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REVIEW ARTICLE

Iron Loading and Chelation in Non-transfusion Dependent Thalassemias

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ABSTRACT

Non-transfusion dependent thalassemia (NTDT) defines thalassemic patients who do not require regular transfusions for survival. However, these patients are still at risk for iron loading related to primarily increased iron absorbtion through intestines. Herein, the iron accumulation mechanisms, complicatrions and management of iron loading in patients with NTDT were summarized.

Key words: NTDT, iron, chelation, LIC

Non-transfusion dependent thalassemias (NTDT) are characterized with no or occasional transfusional requirements and β-thalassemia intermedia, HbEβ and HbH disease are among the NTDT group of disorders [1].

Pathophysiology of iron loading in NTDT

The iron loading is also a problem in patients with NTDT related to ineffective erythropoiesis, although being less severe compared to transfusion dependent thalassemias. The major cause of iron loading in patients with NTDT is related to ineffective erythropoiesis, in addition to occasional transfusions, if applied. Ineffective erythropoiesis ends-up with hepcidin down-regulation related to high growth differentiation factor -15 (GDF-15) and twisted gastrulation factor-1 (TWGF-1) [2,3]. The down-regulation of hepcidin causes ferroportin to be active throughout the enterocytes and macrophages. The increased ferroportin activity in the enterocytes causes increased intestinal iron absorbtion, whereas the active ferroportin on the macrophages causes release of stored iron from macrophages [4]. Strikingly, serum GDF-15 levels are higher in patients with β-thalassemia major compared to those with β-thalassemia intermedia [5]. This finding is related to the suppression of the erythropoietic activity with transfusions in patients with β-thalassemia major. However, the erytropoietic activity and inturn serum GDF-15 levels are higher in patients with β-thalassemia intermedia, since these patients are not regularly transfused.

Complications of iron loading in NTDT

In patients with NTDT, the export of iron from macrophages related to low hepcidin and in-turn active ferroportin protein causes some of the differences of iron loading patterns of transfusional and non-transfusional iron loading. Since iron is exported form the macrophages of liver, the iron accumulates in the hepatocytes dominantly [6-8]. Secondly, as serum ferritin reflects the iron accumulated in macrophages, serum ferritin screening becomes a less reliable surrogate marker of iron accumulation in patients with NTDT [9,10]. The serum ferritin levels corresponding to same liver iron concentration (LIC) values of β-thalassemia major are lower in patients with β-thalassemia intermedia [9]. On the other hand, cardiac iron accumulation is not a regular finding of the patients with β-thalassemia intermedia [11]. Among 19 patients with β-thalassemia intermedia, mean cardiac T2* was found as 47.3±7.1 ms (35-66.9), indicating that none of the patients had cardiac T2* above 20 ms [11]. This might be related to the major route of iron accumulation in patients with NTDT, which is mainly intestinal absorbtion; whereas the transfusional iron accumulation in patients with

β-thalassemia major ends-up with both cardiac and hepatic iron loading.

On the other hand, the risk of hepatocellular carcinoma is much higher in patients with β-thalassemia intermedia compared to patients with β-thalassemia major, even in the absence of hepatitis C infection [12,13]. This could partially be explained with the hepatocellular iron loading pattern of β-thalassemia intermedia compared to iron accumulation of primarily in macrophages of patients with β-thalassemia major. Additionally, the higher risk of hepatocellular carcinoma might be related to the underestimation of iron accumulation and underchelation of NTDT patients related to mainly iron loading follow-up with serum ferritin measurements.

The outcomes of OPTIMAL CARE study indicates that transfusions applied to patients with β-thalassemia intermedia decrease the risks of extramedullary hematopoiesis, pulmonary hypertention, thrombosis, cholelithiasis and leg ulcers, while increasing the risk of endocrinopathies associated to iron accumulation [14]. The striking finding of OPTIMAL CARE study was the mean number of complications among patients with β-thalassemia intermedia who received neither hydroxyurea, transfusions or chelation therapy was 2.43; whereas the mean number of complications among patients who received transfusions and chelation with or without hydroxyurea was 0.83 and 0.85, respectively [14].

Treatment of iron loading in patients with NTDT

Although the rate of hepatic iron accumulation in NTDT is slower compared to that of patients with β-thalassemia major, this iron also needs to be monitored and chleated, in order to prevent the above-mentioned complications [6]. Among the currently available iron chelators, deferasirox is the first approved for the chelation of patients with NTDT (15). In the reported literature, there are small series of patients reported to be treated with deferoxamine or deferiprone, as well [16-20]. Deferoxamine has been reported to decrease serum ferritin levels by the 6th month in a group of patients (n=10) aged 1.2-17.3 years-old, in addition to increasing the urinary iron excretion [16]. On the other hand, in a prospective, open-label study, the use of deferiprone in three patients over 18 years of age were found to have decrease in serum ferritin levels in six months of treatment duration [17

THALASSA study is a one-year, prospective, randomized, double-blind, placebo-controlled phase 2 study, in which deferasirox (5 mg/kg/day and 10 mg/kg/day) was compared to placebo group among patients with NTDT of ≥10 years of age who had LIC of ≥5 mg Fe/g dw in R2-MRI and serum ferritin >300 ng/ml [21]. By the end of the first year of THALASSA study, LIC levels were found to decrease significantly more among the deferasirox group compared to placebo (p=0.001). Besides, LIC decrease was much prominent at deferasirox dose of 10 mg/kg/day compared to 5 mg/kg/day (p=0.009) [21]. The one-year results of THALASSA study revealed no adverse event ending with death and the most common adverse event was reported as those related to gastrointestinal complaints including nausea, diarrhea and abdominal pain [21]. In 2013, one-year extention results of THALASSA study was reported, indicating the further decline in LIC levels in a dose-dependent manner [22].

In the THALASSA studies, the dose escalations or descalations were made according to LIC levels measured with MRI methods [21,22]. However, the unavailability of MRI methods in many centers which follow patients with NTDT, prompted a recent study of finding cut-off values of serum ferritin levels which may predict either significant LIC requiring chelation treatments, increases in LIC requiring dose escalation or the need for chelation cessation [23]. This study by Taher et al revealed that serum ferritin levels above a cut-off value of 800 ng/ml were predictive for a LIC of ≥5 mg Fe/g dw and could be an indicator of initiation of chelation for centers where MRI evaluations were not possible. Secondly, serum ferritin levels above 2000 ng/ml were highly correlating with LIC levels ≥7 mg Fe/g dw and was indiicating the need for dose increment for patients who are already on chelation. Lastly, the serum ferritin levels <300 ng/ml were highly in concordance with LIC <3 mg Fe/g dw and was suggested to make a decision for cessation of chelation treatment [23].

In the guidelines of Thalassemia International Federation (TIF), iron chelatiion was suggested to be done in patients with NTDT in close follow-up and according to iron overload of the patient (Figure 1) [1]. The patients with NTDT were suggested to be screened for iron loading starting at 10 years of age (15 years of age for patients with HbH) by LIC measurements in centers where MRI methods were available or by serum ferritin measurements if MRI

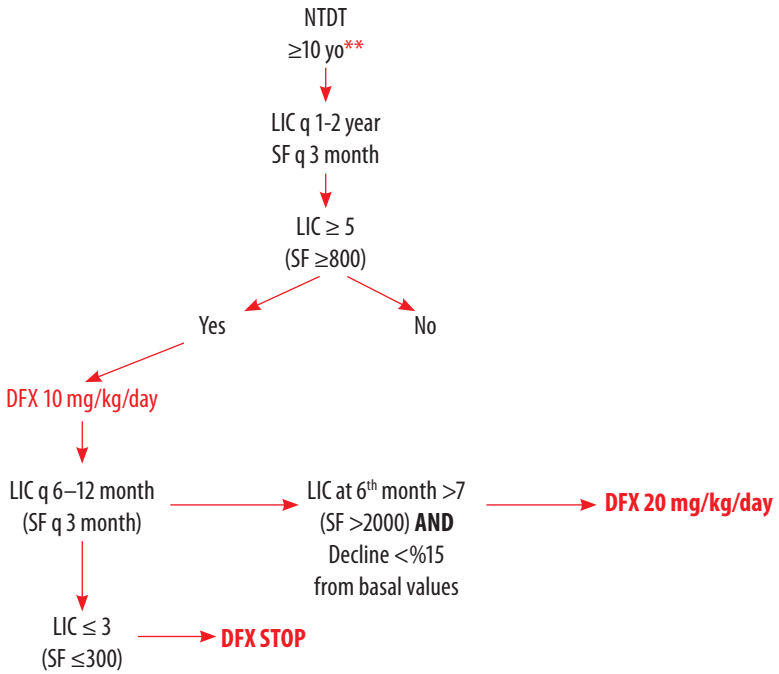

Figure 1. Iron loading monitorization and chelation according to iron load in patients with NTDT (adopted from reference 1)

NTDT: non-transfusion dependent thalassemia, yo: year-old, LIC: liver iron concentration, SF: serum ferritin, DFX: deferasirox

** (≥ 15 year-old in patients with deletional HbH disease)

was not availale. If LIC ≥5 mg Fe/g dw or serum ferritin ≥800 ng/ml, iron chelation wtih deferasirox was suggested to be initiated at a dose of 10 mg/kg/day and a follow-up LIC or serum ferritin was suggested to be done q 6 to 12 months or q 3 months, respectively. If LIC increases above ≥7 mg Fe/g dw or serum ferritin > 2000 ng/ml, the dose of deferairox was suggested to be increased to 20 mg/kg/day. On the other hand, when LIC decreases <3 mg Fe/g dw or when serum ferritin is below 300 ng/ml; cessation of chelation was suggested [1,23].

In conclusion, iron overload and iron chelation have usually been underestimated for long among patients with NTDT. However iron overload is a potential concern among these patients although not being regularly transfused. The guidelines that were developed with the data obtained from randomized controlled studies in large cohorts provided valuable information on chelation in patients with NTDT.

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