

Iron chelation in sickle cell disease

Opinion

In the past decades, progress in diagnosis and treatment of sickle cell anemia has given rise to an increase in life expectancy. Life expectancy as outlined by Curtis et al.,¹ in 1973 was estimated that the median age of survival was 14.3 years for both sexes, however in 2010 it was estimated that 93.4% of all those with sickle cell disease (SCD) would survive to age 18, and a study in 2014 estimated a median survival of 58 years for both sexes with SCA.

So far the available treatments that have been used were based on systemic (prophylactic) or sporadic blood transfusion/exchange blood transfusion due vaso-occlusive crises. Chronic transfusion therapy to maintain hemoglobin S <30% has been proved effective for stroke prevention, progressive pulmonary hypertension (PH), severe anemia and to a lesser extent to prevent episodes of acute pain in children and adults. Hydroxyurea's ability to induce Hb F production was observed at the early 80's and a large number of clinical trials in children and adults has been associated with improved survival without accompanying serious adverse events. Bone marrow transplantation is the ideal and definitive treatment but the difficulty of finding a compatible donor due to the lack of availability of fully adapted HLA donor donors for patients who meet transplantation criteria limits their use.

Cirrhosis and hemochromatosis is a common finding in patients with sickle cell disease, and it's the result of multiple causes that occur: VOC, transfusions, infections, and chronic hemolysis. Patients presented with liver necrosis, portal fibrosis, regenerative nodules and cirrhosis as the result of recurrent vascular obstruction, necrosis and rehabilitation involved in the pathophysiology of sickle cell disease.

Iron chelation treatment is an important component of the transfusion program. There are currently three iron chelators that are available. All three are effective and have provided a significant improvement in the quality of life of patients.

Chelation therapy with deferoxamine was the gold standard of care for thalassemic patients with transfusional iron overload since the late 60's. Unfortunately the compliance was limited due to parenterally administration. Deferiprone was the first extensively studied oral chelating agent in the early 2000s for patients who were unable to use deferoxamine effectively or safely. Although deferiprone-treated patients had good compliance, some serious side effects such as neutropenia and agranulocytosis were reported that limited its use. However, deferiprone in combination with desferal significantly reduced heart disease in thalassemic patients.

Deferasirox an oral iron chelator in a single dose developed for treating transfusional iron overload. Adverse events were mild, including transient nausea, abdominal pain and skin rash. Abnormal laboratory studies with deferasirox were occasionally associated with mild increases in serum creatinine and reversible elevations in liver function tests. However in all studies reviewed none of the patients developed kidney or liver damage.

The need for a reliable assessment of excess iron load and accurate quantitative measurement has been perceived since the early years of the development of chelating agents.

Over the past 20years, non-invasive techniques such as

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Magnetic Resonance Imaging (MRI) developed and led to improved quantification of Liver iron without a biopsy (LIC). The Magnetic Resonance Imaging and Transient Elastography combined with the haematological and biochemical parameters gives us the best overall results for iron overload evaluation.²⁻⁴

Almost all recommendations and guidelines for iron chelation in patients with SCD are similar to those for other multi-transfused patients such as those with thalassemia major or myelodysplastic syndromes. Some of them did not meet the inclusion criterion of SF lower than 2,000ng/mL. However, all of them met the criterion of LIC lower than 7mg Fe/g d.w.

Ferritin is not a reliable marker and must be measured in steady state separate from acute inflammatory or vaso-occlusive events. Whenever available, measurement of liver iron concentration by non-invasive means (R2 or R2* magnetic resonance imaging) is recommended. LIC is highly linearly related to total body iron content.

Transient Elastography has been studied in patients with iron overload diseases such as β -thalassemia and primary hemochromatosis and may constitute a reliable and easy to apply noninvasive method to assess liver fibrosis in patients with SCD; Considering the slow kinetics of heart iron loading in SCD cardiac magnetic resonance T2* assessment can be measured at two-year intervals.

What about non transfusional sickle cell disease?

The same measures available for the assessment of iron overload in patients with transfusion-dependent β -thalassemia major and SCD can be used in non transfusional SCD. There's also ineffective erythropoiesis, chronic anemia, hemolysis that leads to iron overload. The initiation of chelation therapy in individuals with non systematic transfusional SCD or sporadic transfusional SCD is dependent upon the degree of iron deposition in the liver and heart, the amount of hepatic and cardiac dysfunction present and the systematic complications of the disease or its treatment. Iron overload can, however, be readily controlled with chelation therapy.

Then how do we manage iron overload in sickle cell disease?

From our experience we use annual liver MRI and initiate chelation if the liver iron is >3mg/g dry weight or if the serum

ferritin is >1000ng/mL on two consecutive measurements. We also use annual Transient Elastography for assessing even early stages of fibrosis, because minor liver fibrosis is often a predictor of disease outcome and can affect therapy and follow-up. We prefer to initiate treatment at lower LIC values in order to achieve better protection of the liver anticipating that liver problems will be increased in aging SCD people. The optimal dose of the chelating agent is determined by the patient's age, iron stores, the frequency of transfusions, the total number of transfusions and the presence of organ dysfunction due to iron overload. We also suggest the combination or iron chelation with hydroxyurea considered as a radical scavenger that contains the hydroxamate function and showed an iron chelation effect in vitro.

I hope that this opinion has helped motivate you to think about iron chelation as an adjuvant treatment to support and managing these patients sufficiently different than the past.

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Conflict of interest

Author declares that there is no conflict of interest.

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