EUROPEAN HEMATOLOGY ASSOCIATION

Update on hemoglobinophaties - Section 2

Iron chelation in hemoglobinopathies

Vip Viprakasit

Department of Paediatrics, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand

Take-home messages

- Iron overload (IOL) is highly prevalent among patients with hemoglobinopathies; both transfusion dependent and non-transfusion dependent thalassemia (TDT & NTDT).
- Serum ferritin (SF) could be used to screen and identified patients with IOL, however a direct tissue iron measurement using magnetic resonance imaging (MRI) has become more effective for a better long term iron monitoring and guiding management.
- With appropriate tailoring based on tissue iron monitoring, three current iron chelators, deferoxamine (DFO), deferasirox (DFX) and deferiprone (DFP), could be used as a monotherapy and in a combination to provide effective iron chelation.

Introduction

Thalassemia is characterized by a reduction of either or both α and β globin chain synthesis, represents the most common and most significant form of hemoglobinopathies. Based on a recent classification, thalassemias are divided based on their clinical presentation, phenotypic severity and transfusion requirement into transfusion dependent thalassemia (TDT)[1] and non-transfusion dependent thalassemia (NTDT).[2] In TDT, iron overload (IOL) was directly resulted from transfused blood (transfusional iron overload) leading to iron related mortality and morbidities. IOL also develops in NTDT patients, even without frequent blood transfusion. Iron dysregulation and clinical management of IOL are somewhat different between TDT and NTDT in several aspects (summarized in Table 1) and would be the main subjects of this review. Iron overload and management in Sickle cell disease (SCD) has recently been reviewed and not covered.[3]

Current state of the art

Role of iron overload and its relevance of clinical complications

At present, management guidelines for transfusional iron overload are generally derived from clinical experience and trials in TDT.[1,4] Due to a lack of physiologic mechanism to remove iron acquired from transfused blood (each unit of blood contains 200-250 mg iron), regularly transfused patients accumulate iron of 0.4-0.5 mg/kg/day and IOL can occur after 10-20 transfusions (Table 1).[4] Despite, infrequent or no transfusion, IOL occur in NTDT due to increased gastrointestinal iron absorption, driven by hepcidin suppression and erythron expansion leading to hepatic iron loading.[5] In TDT, heme catabolized iron will readily saturate transferrin generating non transferrin bound iron (NTBI) in plasma. This NTBI can be rapidly taken through calcium channels into primarily hepatocytes and extra-hepatic iron accumulation i.e. heart and endocrine glands leading to several iron related complications (Table 1).[5] Although cardiac siderosis is a major cause of morbidity and mortality and a key factor in management decisions in patients with TDT, it does not seem to be a major concern in NTDT.[2] However, IOL in NTDT was associated with several morbidities (Table 1) leading to a recommendation of treatment.[2] Interestingly, a subgroup of NTDT patients who were previously transfused, splenectomized and high transferrin saturated (>70%) have increased NTBI and can be significantly susceptible to extrahepatic IOL.[5]

Role of iron monitoring: serum ferritin (SF) vs magnetic wresonance imaging (MRI)

Non-invasive iron monitoring using MRI for liver iron concentration (LIC) and cardiac T2* have become the gold standard to diagnose IOL and guide iron chelation therapy (ICT).[6] Several clinical surveys have demonstrated a geographical difference on prevalence of IOL among different regions of the world.[7-9] β-thalassemia major (TM) patients in Southeast Asia had the highest prevalence of cardiac IOL (T2*<20 msec), followed by Europe and the Middle East.[7] This result was consis-

tent with another survey using baseline SF to determine IOL in TDT.[8] Further evidence of considerable cardiac and liver iron burden across regions was reported.[9] The underlying mechanism of this difference remains unknown but it may suggest different local and regional ICT practice. Although, MRI can provide a direct organ specific iron determination, however its clinical use should be optimized for a cost-benefit in real-life practice.[10-12] To this regard, SF cut-offs of 1900, 1100 and 650 ng/mL for detection of liver IOL were proposed in β–TM, transfused and non-transfused β–TI respectively.[11] However, SF is not appropriate for diagnosing cardiac IOL, but can be used for exclusion when SF <2500 ng/mL.[12]

Role of iron chelation and its relevance to morbidity and mortality

Currently, the primary goal of ICT has shifted from treating or rescuing IOL to maintaining at all time the safe levels of body iron.[1] To achieve this, iron intake must be balanced with iron excretion by chelators to prevents iron accumulation and end-organ complications leading to normal survival and quality of life.[1] Therefore, appropriate, tailoring ICT with chelator choices and dose adjustment must be implemented at a timely manner, especially in pediatric patients.[4] It leads to a dramatic improvement of life expectancy in TDT patients in the last 50 years.[13]Three iron chelators, deferoxamine (DFO), deferasirox (DFX) and deferiprone (DFP), are currently available as

Table 1. Iron overload (IOL) and iron chelation therapy (ICT) in patients with transfusion dependent thalassemia (TDT) *vs.* non-transfusion dependent thalassemia (NTDT).

	Factors	TDT[1]	NTDT[2]
Underlying disease	Common types of thalassemia	β-thalassemia major (β-TM), severe Hb E/β-thalassemia, transfusion dependent Hb H disease, Hb Bart's hydrops	β-thalassemia intermedia (β-TI), Hb E/β-thalassemia, Hb H disease, Hb C/ β-thalassemia
IOL	Mechanism	Major: Blood transfusion Minor: Increased intestinal absorption	Major: Increased intestinal absorption Minor: Occasional blood transfusion
	Rate of iron accumulation	Rapid with marked generation of NTBI and LPI	Slow and lower NTBI
	Onset	Usually after 10-20 units of blood transfusions	Later on, usually after 10 yrs (or 15 yrs in patients with Hb H disease)
	Risk of extrahepatic IOL*	High	Low
	Common IOL related complications	Cardiac siderosis, heart failure and cardiac arrhythmia Liver fibrosis, cirrhosis and carcinoma Endocrinopathies i.e. diabetes, hypothyroidism, hypoparathyroid, adrenal insufficiency, hypogonadism, low bone mass, osteoporosis and growth failure	Liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) Associated with increased risk of thrombosis, pulmonary hypertension (PHT), osteoporosis, hypothyroidism, hypogonadism, right heart failure, gallstones and infections
ICT	Indication to initiate ICT	SF ≥ 1000 ng/mL	SF ≥ 800 ng/mL and/or LIC ≥ 5 mg/g dry weight liver
	Optimal levels of iron status after ICT	SF <1000 ng/mL and LIC <7 mg/g dry wt. liver and Cardiac T2* ≥ 20 msec.	NA
	Indication to intensify ICT	SF ≥ 2500 ng/mL and/or LIC >7 mg/g dry wt. liver and/or Cardiac T2* < 20 msec.	LIC after 6 months of treatment > 7 mg/g dry wt. liver or SF >1500-2000 ng/mL and < 15% decrease from baseline
	Indication to stop ICT	SF < 300 ng/mL and/or LIC <3 mg/g dry wt. liver	SF < 300 ng/mL and/or LIC < 3 mg/g dry wt. liver
	Choices of ICT** Monotherapy	First line of treatment: DFO 40-60 mg/kg/day DFX 20-40 mg/kg/day Second line of treatment: DFP 75-100 mg/kg/day	DFX 10-20 mg/kg/day NA
	Combination***	DFO+DFP, DFO+DFX and DFP+DFX	NA

*NTBI: non-transferrin bound iron; LPI: labile plasma iron; SF: serum ferritin; LIC: liver iron concentration; yrs; years; DFO: deferoxamine; DFX: deferasirox; DFP: deferiprone; wt.: weight; NA: not available; *including pancreas, endocrine glands and kidney; **based on current drug registration in Europe, USA and Asia; ***only compassionate use based on published data.*

monotherapy. Clinical decision to initiate, adjust and stop (or maintaining) of ICT are based on SF, MRI-LIC and cardiac T2* (Table 1). Development of new tridentate molecules of desferrithiocin class such as FBS0701[14] and SP-420[15] were now on hold due to reported toxicities. Therefore, recent clinical studies of ICT focused on current chelators by improving formulation, optimizing dose administration and adapting different chelator combination. A new film-coated tablet (FCT) of DFX was studied in a randomized trial comparing with original dispersible tablets (DT).[16] Based on Patient-Reported Outcomes (PROs), FCT showed greater adherence and satisfaction, better palatability and higher compliance than DT. However, it remains to be seen whether this improvement could be translated into a meaningful clinical efficacy. By adjusted administrative dose of DFX; from once into twice daily, improvement on efficacy was observed.[17] Combination of iron chelators have been reported with improving effectiveness.[18,19] A rapid decrease in LIC from heavily iron-overloaded TDT patients was observed in DFX-DFO.[18] A study of DFX in NTDT provided evidence of better ICT by early dose escalation.[20] However, these studies did not change on official label of the drugs and clinicians must warn their patients for an off-label use if they apply these reported experiences into their clinical practice.

Future perspectives

Further longitudinal studies are needed to assess causal relationship between iron overload and certain morbidities in NTDT patients in particular, those with higher risk of generating NTBI and extrahepatic IOL. Although safe and adequate blood transfusion with optimal chelation can normalize survival and improve quality of life in TDT patients. However, applying this approach to 'all thalassemia patients' might be limited in several parts of the world where resources are restricted. A long term randomized study comparing between current standard practice and a more proactive transfusion and chelation is highly required. Moreover, several practical questions remain unanswered; i.e., roles of early chelation in younger children (<2 yrs.) before IOL developed, the best optimal levels of iron status balancing risk of chelators *vs.* iron toxicities and which strategy between 'stop and re-start' or continuous ICT when iron level reach a certain threshold. To interrogate these unsolved puzzles, an international effort on multicenter international collaborating studies would be valuable and lead to further evidence based recommendations for ICT in hemoglobinopathies.

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This article further demonstrated dose escalation of DFX in NTDT patients based on baseline LIC and LIC response at 6 months with the maximum DFX dose of 30 mg/kg/day could provide a better chelation efficacy. DFX was registered for NTDT at dose of 10-20 mg/kg/day.