Adapted from Borgna-Pignatti et. al., 2004,[2] with permission.



SUPPLEMENTARY FIGURE 2

Changes in serum ferritin and hepatic iron concentrations in chronically transfused patients with sickle disease. These patients were participating in the STOP and STOP2 trials of stroke prevention. Dashed lines indicate changes in individual patients. The averaged correlation coefficient between the serum ferritin and hepatic iron was R = 0.55, suggesting that the hepatic iron concentration accounts for only about 30 per cent of the variation in serum ferritin and is of limited value in monitoring individual patients. Adapted from Adamkiewicz et. al., 2009,[19] with permission.



SUPPLEMENTARY FIGURE 3

Average rates of iron accumulation from red blood cell transfusions in sickle-cell disease, myelodysplastic syndromes and thalassemia major. In recent studies,[23] the mean rate of transfusional iron loading in patients with sickle-cell disease was 0.21 mg/kg per day, in those with myelodyspastic syndromes, 0.28 mg/kg per day, and, in those with thalassemia major, 0.40 mg/kg per day (roughly equivalent to 3.5 units of blood per month in a 60 kg individual) Changes in hepatic iron were estimated from rates of iron accumulation.[11]

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