Hematopoietic Stem Cell Transplantation in Thalassemia

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KEYWORDS

• Thalassemia • Hematopoietic stem cell transplantation
• Sibling donor transplantation • Unrelated donor transplantation
• Haploidentical transplantation • Cord blood transplantation

KEY POINTS

- HLA-matched family donors are still considered the gold standard for hematopoietic stem cell transplantation (HSCT) in thalassemia major (TM), with excellent results after either bone marrow or cord blood transplantation.
- TM children with a suitable HLA-identical sibling donor should be offered HSCT at an early disease stage, before the development of significant iron overload-related complications.
- Using strict criteria of donor/recipient compatibility (ie, high-resolution molecular typing for HLA class I and II), outcomes after MUD-HSCT now approach those of HLA-identical sibling recipients.
- Unrelated cord blood transplantation appears to be a suboptimal option in TM patients and is not routinely advisable, unless it is performed in the context of clinical trials.
- Despite few data available to date, results after haploidentical HSCT in children with TM appear encouraging.

INTRODUCTION

The improvements achieved over the last decades in supportive care for transfusion-dependent thalassemia (thalassemia major, TM) have dramatically improved survival rates and quality of life of patients. This holds particularly true for high-income countries, where life expectancy may now achieve the fourth/fifth decade of life.[1] However, TM still represents a relevant cause of childhood mortality in countries where access to regular and safe transfusion programs and/or iron chelation therapy remains difficult.

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Allogeneic hematopoietic stem cell transplantation (HSCT), as a way to replace the ineffective endogenous erythropoiesis and correct the phenotypic expression of the disease, has represented a turning point in the treatment of TM, holding the potential to release patients from both a life-long demanding treatment and long-term disease-related and/or therapy-related complications.

Although recent advances in gene therapy are expected to increase the chance of curing TM, this therapeutic approach is currently performed only in the context of clinical trials, and many obstacles remain to be overcome before it becomes available as an effective and routinely accepted clinical practice. Strategies of genome editing, although promising, are still at the preclinical level.

Therefore, at the present time, HSCT is the only consolidated approach holding the potential to definitively cure TM.

PRETRANSPLANTATION RISK STRATIFICATION

Since the curative potential of allogeneic HSCT for TM was first demonstrated,[2] more than 3000 transplant procedures have been reported worldwide.[3]

Outcomes have been shown to depend on patient age and disease status at time of transplantation. Indeed, since earlier experiences with HSCT in the 1980s and early 1990s, better survival rates have been observed in children, compared with adults.[4,5]

A prognostic score predicting transplant outcome in the pediatric population (patients younger than 17 years) was developed by the Pesaro group (**Table 1**). The Pesaro score system identified 3 independent prognostic factors, representing indirect estimates of the degree and extent of iron overload, predicting the risk of transplant-related complications and the chance to benefit from HSCT. These factors allow the stratification of patients into 3 risk groups, as shown in **Table 1**.[4,5]

The extensive Pesaro experience showed a thalassemia-free survival (TFS) estimate of 85% to 90%, 80%, and 65% to 70% for patients belonging risk class 1, 2, and 3, respectively, with probability of transplant-related mortality (TRM) progressively increasing from Pesaro class 1 to class 3, being highest for adult patients.[4–7]

The Pesaro classification has been validated in children having received adequate medical care before HSCT. Limitations of this risk stratification approach become evident when it is applied to patients with a history of inadequate pretransplantation medical care, as commonly seen in developing countries. For such high-risk children, Mathews and colleagues[8] proposed a risk evaluation based on patient age (above or below 7 years) and liver size (more or <5 cm below the costal margin), identifying a very high-risk subset within the Pesaro class 3 group. This observation was confirmed by an analysis based on data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).[9]

Table 1
Pesaro risk classification for predicting outcome of hematopoietic stem cell transplantation for thalassemia major patients

Risk Factors	Class 1	Class 2 (1 or 2 Risk Factors)	Class 3
Hepatomegaly >2 cm	No	Yes/No	Yes
Portal fibrosis	No	Yes/No	Yes
History of inadequate iron-chelation therapy	No	Yes/No	Yes

Data from Refs.[4,5,56]

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