Interaction of Transfusion and Iron Chelation in Thalassemias

John B. Porter, MA, MD, FRCP, FRCPath[a,*],
Maciej W. Garbowski, MD, PhD[b]

KEYWORDS

• Iron • Chelators • Iron overload • Transfusion • Erythropoiesis • Hepcidin
• Soluble transferrin receptor • Cardiosiderosis

KEY POINTS

- The goals of blood transfusion in thalassemias are to ameliorate anemia and decrease ineffective erythropoiesis and its associated erythron expansion.
- Low transfusion regimens increase residual erythropoiesis, allowing for apotransferrin-dependent clearance of non–transferrin-bound iron (NTBI) species otherwise destined for myocardium.
- Cardiac iron retention depends both on iron uptake via NTBI route and iron egress via cardiac ferroportin, which is sensitive to transfusion-dependent modulation of hepcidin.
- Iron chelation is a successful modality in prolonging life expectancy and decreasing morbidity in thalassemia but requires a dose balanced to the iron intake rate.
- A 24-hour per day exposure to chelation is required when transferrin nears saturation exceeding 70% to prevent extrahepatic NTBI uptake.

INTRODUCTION

The benefits of both transfusion and chelation when used together are well established for transfusion-dependent thalassemias (TDTs). With the advent of newer chelation regimens and monitoring techniques, and in light of recent data linking low erythron activity to increased risk of cardiosiderosis, a reappraisal of the optimal balance between transfusion rates and chelation may be warranted. In this article, current transfusion and

Disclosure Statement: Advisory Board and consultancy to Novartis, Cerus, Celgene, Anaylam (J.B. Porter). Advisory Board to Vifor (M.W. Garbowski). Dr J.B. Porter is supported by the BRC at UCL.
[a] Haematology Department, University College London, UCLH and Whittington Hospitals, UCL Cancer Institute, Paul O'Gorman Building, 72 Huntley Street, London WC1E 6BT, UK;
[b] Haematology Department, University College London, Cancer Institute, UCL Cancer Institute, Paul O'Gorman Building, 72 Huntley Street, London WC1E 6BT, UK
* Corresponding author.
E-mail address: j.porter@ucl.ac.uk

Hematol Oncol Clin N Am 32 (2018) 247–259
https://doi.org/10.1016/j.hoc.2017.11.010
hemonc.theclinics.com

chelation practices are critically reviewed, with emphasis on how transfusion strategy affects iron distribution and the mechanisms through which this interaction occurs. The implications of this interaction for chelation strategy are also examined.

OBJECTIVES OF TRANSFUSION IN THALASSEMIAS

Blood transfusion in thalassemia aims to correct anemia so that physical and cognitive performances are close to healthy individuals, while preventing harmful or potentially disfiguring expansion of the erythron and not transfusing more blood and hence iron than necessary. Evidence for optimal hemoglobin (Hb) to achieve these goals was initially contradictory: some studies showed transfusion requirements remained constant at mean transfusion Hb levels of 10 g/dL to 14 g/dL (equivalent to pretransfusion Hb 8–12 g/dL),[1,2] whereas others showed that transfusion requirements were directly proportional to the mean Hb.[3,4] In a later study, transfusion requirement was measured in the same patients under 2 transfusion regimens[5]: those with mean pretransfusion Hb of 11.3 g/dL had mean annual transfusion of 137 mL/kg, but when the mean was subsequently lowered to Hb 9.4 g/dL, annual consumption decreased to 104 mL/kg/L and ferritin values fell.

Current guidelines recommend pretransfusion Hb values of 9.5 g/dL to 10.5 g/dL, thus keeping the mean Hb at approximately 12 g/dL with a post-transfusion Hb not above 14 g/dL.[6] This sweet spot for balancing considerations of iron loading and correction of anemia and ineffective erythropoiesis (IE) is based on a study of Italian patients[5] and may not be applicable to patients with different levels of effective erythropoiesis (discussed later). Under certain circumstances, higher Hb levels may be appropriate, for example, when some patients experience low back pain at Hb less than 10 g/dL to 11 g/dL, when the spleen size is expanding, or during pregnancy. The recommended frequency of transfusion every 2 weeks to 4 weeks has been determined to some extent by the convenience to patients and the availability of blood in some regions. Mathematical modeling suggested pretransfusion Hb of 9 g/dL with transfusions every 2 weeks rather than every 4 weeks would reduce requirements by 20% but no measurable effect was seen in a study comparing 3-week or 4-week intervals.[4]

Some populations are managed on lower pretransfusion Hb values: for example, in 464 Egyptian TDT patients aged 10 months to 31 years,[7] the mean pretransfusion Hb was 5.7 g/dL. In another study, the Hb values were significantly lower in patients from Cairo, Egypt (6.9 g/dL), than from Ismir, Turkey (Hb 8.9 g/dL) (Yesim Aydinok, MD, personal communication, 2017). The authors suggest that this variation in practice may account for differences in the proportion of patients with cardiosiderosis (discussed later).

Further considerations are whether and when to start transfusion, particularly for milder syndromes. Many patients with milder phenotypes may not require transfusion in the first few years of life, but as Hb values fall, particularly if there is failure to thrive, transfusion may become necessary. Guidelines generally suggest Hb values repeatedly less than 7 g/dL are suitable to begin transfusion but this approach may not be universally applicable, particularly in Eβ-thalassemia (haemoglobin E beta thalassaemia) syndromes, where the oxygen dissociation curve is right-shifted relative to β-thalassemia syndromes. For example, in a study where 109 Eβ-thalassemia patients from Sri Lanka were followed for 5 years, the untransfused group had Hb levels of 6.1 g/dL and, based on performance status, did not require starting transfusion, whereas in a second group with mean Hb values of 7.0 g/dL, 40% were able to stop transfusion without deleterious effects, despite the low Hb values.[8] These findings suggest that Eβ-thalassemia can be often managed without transfusion, even with low Hb levels.